TECHNISCHE UNIVERSITÄT
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Nachhaltige Konzepte zur C–C, C–N und C–S Bindungsknüpfung

vom Fachbereich Chemie der Universität Kaiserslautern

zur Verleihung des akademischen Grades

„Doktor der Naturwissenschaften“

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vorgelegt von

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angefertigt im Arbeitskreis von

Prof. Dr. Lukas J. Gooßen

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Meinen Eltern

Twenty years from now you will be more disappointed by the things you didn't do than by the ones you did do. So throw off the bowlines. Sail away from the safe harbor. Catch the trade winds in your sails. Explore. Dream. Discover.

Mark Twain

Die vorliegende Arbeit wurde im Zeitraum von November 2010 bis Juli 2014 im Arbeitskreis von Prof. Dr. Lukas J. Gooßen am Fachbereich Chemie der Technischen Universität Kaiserslautern angefertigt.

Promotionskommission

Vorsitzender:	Prof. Dr. Werner R. Thiel
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Eidesstattliche Erklärung

Hiermit versichere ich, dass ich die vorliegende Arbeit eigenständig verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel verwendet, sowie Literaturzitate kenntlich gemacht habe. Kooperationsprojekte sind ausdrücklich als solche gekennzeichnet und die Mitarbeiter genannt. Die Arbeit liegt weder in gleicher noch in ähnlicher Form in einem anderen Prüfungsverfahren vor.

Kaiserslautern, den _____ _____

Matthias F. Grünberg

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Abkürzungsverzeichnis

Ac	Acetyl
acac	Acetylaceton
Ad	Adamantyl
Alk	Alkyl
Anal.	Analyse
Ar	Arylrest
Äquiv.	Äquivalent
BINAP	2,2'−Bis(diphenylphosphino)−−1,1'−binaphthyl
bipy	2,2‘−Bipyridin
Calcd.	calculated
COD/cod	1,5−Cyclooctadien
Cy	Cyclohexyl
DABCO	1,4−Diazabicyclo[2.2.2]octan
dba	Dibenzylidenaceton
DBU	1,8−Diazabicyclo[5.4.0]undec−7−en
DC	Dünnschichtchromatographie
DCC	*N*,*N*′−Dicyclohexylcarbodiimid
dcype	1,2−Bis(Dicyclohexylphosphino)ethan
dcypp	1,3−Bis(Dicyclohexylphosphino)propan
DFT	Dichtefunktionaltheorie
DG	Dirigierende Gruppe
dippf	Bis(Diisopropylphosphino)ferrocen
DMAc	*N*,*N*−Dimethylacetamid
DMAP	4−*N*,*N*−Dimethylaminopyridin
DMF	*N*,*N*−Dimethylformamid
dmpe	1,2−Bis(dimethylphosphino)ethan
DMSO	Dimethylsulfoxid
dppb	1,4−Bis(diphenylphosphino)butan
dppe	1,2−Bis(diphenylphosphino)ethan
dppf	1,1‘−Bis(diphenylphosphino)ferrocen
dppm	Bis(diphenylphosphino)methan
dppp	1,3−Bis(diphenylphosphino)propan
ee	Enantiomeric exces
EI	Elektronenstoßionisation
Eintr.	Eintrag
et al.	et alii/aliae; und andere
Et	Ethyl
Fur	Furyl
GC	Gaschromatographie
Hal	Halogenid
HRMS	High Resolution Mass Spectrometry
i. Vak.	im Vakuum
^{i}Pr	Isopropyl
IPr	1,3−Bis(2,6−diisopropylphenyl)−imidazol−2−yliden
IR	Infrarot
J	Kopplungskonstante
Kat.	Katalysator
L	Ligand
LM	Lösungsmittel
M	Metall
Me	Methyl
Mes	Mesityl oder Mesitylen
MS	Molekularsieb
^{n}Bu	*n*−Butyl
NHC	*N*−heterocyclischer Carbenligand
NMP	*N*−Methyl−2−pyrrolidon
NMR	Nuclear Magnetic Resonanc
od.	Oder
OLED	Organic Light Emitting Diode
org.	organisch
Ph	Phenyl
Phen	1,10−Phenanthrolin
pK_s	Säurekonstante
pmdba	4,4’−Methoxydibenzylidenaceton
ppm	parts per million
p-TSA	4-Toluolsulfonsäure
quant.	quantitativ
Quin	Chinolin

R	organischer Rest	TFA	Trifluoressigsäure
rt	Raumtemperatur	ThDP	Thiaminpyrophosphat
SET	single electron transfer	THF	Tetrahydrofuran
SIPr	1,3–Bis(2,6–diisopropylphenyl)–4,5–dihydroimidazol–2–yliden	TMEDA	*N*,*N*,*N*',*N*'–Tetramethylethylendiamin
		TMS	Trimethylsilyl
t	Zeit	Tol	Tolyl oder Toluol
T	Temperatur	Ts	4–Tolylsulfonyl
TBAC	Tetrabutylammoniumchlorid	UV	Ultraviolett
^{t}Bu	*tert*–Butyl	vs	1,3–Divinyl–1,1,3,3–tetramethyldisiloxan
terpy	2,2′:6′,2″–Terpyridin	X	allgemein Abgangsgruppe
Tf	Trifluormethylsulfonyl	Y	allgemein Abgangsgruppe

Nummerierung der Verbindungen

Die vorliegende Doktorarbeit besteht zu einem großen Teil aus originalen Veröffentlichungstexten, in denen alle Verbindungen unabhängig voneinander nummeriert wurden. Zum besseren Verständnis wurde die Nummerierung der Publikationen beibehalten und die Verbindungen in den jeweiligen Unterkapiteln getrennt voneinander nummeriert. Werden Verbindungen in einem Unterkapitel hinzugefügt, die nicht in einer Publikation enthalten sind, dann werden diese im entsprechenden Kapitel entweder neu nummeriert oder die Nummerierung knüpft an der letzten erwähnten Nummer einer vorhandenen Publikation an. Die Bezeichnung setzt sich jeweils aus der Nummer der dritten Überschriftsebene und einer durchlaufenden Nummer zusammen, sodass Doppelbenennungen, vor allem im experimentellen Teil, vermieden werden. Beispielsweise trägt die 2. Verbindung aus Unterkapitel 4.1.2 die Nummer **4.1.2–2**. Für stark verallgemeinerte Strukturen aus Schemata, die etwa Reaktionsprinzipien verdeutlichen, wurde auf eine Nummerierung verzichtet. Alle Zwischenstufen aus Katalysezyklen wurden mit römischen Zahlen bezeichnet.

Veröffentlichungen

Die meisten Ergebnisse dieser Arbeit wurden bereits in wissenschaftlichen Fachzeitschriften veröffentlicht:

1. N. Rodríguez, F. Manjolinho, M. F. Grünberg, L. J. Gooßen, *Chem. Eur. J.* **2011**, *17*, 13688–13691: *Synthesis of α,β–Unsaturated Ketones by Pd–Catalyzed Decarboxylative Allylation of α–Oxocarboxylates*.
2. P. Mamone, M. F. Grünberg, A. Fromm, B. A. Khan, L. J. Gooßen, *Org. Lett.* **2012**, *14*, 3716–3719: *$[Pd(\mu\text{–}Br)(P^tBu_3)]_2$ as a Highly Active Isomerization Catalyst: Synthesis of Enol Esters from Allylic Esters.*
3. F. Manjolinho, M. F. Grünberg, N. Rodríguez, L. J. Gooßen, *Eur. J. Org. Chem.* **2012**, 4680–4683: *Decarboxylative Allylation of Glyoxylic Acids with Diallyl Carbonate*.
4. M. F. Grünberg, L. J. Gooßen, *Chem. Eur. J.* **2013**, *19*, 7334–7337: *Synthesis of Arylacetates from Benzylic Alcohols and Oxalate Esters through Decarboxylative Coupling.*
5. M. F. Grünberg, L. J. Gooßen, *J. Organomet. Chem.* **2013**, *744*, 140–143: *Decarboxylative allylation of arylglyoxylic acids with allyl alcohol*.
6. G. Danoun, B. Bayarmagnai, M. F. Grünberg, L. J. Gooßen, *Angew. Chem.* **2013**, *125*, 8130–8133: *Sandmeyer–Trifluormethylierung von Aryldiazoniumtetrafluorboraten*; *Angew. Chem. Int. Ed.* **2013**, *52*, 7972–7975 (**hot paper**): *Sandmeyer–Trifluoromethylation of Arenediazonium Tetrafluoroborates*.
7. G. Danoun, B. Bayarmagnai, M. Grünberg, L. J. Gooßen, *Chem.Sci.* **2014**, *5*, 1312–1316: *Sandmeyer trifluoromethylthiolation of arenediazonium salts with sodium thiocyanate and Ruppert–Prakash reagent*.
8. G. Danoun, B. Bayarmagnai, M. F. Grünberg, C. Matheis, E. Risto, L. J. Gooßen, *Synthesis* **2014**, zur Veröffentlichung akzeptiert: *Sandmeyer Trifluoromethylation*.
9. K. F. Pfister, M. F. Grünberg, L. J. Gooßen, *Adv. Synth. Catal.* **2014,** zur Veröffentlichung akzeptiert: *Synthesis of Allyl Arenes* via *Catalytic Decarboxylation of Allyl Benzoates*.

10. M. F. Grünberg, L. J. Gooßen, **2014,** Manuskript in Vorbereitung: *Pd(dippf)maleimide as highly selective catalyst for the monoarylation of primary amines*.
11. D. I. Hackenberger, B. Song, M. F. Grünberg, S. Farsadpour, L. T. Ghoochany, F. Menges, G. Niedner–Schatteburg, W. R. Thiel, L. J. Gooßen, **2014**, Manuskript in Vorbereitung: *Low–Temperatur Decarboxylative Cross–Coupling of Aryl Triflates.*

Patente

Die Ergebnisse aus Kooperationen mit der Umicore AG & Co. KG wurden in den folgenden Patenten veröffentlicht:

1. L. J. Gooßen, M. Arndt, P. Mamone, M. F. Grünberg, WO2013000874, **2013**: *Method for the preparation of a palladium catalyst dimer and process for its use in isomerization reactions.*
2. L. J. Gooßen, M. F. Grünberg, **2014**, zur Patentanmeldung eingereicht: *Monoarylierung aromatischer Amine*.

Posterpräsentationen

1. M. F. Grünberg, P. Mamone, L. J. Goossen, 44. Jahrestreffen Deutscher Katalytiker, Weimar **2011**: *Pd–Catalyzed Double Bond Isomerisation of Allylic Esters.*
2. M. F. Grünberg, N. Rodríguez, F. Manjolinho, L. J. Gooßen, GDCh–Wissenschaftsforum Chemie, Bremen **2011**: *Pd–Catalyzed Decarboxylative Allylation of α–Oxocarboxylates.*
3. M. F. Grünberg, N. Rodríguez, F. Manjolinho, L. J. Gooßen, Nachhaltigkeit in der chemischen Synthese, Kaiserslautern **2012**: *Decarboxylative Allylation of Glyoxylic Acids.*
4. M. F. Grünberg, Lukas J. Gooßen, 18th European Symposium on Organic Chemistry, Marseille **2013**: *Synthesis of Arylacetic Esters from Benzyl Alcohols and Oxalates.*
5. M. F. Grünberg, Lukas J. Gooßen, GDCH–Wissenschaftsforum, Darmstadt **2013**: *Synthesis of Arylacetates from Benzylic Alcohols and Oxalate Esters through Decarboxylative Coupling.*

Inhaltsverzeichnis

1. Struktur der Doktorarbeit

Die vorliegende kumulative Doktorarbeit besteht aus drei eigenständigen Themengebieten. Dabei bilden die Transformationen von Carbonsäuren den Hauptteil der Arbeit und die Sandmeyer−analogen Trifluormethylierungen und Trifluormethylthiolierungen, sowie die selektive Monoarylierung primärer Amine jeweils nur kleinere Projekte.

Aufgrund der kumulativen Promotionsform enthält diese Ausarbeitung sieben englische Originaltexte und drei Manuskriptentwürfe eigener wissenschaftlicher Veröffentlichungen, sowie ergänzende deutschsprachige Passagen, die die Publikationen thematisch einleiten, im Gesamtkontext einordnen und wichtige, unveröffentlichte Ergebnisse darlegen.

Kapitel 2 besteht aus einer Einleitung, in der auf den Hauptteil der Arbeit eingegangen wird. Dabei werden Carbonsäuren zunächst als wertvolle Substanzklasse vorgestellt und ihr Einsatz in decarboxylierenden Kreuzkupplungen und Allylierungsreaktionen gezeigt. Weiterhin werden Nickel−katalysierte C–O Aktivierungen gezeigt. Im Anschluss werden die Zielsetzung und Aufgabenstellung der Doktorarbeit dargelegt.

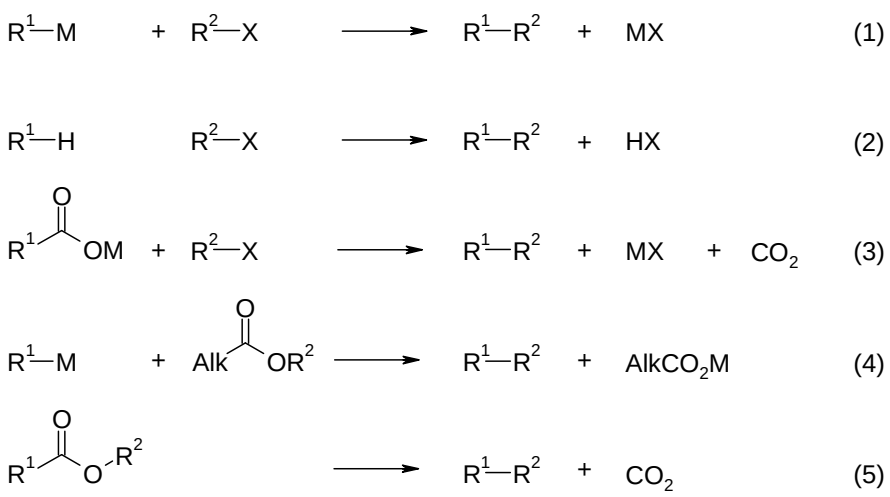
Im Ergebnis− und Diskussionsteil werden zunächst die im Rahmen dieser Arbeit erzielten Fortschritte in der Palladium−katalysierten decarboxylierenden Allylierung und Benzylierung beschrieben, woraufhin Nickel−katalysierte Varianten der Allylierungsreaktion und der decarboxylierenden Biarylsynthese vorgestellt werden. Das Gebiet der Carbonsäuren wird mit der Isomerisierung von Allylestern abgeschlossen. Daraufhin folgen die Abschnitte der Sandmeyer−analogen Reaktionen und der Monoarylierung primärer Aniline jeweils mit kurzer Einleitung direkt im Kapitel. Alle Themengebiete werden in Kapitel 5 zusammengefasst.

Kapitel 6 umfasst den experimentellen Teil dieser Arbeit und enthält neben den Spezifikationen der eingesetzten Messinstrumente auch alle verwendeten Versuchsvorschriften und die Charakterisierungen der Verbindungen. Das Kapitel wurde teilweise auf Englisch verfasst, da es zum größten Teil aus dem Material der englischsprachigen Supporting Informations besteht.

Im Anschluss folgen die kristallographischen Daten, das Literaturverzeichnis und ein kurzer Lebenslauf.

2. Einleitung

Die Entwicklung nachhaltiger Methoden zur C–C und C–Heteroatom Bindungsknüpfung gehört zu den Hauptzielen der modernen organischen Synthesechemie.[1,2] Übergangsmetall–katalysierte Kupplungsreaktionen sind dabei besonders effiziente und vielseitige Werkzeuge zum Aufbau komplexer Molekülstrukturen. In klassischen redox–neutralen Kreuzkupplungsreaktionen werden Organohalogenide, als Kohlenstoffnukleophile, regioselektiv mit Kohlenstoffelekrophilen, meist präformierte Organometallverbindungen der Elemente Bor,[3] Kupfer,[4] Magnesium,[5] Zink[6] oder Zinn[7] gekuppelt (Gleichung 1, X = Halogenid). Die verwendeten Abgangsgruppen bilden neben den eigentlichen Kupplungsprodukten stets Nebenprodukte, meist Metallsalze. Innerhalb der letzten Dekade wurden zahlreiche Strategien zur Überwindung solch inhärenter Limitierungen entwickelt, sodass die Präformierung sensibler organometallischer Reagenzien, sowie ökologisch bedenklicher Organohalogenide und die damit verbundene Salzfracht umgangen werden kann.



Eine dieser Strategien basiert auf der Kreuzkupplung azider Kohlenwasserstoffe mit Kohlenstoffelektrophilen (Gleichung 2). Dieses Konzept der C–H–Aktivierung ermöglicht eine hohe Atomökonomie. Die regio– und chemoselektive Kontrolle dieser Reaktionen ist allerdings oft nur mit speziellen Substraten, etwa Oxazolen, oder mit dirigierenden Gruppen möglich.[8–13]

Eine regioselektive Alternative zu traditionellen Kreuzkupplungsreaktionen sind decarboxylierende Kupplungen, bei denen leicht verfügbare und lagerstabile Carbonsäurederivate anstelle der Organometallverbindungen als Kohlenstoffnukleophile verwendet werden (Gleichung 3).[14–20] Dieses Konzept findet unter anderem Anwendung in der regioselektiven Synthese von Biarylen[21–27] und Arylketonen,[28–30] sowie der Einführung von Allyl– und Benzylgruppen.[31,32] Eine weitere Strategie involviert die Nutzung von Carboxylaten anstelle der Organohalogenide in der Kreuzkupplung mit Organometallverbindungen (Gleichung 4).[33,34] Ein bekanntes Beispiel dafür sind Tsuji–Trost Allylierungen (R^2 = Allyl).[35,36] Beide Konzepte werden in der decarboxylierenden Allylierung präformierter Allylcarboxylate vereinigt, bei der lediglich Kohlenstoffdioxid als Nebenprodukt generiert wird (Gleichung 5).[37] Auf die Nutzung von Carbonsäuren in der organischen Synthese und insbesondere in der Katalyse soll im Folgenden näher eingegangen werden.

2.1. Eigenschaften und Darstellung von Carbonsäuren

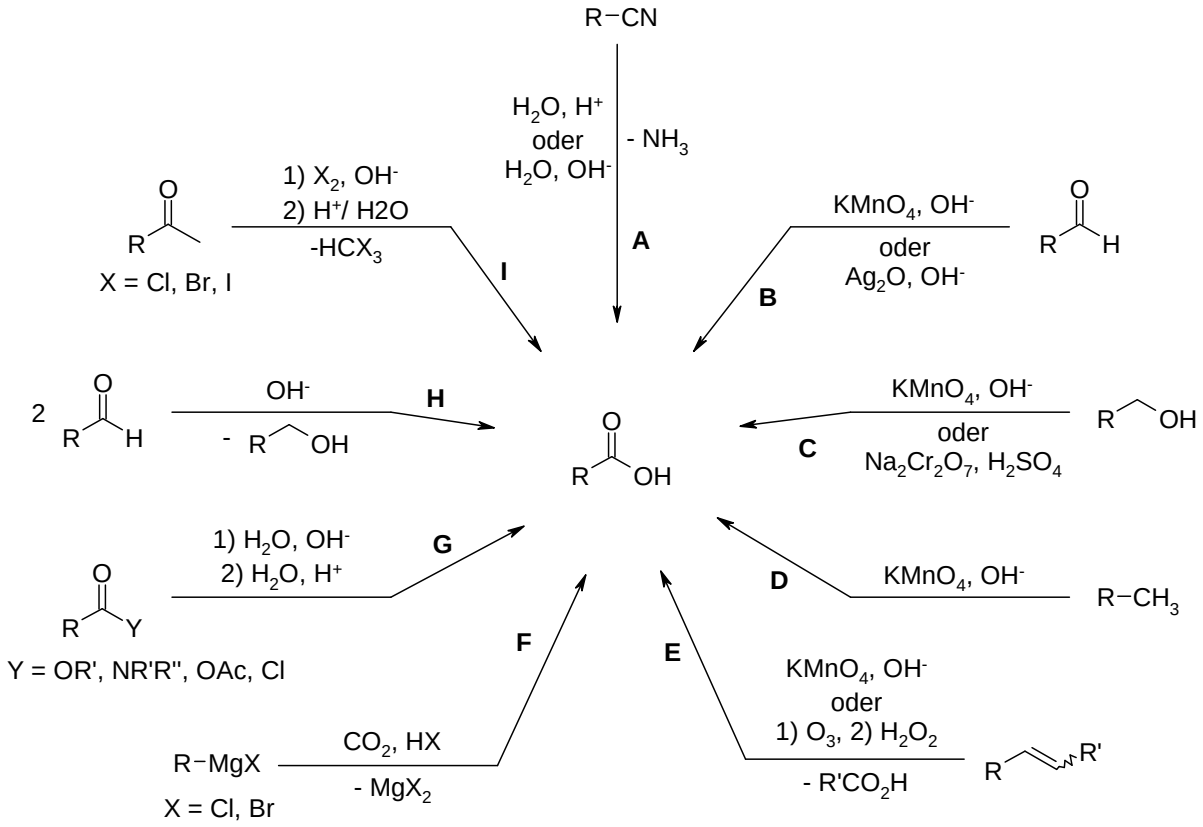
2.1.1. Eigenschaften von Carbonsäuren

Die Carboxygruppe gehört zu den am häufigsten vorkommenden Funktionalitäten organischer Moleküle. Weiterhin sind Carbonsäuren kommerziell in großer struktureller Vielfalt verfügbar.[38,39] Die chemischen Eigenschaften von Carbonsäuren werden maßgeblich von der Carboxygruppe bestimmt, deren Carbonylfunktion einen starken elektronenziehenden Effekt auf die Hydroxygruppe ausübt und diese entsprechend polarisiert. Unter basischen Bedingungen kommt es zur Deprotonierung und Ausbildung des resonanzstabilisierten Carboxylats. Im sauren Medium kann der nukleophile Angriff an das Carbonylkohlenstoffatom erfolgen, der zur Substitution der Hydroxygruppe führt und so z. B. die Synthese von Estern ermöglicht. Durch Umwandlung zum Säurechlorid, Anhydrid oder Aktivester sind außerdem Derivate zugänglich, die einen nukleophilen Angriff des Kohlenstoffatoms auch im Basischen erlauben und Substitutionen durch Additions–Eliminierungs–Reaktionen ermöglichen.[39]

2.1.2. Traditionelle und großtechnische Darstellung von Carbonsäuren

Die Synthese von Carbonsäuren kann auf verschiedensten Wegen aus diversen Substanzklassen erfolgen.[38,39] Traditionell werden Carbonsäuren oft durch die Hydrolyse

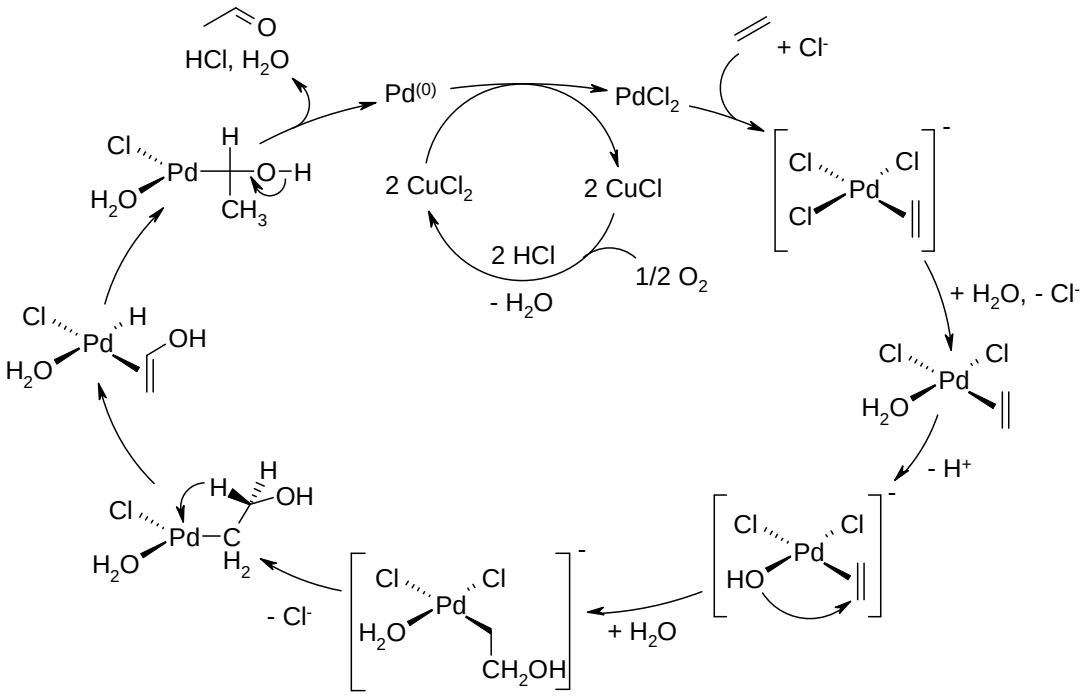
von Nitrilen erhalten (Schema 1, **A**), die ihrerseits über die Kolbe–Nitrilsynthese aus Alkylhalogeniden oder die von–Richter–Reaktion aus Nitroaromaten und Kaliumcyanid zugänglich sind.[39,40] Weitere klassische Zugänge sind die Oxidation von Aldehyden (**B**), Alkoholen (**C**) oder Alkylgruppen (**D**) mit Kaliumpermanganat oder Silberoxid im Basischen oder Natriumdichromat in Gegenwart von Schwefelsäure.[38] Olefine sind unter solch oxidativen Bedingungen oft nicht stabil und zersetzen sich unter oxidativer Spaltung in die entsprechenden Carbonsäuren (**E**).[38] Halogenierte Verbindungen können mit Magnesium in die Grignard–Verbindungen überführt und mit CO_2 carboxyliert werden (**F**).[38] Auf einem ähnlichen Prinzip basiert auch die Kolbe–Schmitt–Reaktion, bei der Natriumphenolate mit CO_2 in Salicylsäuren überführt werden.[41,42] Die Hydrolyse von Amiden, Estern, Anhydriden oder Säurechloriden (**G**) ist eine weitere Darstellungsmöglichkeit.[38] Darüber hinaus disproportionieren Aldehyde im stark basischen Medium in der Cannizzaro–Reaktion zu Carboxylaten und Alkoholen (**H**) und in der Haloformreaktion reagieren Methylketone mit Halogenen im Basischen zur Carbonsäure und Trihalogenmethan (**I**).[38,39]



Schema 1: Traditionelle Synthesemethoden von Carbonsäuren.

Großtechnisch von Bedeutung sind vor allem abfallminimierte Prozesse, wie etwa Oxidationsreaktionen mit Luftsauerstoff oder Carbonylierungen organischer

Verbindungen.[43] Die Spaltung von Erdgas und Naphtha ermöglicht den leichten Zugang zu Ethylen und damit einem der wichtigsten Grundbausteine großtechnischer Direktoxidationsverfahren, etwa dem Wacker–Hoechst Prozess, bei dem Ethen mit Luftsauerstoff in Gegenwart eines Palladium/Kupfer–Katalysators zum Acetaldehyd oxidiert wird (Schema 2).[44] Acetaldehyd ist ein besonders vielseitiges Zwischenprodukt, da es zur Darstellung zahlreicher organischer Grundbausteine genutzt werden kann. Dazu zählen die Essigsäure und deren Derivate, beispielsweise Ethylacetat und Acetanhydrid. Ein weiterer Zugang zur Essigsäure besteht in der Oxidation von Alkanen und Alkenen. British Distillers entwickelten ein Verfahren zur Oxidation leichtsiedender Rohöldestillate im C_4–C_8 Bereich.[43] Die Luftoxidation erfolgt dabei in der Flüssigphase bei 160–200 °C und 40–50 bar radikalisch und ohne zusätzlichen Katalysator. Beim Celanese–LPO–Verfahren (liquid phase oxidation) wird Butan bei 175 °C und 54 bar in Gegenwart von Cobaltacetat zur Essigsäure, oder, je nach Prozessführung, auch zu anderen Produkten wie Methylethylketon umgesetzt.



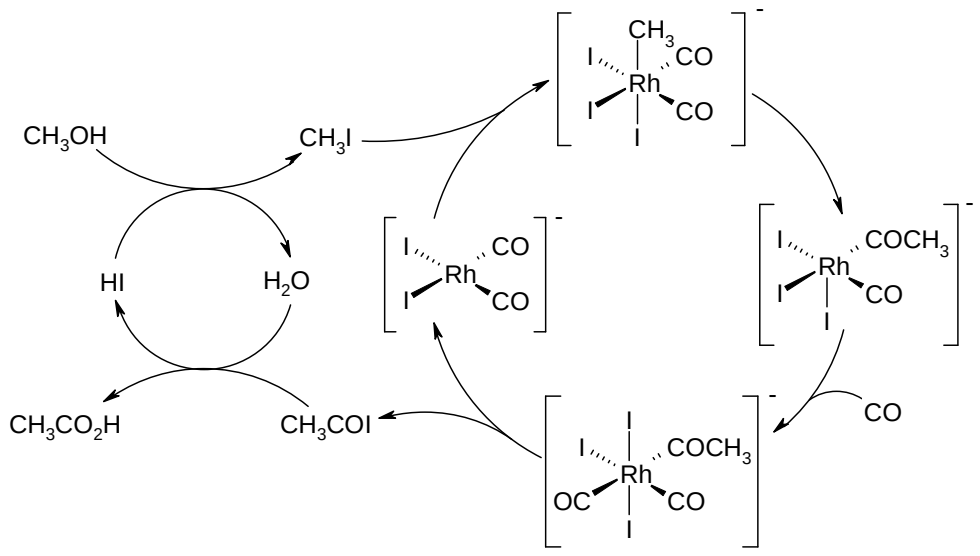
Schema 2: Mechanismus der Wacker–Oxidation.

Die Oxidation von Toluol, *meta*– oder *para*–Xylol zur Benzoesäure, Isophthalsäure bzw. Terephthalsäure erfolgt analog im Amoco–Verfahren.[45] Dieser Prozess verläuft mit einer Katalysator–Kombination aus Cobalt– und Manganacetat in Essigsäure bei 190–205 °C und

15–30 bar Luftsauerstoff in Gegenwart der Cokatalysatoren Ammoniumbromid und Tetrabromethan.[43]

Die katalytische Oxidation von Propen ermöglicht weiterhin den Zugang zur wichtigen Basischemikalie Acrylsäure. Die Prozessführung verläuft entweder einstufig mit einem Vierkomponenten–Katalysator bei 200 °C und bis zu 10 bar direkt zur Acrylsäure, oder im Zweistufen–Prozess über das Intermediat Acrolein.[43] Bis in die 1960er Jahre wurde alternativ auch das Reppe–Verfahren eingesetzt, bei dem Acetylen in Gegenwart von Wasser carbonyliert und in die Acrylsäure überführt wird.[40]

Besonders atomökonomisch ist die Carbonylierung von Alkoholen, wie es großtechnisch im Monsanto–Prozess erfolgt (Schema 3).[43,46] Dabei werden Methanol und CO bei 30–60 bar und 150–200 °C Rhodium–katalysiert zur Essigsäure umgesetzt. Seit seiner Einführung in den 1960er Jahren wurde der Monsanto–Prozess stets weiterentwickelt, beispielsweise zum Iridium–katalysierten Cativa–Prozess.[47] Dieser ermöglicht die Verringerung der im Prozess benötigten Wassermenge und damit einhergehend den Aufwand zur anschließenden Trocknung. Weiterhin wird damit die Menge der Nebenprodukte, etwa Propionsäure, reduziert und die Wassergas–Shift Reaktion unterdrückt. Mit dem verwandten Rhodium–katalysierten Tennessee–Eastman–Prozess steht eine Möglichkeit zur Synthese von Essigsäureanhydrid aus Methylacetat und CO zur Verfügung.[48]



Schema 3: Monsanto Essigsäuresynthese.

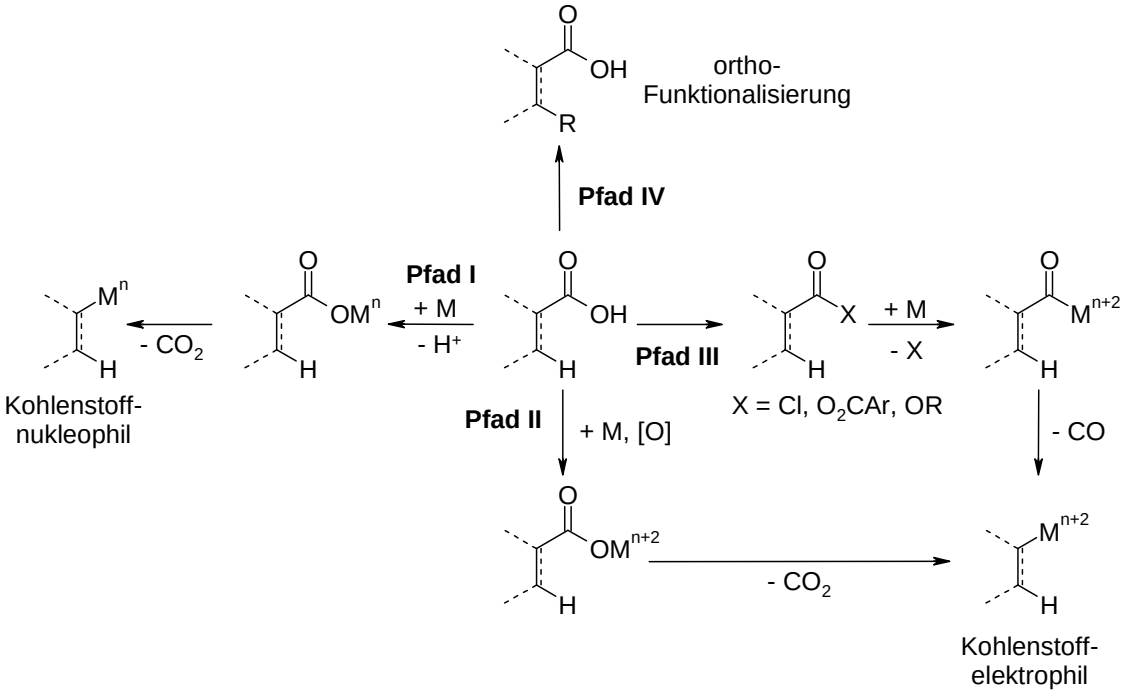
Von industrieller Bedeutung ist weiterhin die Koch–Reaktion zur Synthese gesättigter, tertiärer Carbonsäuren aus leicht verfügbaren und günstigen Olefinen, Kohlenstoffmonoxid

und Wasser.[43] Neben der chemischen Synthese ermöglicht auch die oxidative Fermentation aliphatischer Alkohole den Zugang zu kurzkettigen Carbonsäuren.[49–51] Viele Carbonsäuren, vor allem Fettsäuren, sind darüber hinaus auch aus natürlichen Quellen zugänglich.

2.2. Carbonsäuren in katalytischen Reaktionen

In den vergangenen Jahren wurde eine Vielzahl Übergangsmetall–katalysierter Transformationen entwickelt, bei denen Carbonsäuren als vielseitige Synthesebausteine eingesetzt werden und ein breites Spektrum unterschiedlichster Substanzklassen zugänglich machen.[17,19,52,53] Ausgehend von den freien Carbonsäuren unterscheidet man im Allgemeinen vier Aktivierungsmodi:

Die Decarboxylierung eines Metall–gebundenen Carboxylats führt zur Ausbildung einer Kohlenstoff–Metall Bindung ohne die Erhöhung der Oxidationszahl des Metallkatalysators (Schema 4, **Pfad I**). Dieser Redox–neutrale Schritt ermöglicht den intermediären Zugang zu Kohlenstoffnukleophilen, die in Gegenwart von Protonen zum protodecarboxylierten Produkt führen, oder mit Elektrophilen gekuppelt werden können. Die Metallcarboxylate selbst können auch Metall–katalysiert funktionalisiert werden, beispielsweise durch Addition an Alkene oder Alkine unter Ausbildung der entsprechenden Ester.



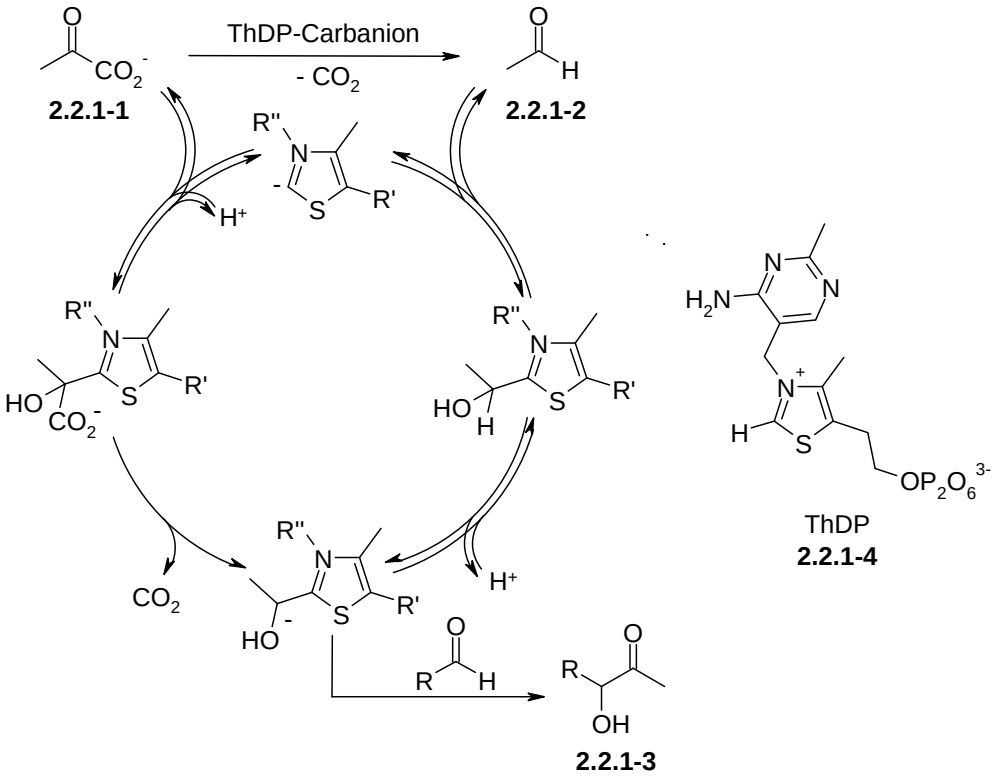
Schema 4: Carbonsäuren in katalytischen Transformationen.

Unter oxidativen Bedingungen führt die Decarboxylierung zu einem Intermediat mit erhöhter Oxidationszahl des Metall–Katalysators (**Pfad II**). Die entstandene Spezies entspricht einem Intermediat, das auch bei der oxidativen Addition von Kohlenstoffelektrophilen gebildet wird. Die Möglichkeiten zur weiteren Funktionalisierung sind analog und beinhalten Heck–Reaktionen und Kupplungen mit Kohlenstoffnukleophilen. Die Kohlenstoffelektrophile können darüber hinaus Redox–neutral durch die Insertion eines Metall–Katalysators in die C(Acyl)–O Bindung aktivierter Benzoesäurederivate, etwa Säurechloride, Anhydride oder Ester, und anschließende Decarbonylierung der Acyl–Metall–Spezies entstehen (**Pfad III**). Wird die Decarbonylierung unterdrückt, können diese Acyl–Metall–Spezies auch anders funktionalisiert werden: Die Anwesenheit von Protonen führt zu Aldehyden und die Kupplung mit Kohlenstoffnukleophilen ermöglicht den Zugang zu Arylketonen. Alle diese Strategien sind komplementär und erlauben die vielfältige *ipso*–Funktionalisierung der Carboxygruppe. Eine weitere Option ist die dirigierte *ortho*–Metallierung und Funktionalisierung aromatischer Carbonsäuren (**Pfad IV**), bei der die Säurefunktion für weitere Modifikationen erhalten bleibt.[54–57]

Relevant für die vorliegende Arbeit ist vor allem die redox–neutrale Decarboxylierung unter Bildung von Kohlenstoffnukleophilen. Auf die Reaktivität von Metallcarobxylaten, deren Protodecarboxylierung und Kupplung mit Kohlenstoffelektrophilen soll nachfolgend näher eingegangen werden.

2.2.1. Katalytische Protodecarboxylierung

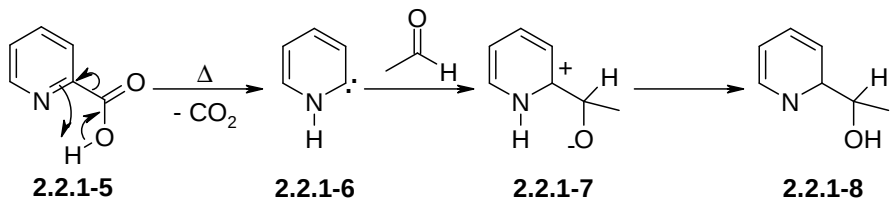
Lebende Organismen entwickelten im Laufe der Evolution effektive enzymatische Strategien zur Decarboxylierung ubiquitärer Verbindungen, mit denen Carboxylate in Aldehyde oder höhermolekulare Verbindungen überführt werden können. Ein Beispiel dafür ist die enzymatische Decarboxylierung von Pyruvat (**2.2.1–1**), dem Endprodukt der Glykolyse (Schema 5).[58] Der enzymgebundene Cofaktor Thiamindiphosphat (ThDP, **2.2.1–4**) wird zunächst deprotoniert und greift das Pyruvat dann nukleophil an. Das gebildete Intermediat wird daraufhin, je nach Enzym, entweder in Acetaldehyd (**2.2.1–2**) überführt oder auf andere Elektrophile übertragen.



Schema 5: Enzymatische Decarboxylierung von Pyruvat.

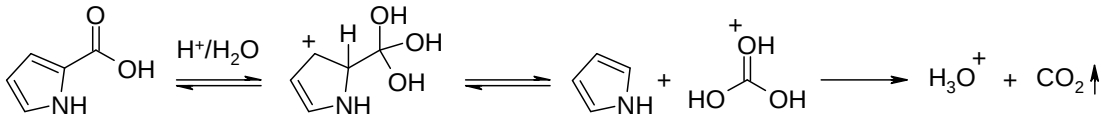
In der klassischen Synthesechemie erfolgt die Extrusion von CO_2 meist thermisch oder unter sauren Bedingungen aus aktivierten organischen Substanzen. Malonsäurederivate beispielsweise decarboxylieren bei Hitzeeinwirkung besonders leicht, da sie einen günstigen sechsgliedrigen Übergangszustand ausbilden können. Die Aktivierungsbarriere des Decarboxylierungsschritts wird dadurch enorm verringert und die Extrusion von CO_2 begünstigt.[38]

Zu den klassischen Decarboxylierungsreaktionen zählt auch die Hammick Reaktion, bei der α–Picolinsäuren (**2.2.1–5**) mit Carbonylverbindungen in 2–Pyridylalkohole (**2.2.1–8**) überführt werden (Schema 6).[59,60] Thermisch induziert kommt es zur Ausbildung einer Wasserstoffbrücke zwischen dem Pyridin–Stickstoff und dem Säureproton. Die darauf folgende Decarboxylierung führt zum Pyridin–Carben **2.2.1–6**, das nukleophil an die Carbonylfunktion des Aldehyds angreift und so ein Alkoholat **2.2.1–7** bildet, welches rearomatisierend zum 2–Pyridylalkohol führt.



Schema 6: Mechanismus der Hammick Reaktion.

Dass bis–*ortho*–substituierte Benzoesäuren unter stark sauren Bedingungen bei 60 °C decarboxyliert werden können, zeigten Hay und Taylor bereits 1966.[61] Diese Säure–katalysierte Protodecarboxylierung wurde später sorgfältig durch Chuchev und BelBruno untersucht.[62] Die Zugabe von Wasser genügt bei Pyrrol–2–carbonsäuren (**2.2.1–9**) bereits zur Säure–katalysierten Protodecarboxylierung und der Bildung von Kohlensäure, die irreversibel CO_2 freisetzt (Schema 7).[63] Im wässrigen Milieu und unter Mikrowellenbestrahlung zeigten weiterhin auch ionische Flüssigkeiten eine hohe Aktivität in der Protodecarboxylierung einiger *N*–Heteroaryl– und Arylcarbonsäuren.[64]



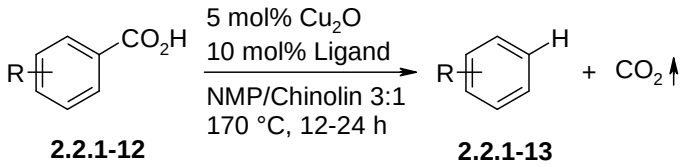
2.2.1-9 **2.2.1-10** **2.2.1-11**

Schema 7: Decarboxylierung von Pyrrol–2–carbonsäuren durch Zugabe von Wasser.

Neben diesen teilweise rauhen und limitierten Methoden ist besonders die Übergangsmetall–katalysierte Protodecarboxylierung von großem Interesse. Diese ermöglicht die kontrollierte und vollständige Entfernung einer Carboxygruppe und bietet darüber hinaus auch die Möglichkeit zur Kupplung intermediärer Metallorganyle mit Kohlenstoffelektrophilen.[57,65] Die Protodecarboxylierung ist zudem eine ideale Modellreaktion zur Entwicklung neuer und effektiverer Katalysatoren des oft begrenzenden Decarboxylierungsschritts solcher Kreuzkupplungsreaktionen. Sie stellt so oft den Schlüssel zur Absenkung der Reaktionstemperatur dar und könnte den Zugang zu einem breiteren Substratspektrum ermöglichen.

Bereits 1930 berichtete Shepard die Protodecarboxylierung halogenierter Furancarbonsäuren in Gegenwart stöchiometrischer Mengen Kupfer.[66] Basierend auf diesen Arbeiten erfolgten Protodecarboxylierungsstudien durch Nilsson,[14,15] Sheppard[67] und Cohen[68,69] an Nitrobenzoesäuren und einigen heteroaromatischen Carbonsäuren. Die erste katalytische Version der Protodecarboxylierungsreaktion wurde 2007 von Gooßen *et al.* beschrieben.[70] Eine Kombination von 5 mol% Cu_2O und 10 mol% 1,10–Phenanthrolin für aktivierte, *ortho*–subsituierte Benzoesäuren bzw. 10 mol% 4,7–Diphenyl–1,10–phenanthrolin für *meta*– und *para*–substituierte Substrate zeigte sich bei 170 °C in einem Lösungsmittelgemisch bestehend aus NMP und Chinolin (3:1) als besonders effektiv, um funktionalisierte Carbonsäuren zu decarboxylieren (Schema 8). Basierend auf diesen Arbeiten folgte zwei Jahre später ein Mikrowellenprotokoll, das die Protodecarboxylierung zahlreicher

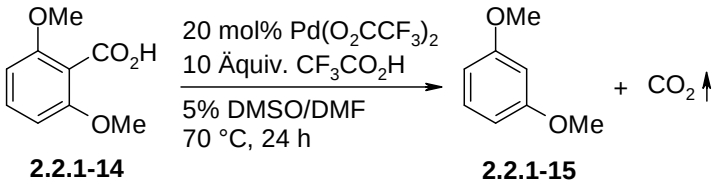
Aryl– und Heteroarylcarbonsäuren innerhalb weniger Minuten mit 5 mol% Cu_2O und 10 mol% Phenanthrolin ermöglicht.[71] Erst kürzlich beschrieben Cahiez *et al.* ein Katalysatorsystem bestehend aus 5 mol% Cu_2O und 10 mol% TMEDA, mit dem zahlreiche *ortho*–substituierte Benzoesäurederivate innerhalb einer Stunde bei 140 °C protodecarboxyliert werden können.[72]



Schema 8: Kupfer–katalysierte Protodecarboxylierung.

Neben diesen Kupfer–Systemen wurden auch Silber–[73–76] und Gold–katalysierte[77,78] Varianten entwickelt. Dabei ermöglichen 10 mol% AgOAc und 15 mol% K_2CO_3 in NMP die vollstänige Protodecarboxylierung bereits bei 120 °C.[73] 0.2 mol% des Gold–Katalysators [Au(SIPr)(O_2CAd)] protodecarboxyliert aktivierte, *ortho*–substituierte Benzoesäuren und heteroaromatische Carbonsäuren in Toluol ebenfalls bei 120 °C, benötigt bei *meta*– und *para*–substituierten Benzoesäuren aber 140–165 °C, das Lösungsmittel DMAc und eine höhere Katalysatorbeladung von 5 mol%.[77]

Besonders elektronenreiche, meist bis–*ortho*–substituierte aromatische Carbonsäuren (**2.2.1–14**) lassen sich auch Palladium–katalysiert bei milden Temperaturen decarboxylieren. Kozlowski *et al.* beschrieben die Palladium(II)–katalysierte Protodecarboxylierung solcher Verbindungen sogar schon bei milden 70 °C, allerdings unter Verwendung von 20 mol% einer teuren Palladium–Quelle und einem Überschuss Trifluoressigsäure (Schema 9).[79,80]



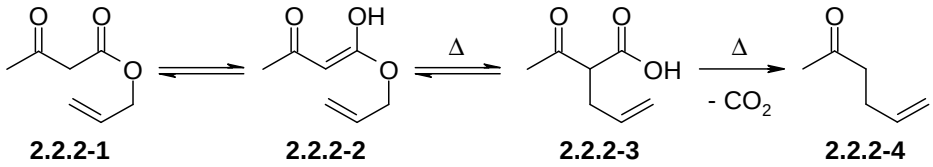
Schema 9: Pd–katalysierte Protodecarboxylierung elektronenreicher Benzoesäurederivate.

Neben Palladium bietet auch Rhodium die Möglichkeit zur Decarboxylierung elektronenreicher Benzoesäuren, Indolcarbonsäuren und Nitrophenylessigsäuren.[81] In Gegenwart einer Base ermöglicht die Kombination aus $[(cod)Rh(OH)]_2$ und dppp eine Protodecarboxylierung bei 90–110 °C.

Da Palladium und Rhodium zu den am häufigsten eingesetzten Übergangsmetallen in katalytischen C–C–Bindungsküpfungen gehören,[1] sind solche Palladium– und Rhodium–katalysierten Decarboxylierungsreaktionen besonders attraktiv. Sie ermöglichen die direkte Kupplung intermediärer Metallorganyle ohne weiteren Transmetallierungsschritt.

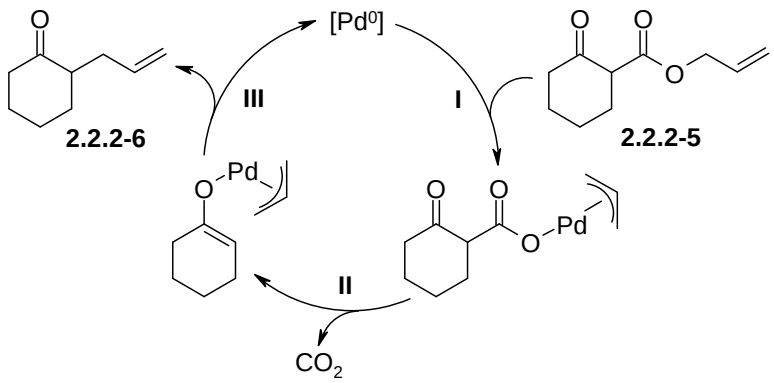
2.2.2. Decarboxylierende Allylierungen und Benzylierungen

Etwa 30 Jahre nach Claisens Bericht zur thermische Umlagerung von Allylvinylethern in γ,δ–ungesättigte Carbonylverbindungen[82] veröffentlichte Carroll 1940 die Synthese γ,δ–ungesättigter Ketone (**2.2.2–4**) durch thermische decarboxylierende Allylierung von Allyl–β–ketocarboxylaten (**2.2.2–1**) in Gegenwart einer Base (Schema 10).[83–85] Die Reaktion verläuft dabei über ein intermediäres Enol **2.2.2–2**, welches eine elektrozyklische Claisen–Umlagerung eingeht und anschließend CO_2 freisetzt.



Schema 10: Mechanismus der thermischen Carroll–Umlagerung.

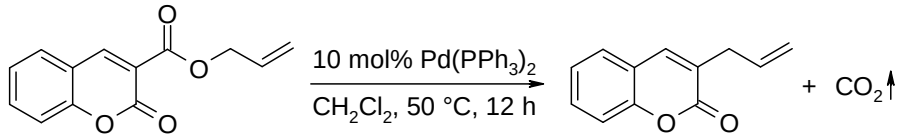
Anfang der 1980er Jahre beschrieben Tsuji[86,87] und Saegusa[88] unabhängig voneinander Palladium–katalysierte Varianten dieser Transformation unter neutralen Reaktionsbedingungen (Schema 11). Die besten Ausbeuten lieferten dabei 1 mol% $Pd(OAc)_2$ mit 4 mol% PPh_3 in THF bei 65 °C. Mechanistisch führt die oxidative Addition einer Palladium(0)–Spezies zur Ausbildung eines π–Allyl–Palladiumcarboxylat–Komplexes (**I**), welcher CO_2 bereits bei Raumtemperatur freisetzt und zum Palladium(II)enolat führt (**II**). Das Produkt wird schließlich reduktiv eliminiert und der Palladium–Katalysator regeneriert (**III**).



Schema 11: Palladium–katalysierte decarboxylierende Allylierung von β–Ketocarboxylaten.

Der Vorteil dieser C–C Bindungsknüpfungen besteht darin, dass die Startmaterialien aus der einfachen Veresterung freier Carbonsäuren mit Allylalkoholen zugänglich sind und keine Organometallverbindungen oder Halogenide benötigt werden. Die Erzeugung der Kohlenstoffelektrophile und –nukleophile erfolgt bei diesem Reaktionstyp *in situ* durch die Insertion des Palladiums in die C(Allyl)–O Bindung des Esters. Da diese reaktiven Intermediate nur in kleinen Mengen im Reaktionsmedium vorkommen, besteht eine hohe Toleranz gegenüber funktionellen Gruppen. Als Nebenprodukt der Kupplung wird darüber hinaus lediglich Kohlenstoffdioxid freigesetzt. Ein weiterer Vorteil ist die große kommerzielle Verfügbarkeit der Allylalkohole, die auch in der Natur weit verbreitet sind.

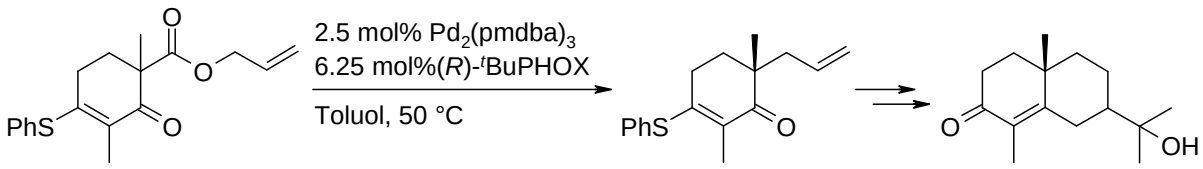
Durch umfangreiche Arbeiten von Tunge und Stoltz wurde dieses Reaktionskonzept zur synthetischen Reife gebracht.[37] So beschrieben Tunge *et al.* beispielsweise die decarboxylierende Allylierung von Cumarinderivaten (**2.2.2–7**)[89] (Schema 12) und anderen Heteroaromaten[90] oder auch asymmetrische Allylierungen.[91]



2.2.2-7 → **2.2.2-8** 67%

Schema 12: Decarboxylierende Allylierung von Cumarin.

Ausgehend von relativ einfachen und racemischen Allylestern nutzten Stoltz *et al.* die decarboxylierende Allylierung als Schlüsselschritt zum enantioselektiven Aufbau quarternärer Stereozentren zahlreicher komplexer Naturstoffgerüste, darunter beispielsweise das Eudesmangerüst des Terpens (+)–Carissone (**2.2.2–11**, Schema 13).[92–98]

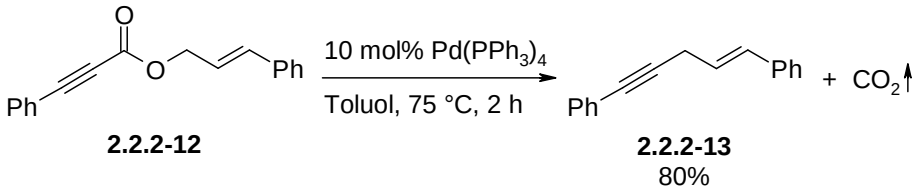


2.2.2-9 racemisch → **2.2.2-10** 85%, 92% ee → **2.2.2-11** (+)-Carissone

Schema 13: Die Decarboxylierende Allylierung in der Naturstoffsynthese.

Auch die Decarboxylierung von Propiolaten ist stark begünstigt und Palladium–katalysiert bereits unter sehr milden Reaktionsbedingungen bei 50 °C möglich. Tunge *et al.* konnten durch die Decarboxylierung entsprechender Propiolsäureallylester (**2.2.2–12**) einen einfachen Zugang zu 1,4–Enin–Verbindungen ermöglichen (Schema 14).[99] Die oxidative Addition des

Palladium(0)–Katalysators führt auch hier zur Ausbildung eines Allyl–Palladium–Carboxylats, das bereits bei 75 °C decarboxyliert und das Enin **2.2.2–13** durch reduktive Eliminierung freisetzt.



2.2.2-12 **2.2.2-13** 80%

Schema 14: Palladium–katalysierte decarboxylierende sp–sp^3 Kupplung.

Neben den Allylierungsreaktionen kann das Konzept auch auf die decarboxylierende Benzylierung präformierter Benzylester übertragen werden, da der Palladium(0)–Katalysator auch hier in die C(Benzyl)–O Bindung insertieren und einen stabilisierten Benzyl–Palladiumkomlex ausbilden kann.[100,101]

Der Nachteil der beschriebenen Allylierungs– und Benzylierungsreakionen ist die Limitierung auf Substrate, die nach der oxidativen Addition besonders leicht Palladium–katalysiert decarboxylieren und dadurch in stabile Kohlenstoffnukleophile, wie beispielsweise Enolate,[88] Alkinyl–,[99] Benzyl–,[90] α–Iminoyl–,[102] α–Cyano–,[100] α–Sulfonyl–[103] oder Nitrotolylanionen,[104] überführt werden können.

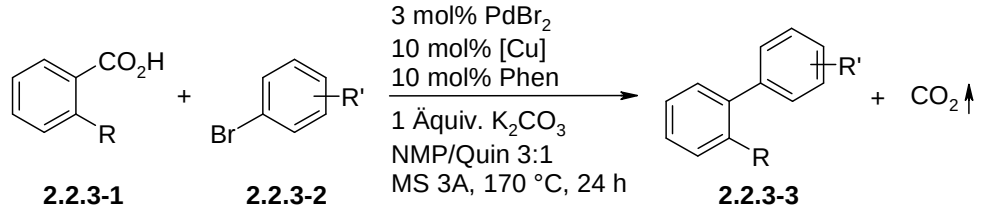
2.2.3. Decarboxylierende Kreuzkupplung aromatischer Carbonsäuren

Basierend auf der Vermutung, dass die klassische Ullmann–Kupplung[105] und die Kupfer–vermittelte Protodecarboxylierung aromatischer Carbonsäuren über die gleichen Kupfer–Organyle verlaufen, entdeckte Nilsson 1966 die erste Kreuzkupplung aromatischer Carbonsäuren mit Aryliodiden in siedendem Chinolin.[14,15] Aufgrund der hohen Kupfermengen, der teuren Aryliodide und hohen Reaktionetemperaturen erregte dieser Meilenstein in der Entwicklung nachhaltiger Kupplungsreaktionen nur wenig Aufsehen und geriet als Variante der Ullmann–Kupplung zunächst in Vergessenheit.

2.2.3.1. Bimetallische Kupfer/Palladium–Katalysatoren

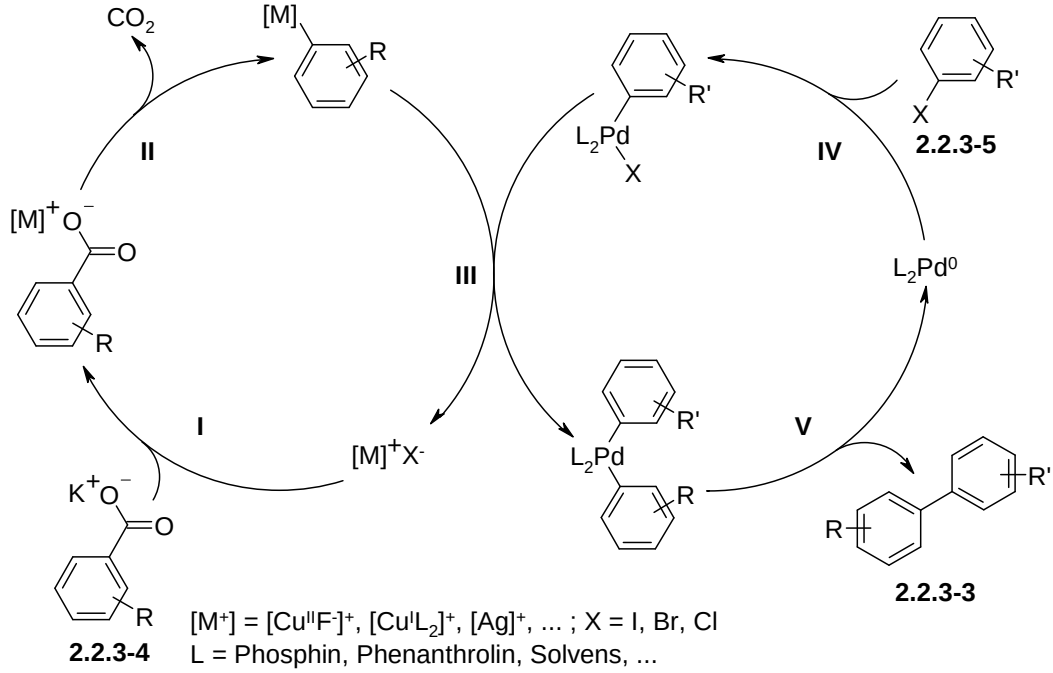
Erst die Kombination der Kupfersysteme mit einem Palladium–Katalysator ermöglichte unserer Arbeitsgruppe die Entwicklung eines potenten und breit anwendbaren, bimetallischen Katalysatorsystems zur decarboxylierenden Kreuzkupplung aromatischer Carbonsäuren. Mit 2 mol% $Pd(acac)_2$, 6 mol% $Ph_2P(^iPr)$ und stöchiometrischen Mengen $CuCO_3$ können vor

allem 2–Nitrobenzoesäure mit zahlreichen elektronenreichen und –armen Arylbromiden bei 120 °C in NMP in die entsprechenden Biaryle überführt werden.[16] Der Zusatz des bidentaten *N*–Donorliganden 1,10–Phenanthrolin ermöglicht eine Verringerung der Kupfermenge und erlaubt die effektive decarboxylierende Kreuzkupplung zahlreicher *ortho*–substituierter Benzoesäuren mit 10 mol% CuBr/1,10–Phenanthrolin und 3 mol% $PdBr_2$ bei 170 °C (Schema 15).[16,106]



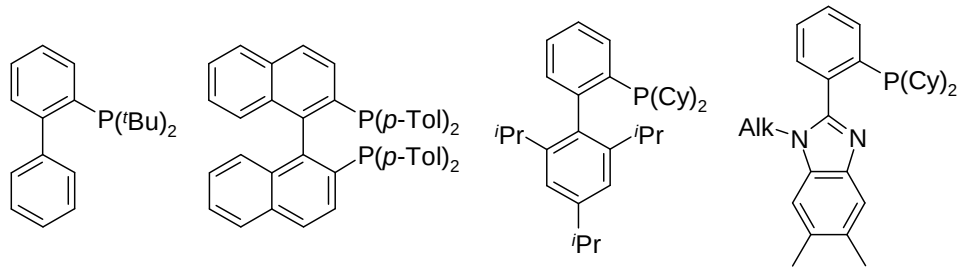
Schema 15: Decarboxylierende Kreuzkupplung von Benzoesäuren mit Arylbromiden.

Mechanistisch startet die Reaktion mit der Salzmetathese des Kaliumbenzoats **2.2.3–4** und der Kupferspezies zum Kupferbenzoat (Schema 16, **I**).[16] Die Extrusion von CO_2 führt zur Aryl–Kupfer–Spezies (**II**), die ihren Arylrest auf einen Aryl–Palladium–Komplex überträgt (**III**), der seinerseits aus der oxidativen Addition des Arylhalogenids **2.2.3–5** an eine Palladium(0)–Spezies entsteht (**IV**). Dieser Transmetallierungsschritt führt zur Regenerierung des Kupferkatalysators und zur Ausbildung eines Diaryl–Palladium–Komplexes, der das Produkt **2.2.3–3** durch reduktive Eliminierung bildet und die Palladium(0)–Spezies freisetzt (**V**).



Schema 16: Mechanismus der decarboxylierenden Biarylsynthese.

Die Reaktionsbedingungen und Katalysatormengen müssen bei einem solchen bimetallischen System exakt aufeinander abgestimmt sein, um unerwünschte Nebenreaktionen der reaktiven Kupferorganyle zu vermeiden.



2.2.3-6 JohnPhos (Arylchloride) | **2.2.3-7** Tol-BINAP (Aryltriflate) | **2.2.3-8** XPhos (Aryltosylate) | **2.2.3-9** Imidazolylphosphane (Arylmesylate)

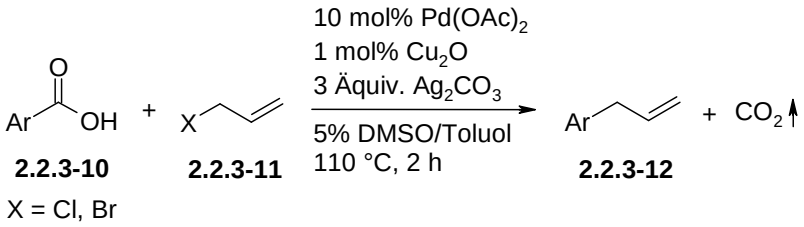
Schema 17: Liganden zur Aktivierung von Arylchloriden und –sulfonsäureestern.

Ausgehend von diesen Arbeiten entstanden in den Folgejahren zahlreiche Protokolle zur Erweiterung der Anwendungsbreite und Absenkung der Reaktionstemperatur.[17] Der Einsatz maßgeschneiderter Ligandensysteme des Palladium–Katalysators ermöglicht beispielsweise die Kupplung der Carbonsäuren mit zahlreichen weiteren Kohlenstoffelektrophilen: Der Einsatz des elektronenreichen und sterisch gehinderten JohnPhos–Liganden (**2.2.3–6**) erlaubt so die Aktivierung der C–Cl Bindung zahlreicher nicht–aktivierter Arylchloride.[23] Mit der Verwendung von Tol–BINAP (**2.2.3–7**) konnten erstmals Aryltriflate eingesetzt werrden, die im Transmetallisierungsschritt keine Kupferhalogenide bilden, sondern nur ein schwach koordinierendes Triflat auf den Kupfer–Katalysator übertragen, welches leicht gegen Benzoate ausgetauscht werden kann.[107,108] Mit dieser Weiterentwicklung konnte die Limitierung auf *ortho*–substituierte Benzoesäuren überwunden werden, da nun keine komplexierenden Gruppen zur Erleichterung der Salzmetathese nötig sind. Mit dem Buchwald–Liganden XPhos (**2.2.3–8**) wurden die günstigeren Aryltosylate[109] und mit maßgefertigten Imidazolylphosphin–Liganden (**2.2.3–9**) schließlich auch die unreaktiven Arylmesylate für die decarboxylierende Kreuzkupplung erschlossen.[110]

2.2.3.2. Bimetallische Silber/Palladium–Katalysatoren

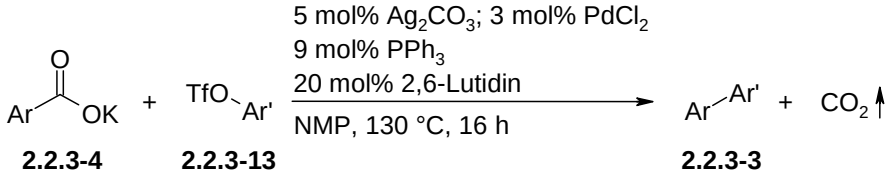
Die Gruppe um Becht entwickelte ein Protokol zur decarboxylierenden Kreuzkupplung aromatischer Carbonsäuren mit Aryliodiden, bei dem 30 mol% $PdCl_2$ und 60 mol% $AsPh_3$ in Kombination mit einem Überschuss von 3 Äquivalenten Silbercarbonat zum Einsatz kommen.[22] Dieses Verfahren wird durch die enormen Mengen der teuren Metallsalze und

eine geringe Anwendungsbreite limitiert. Ebenfalls unter Verwendung solch hoher Silbermengen beschrieben Liu *et al.* erst kürzlich die Synthese von Allylbenzolen durch die decarboxylierende Allylierung elektronenreicher, *ortho*–substituierter Benzoesäuren mit Allylhalogeniden in Gegenwart eines komplexen Palladium/Kupfer–Katalysatorsystems bei 110 °C (Schema 18).[31]



Schema 18: Decarboxylierende Allylierung elektronenreicher Silberbenzoate.

DFT Berechnungen und umfangreiche experimentelle Studien zur Silber–katalysierten Protodecarboxylierung[73,74] führten schließlich auch zur Entwicklung eines bimetallischen Silber/Palladium–Katalysatorsystems zur decarboxylierenden Kreuzkupplung bei 120–130 °C (Schema 19) und damit einer Temperaturabsenkung von 50 °C gegenüber den Kupfer/Palladium–Katalysatoren.[25]



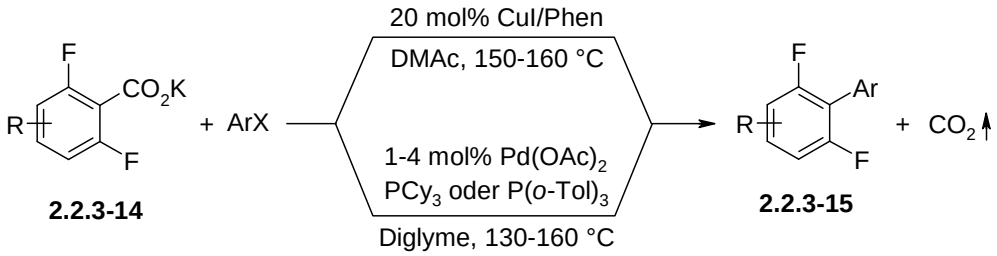
Schema 19: Silber/Palladium–katalysierte decarboxylierende Kreuzkupplung.

Das große synthetische Potential der decarboxylierenden Kreuzkupplung aromatischer Carbonsäuren und die Reife der bestehenden Verfahren wurden in den Synthesen der Blutdrucksenker Valsartan[111] und Telmisartan[112] und Biarylsynthesen im präparativen Maßstab demonstriert.[113] Praktische Mikrowellenprotokolle[26] und Reaktionen im kontinuierlichen Durchflussreaktor[114] bereichern das Repertoire der Prozessführung bimetallisch katalysierter decarboylierender Kreuzkupplungen.

2.2.3.3. Monometallische Katalysatorsysteme

Monometallische Katalysatorsysteme zur decarboxylierenden Kreuzkupplung besonders reaktiver Polyfluorbenzoate (**2.2.3–14**) beschrieben Liu *et al.* 2009 und 2010 (Schema 20).[24,115] Dabei katalysiert entweder ein reiner Kupfer–Katalysator oder ein Palladium–Katalysator sowohl den Decarboxylierungsschritt als auch die anschließende

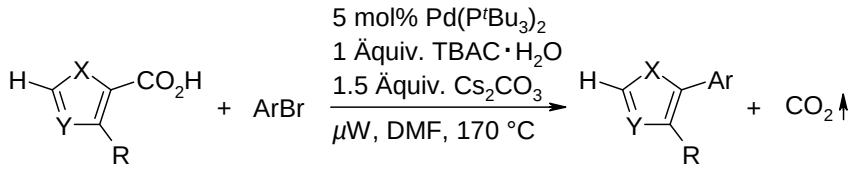
Kupplung. DFT–Studien dieser stark limitierten Kreuzkupplungen zeigten, dass die oxidative Addition den geschwindigkeitsbestimmenden Schritt der Kupfer–katalysierten Variante darstellt und dass das Palladium–System durch den Decarboxylierungsschritt begrenzt wird. Während das Kupfer–System nur die Kupplung mit Arylbromiden und –iodiden ermöglicht, kann der Palladium–Katalysator auch Arylchloride und –triflate aktivieren und umsetzen.



Schema 20: Decarboxylierende Kreuzkupplung von Perfluorbenzoaten.

2.2.3.4. Decarboxylierende Kreuzkupplung aktivierter Heteroaromaten

Bilodeau und Forgione beschrieben erstmals die rein Palladium–katalysierte decarboxylierende Kreuzkupplung heteroaromatischer Carbonsäuren mit Arylhalogeniden bei 170 °C. (Schema 21).[21,116] Aufgrund der regioselektiven C–C Bindungsknüpfung besitzt diese Heterobiarylsynthese große Vorteile gegenüber der direkten C–H–Arylierungen, bei der auch andere C–H–Bindungen funktionalisiert und dadurch Produktgemische erhalten werden.

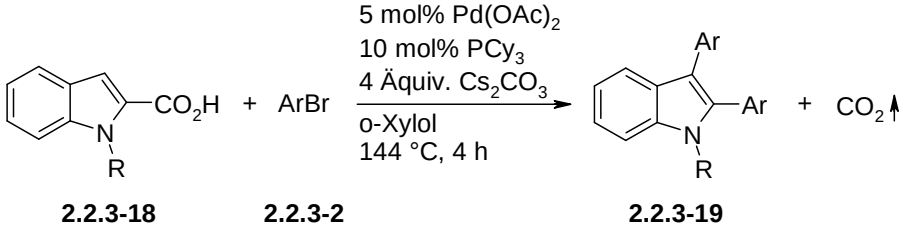


Schema 21: Decarboxylierende Kreuzkupplung heteroaromatischer Carbonsäuren.

Der genaue Mechanismus ist allerdings noch immer umstritten. Während die Autoren selbst eine Decarboxylierung vor dem eigentlichen Kupplungsschritt postulieren, beschreibt Steglich eine analoge intramolekulare Reaktion als Variante der Heck–Reaktion, bei der die Decarboxylierung erst nach der C–C Bindungsknüpfung erfolgt.[117] Für diese zweite These spricht der Befund, dass lediglich Heteraromaten mit der Carboxyfunktion in 2–Position reagieren und Furan–3–carbonsäuren keinerlei Reaktion zeigen. Zudem befindet sich die

Carboxygruppe stets an der Position, die auch die bevorzugte Position einer Heck–analogen Reaktion wäre.

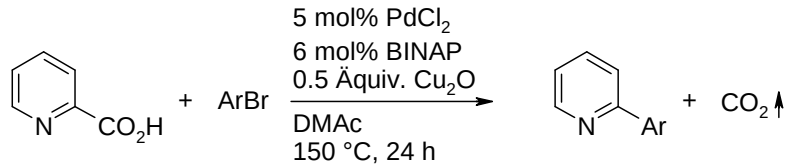
Die Palladium–katalysierte decarboxylierende Kreuzkupplung von Indol–2–carbonsäuren (**2.2.3–18**) mit Arylhalogeniden erfolgte durch Miura *et al.* und ermöglicht die Synthese von Diarylindolen (**2.2.3–19**). Die Reaktion verläuft dabei zunächst über die *ortho*–Funktionalisierung der Carboxygruppe und anschließend über die decarboxylierende *ipso*–Arylierung der Indol–2–carbonsäuren (Schema 22).[118]



2.2.3-18 **2.2.3-2** **2.2.3-19**

Schema 22: Decarboxylierende Kreuzkupplung von Indol–2–carbonsäuren.

Erst kürzlich beschrieben Wu *et al.* die decarboxylierende Kreuzkupplung von Picolinsäure (**2.2.3–20**) mit zahlreichen Aryl– und Heteroarylbromiden bei 150 °C (Schema 23).[119] Die Kupfer–vermittelte Decarboxylierung der günstigen Picolinsäure führt zunächst zur instabilen und daher sonst nur schwer zugänglichen 2–Pyridyl–Kupferspezies, die nach der Transmetallierung des Pyridylrestes auf Palladium zu wertvollen 2–Aryl– und 2–Heteroarylpyridinen führt.



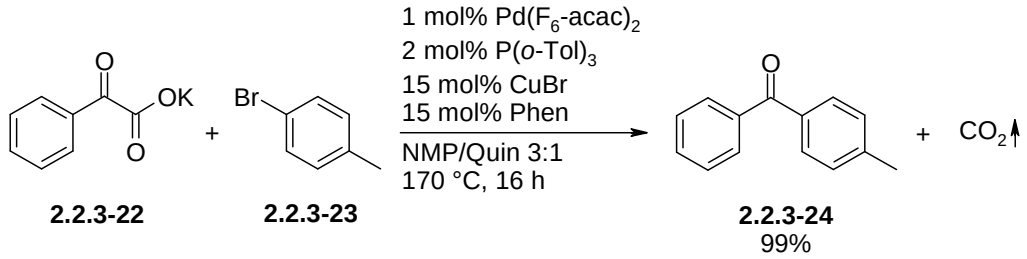
2.2.3-20 **2.2.3-2** **2.2.3-21**

Schema 23: Decarboxylierende Kreuzkupplung von Picolinsäure.

2.2.3.5. Decarboxylierende Kreuzkupplung von Arylglyoxylaten und Oxalaten

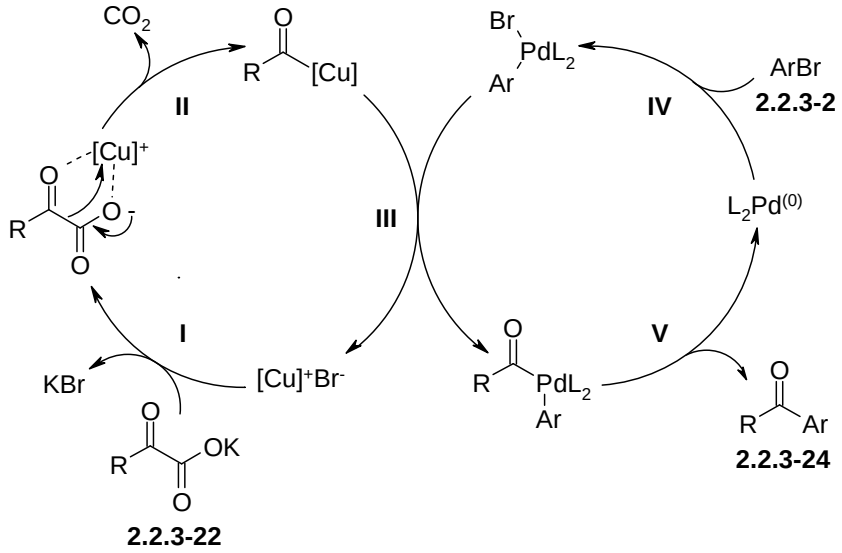
Das Konzept der decarboxylierenden Kreuzkupplung kann von aromatischen und heteroaromatischen Carbonsäurederivaten auch auf Arylglyoxylate (**2.2.3–22**) übertragen werden und ermöglicht den Zugang zu Arylketonen (**2.2.3–24**, Schema 24).[28] Klassisch erfolgt die Darstellung solcher Verbindungen neben der klassischen Friedel–Crafts–Acylierung,[120] bei der die Produkte meist als Isomerengemische entstehen, vor allem durch die Reaktion aktivierter Carbonsäuren, etwa Weinreb–Amide,[121] mit

Organometallverbindungen. Weiterhin sind Übergangsmetall–katalysierte Verfahren mit Organozink–Verbindungen[122] oder *in situ* aktivierten Carbonsäuren[123–126] und Boronsäuren bekannt. Im Gegensatz dazu ist die decarboxylierende Kupplung eine breit anwendbare, regioselektive und einstufige Alternative, die auf präformierte metallorganische Reagenzien verzichtet. Die verwendeten Arylglyoxylsäuren sind als Zwischenprodukte der Aminosäuresynthese teilweise großtechnisch verfügbar.



Schema 24: Arylketonsynthese ausgehend von Phenylglyoxylaten.

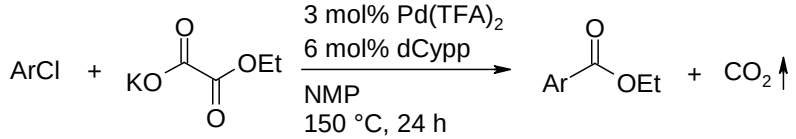
Der Mechanismus der Arylketonsynthese (Schema 25) verläuft analog zur decarboxylierenden Biarylsynthese. Nach Anionenaustausch am Kupfer/1,10–Phenanthrolin–Katalysator (**I**) wird das Glyoxylat **2.2.3–22** decarboxyliert (**II**) und der Acylrest auf eine Aryl–Palladium(II)–Spezies transmetalliert (**III**), die aus der oxidativen Addition von Arylhalogeniden an einen Palladium(0)–Komplex hervorgegangen ist (**IV**). Die reduktive Eliminierung setzt das Produkt **2.2.3–24** frei und regeneriert gleichzeitig den ursprünglichen Palladium(0)–Katalysator (**V**). Bei dieser Transformation wird die elektrophile Oxo–Gruppe formal in ein Kupfer–stabilisiertes Acylanionen–Äquivalent umgepolt.



Schema 25: Mechanismus der Arylketonsynthese ausgehend von Phenylglyoxylaten.

Die traditionelle Umpolung einer Carbonylfunktion erfolgt durch Umwandlung eines Aldehyds in das entsprechende Cyanhydrin,[127] Acetal,[128] Thioacetal[129] oder Hydrazon.[130] Nachteile dieser Vorgehensweisen sind die zusätzlichen Derivatisierungs– und Hydrolyseschritte, sowie der Einsatz starker Basen. Im Vergleich dazu wird das Acyl–Nukleophil bei der decarboxylierenden Kreuzkupplung *in situ* am Kupferkatalysator gebildet und benötigt keine Schutzgruppen.

Ein weiteres Beispiel, bei dem die Decarboxylierung zu Acylanionen führt, ist die rein Palladium–katalysierte decarboxylierende Kupplung von Kaliumethyloxalat (**2.2.3–26**) mit Arylbromiden und –chloriden bei 150 °C (Schema 26).[30] Die Kombination von 1–3 mol% $Pd(TFA)_2$ und den sterisch anspruchsvollen, bidentaten Liganden dppp oder dCypp führt in NMP zu Benzoesäureestern (**2.2.3–27**) und bietet eine praktische Alternative zur Carbonylierung aromatischer Halogenide.



2.2.3-25 **2.2.3-26** **2.2.3-27**

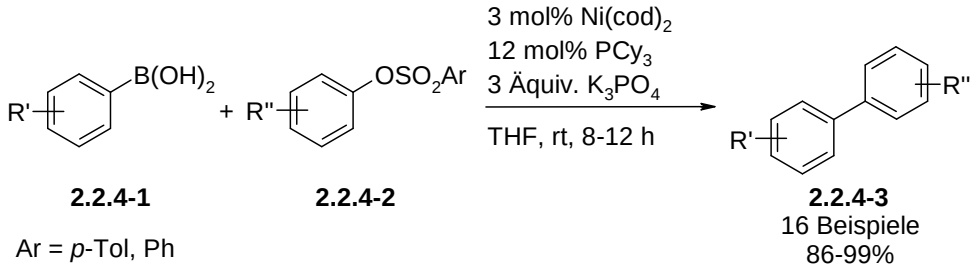
Schema 26: Synthese aromatischer Ester ausgehend von Oxalaten.

2.2.4. Carbonsäureester als Kohlenstoffelektrophile

Neben Arylhalogeniden haben sich vor allem auch Sulfonsäureester als Kohlenstoffelektrophile in Kreuzkupplungsreaktionen etabliert. Aufgrund ihrer besonders hohen Reaktivität und der leichten Palladiuminsertion in die C(Aryl)–O Bindung umfassten frühe Arbeiten zunächst nur Alkenyl– und Aryltriflate.[3,131] Die Entwicklung besserer Katalysatorsysteme zur C–O–Bindungsaktivierung führte zur Erschließung günstigerer Tosylate, Mesylate und Phosphonate, die sich nicht nur durch eine einfachere Synthese auszeichnen, sondern auch eine weitaus höhere Hydrolysestabilität besitzen.[132–136]

In den letzten 20 Jahren erlebten, neben den Palladium–Katalysatoren, vor allem auch die günstigeren Nickel–Katalysatoren eine rasante Entwicklung.[137–141] Umfangreiche Studien belegen, dass Nickel–Katalysatoren bei C–C, C–N und C–P Bindungsknüpfungen einiger Kohlenstoffelektrophile sogar vielseitiger und leistungsfähiger sind als vergleichbare Palladium–Komplexe.

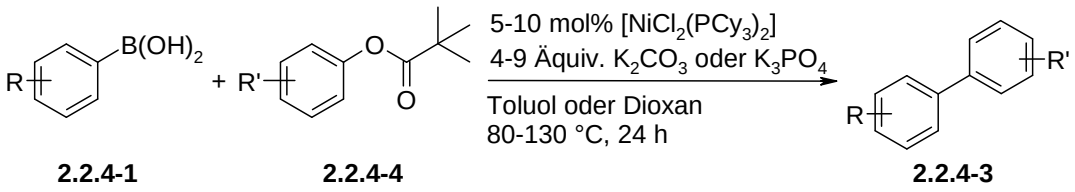
Die erste Nickel–katalysierte Suzuki–Miyaura Kupplung von Phenolderivaten erfolgte 1995 durch Percec *et al.* mit der Umsetzung von Arylboronsäuren mit Arylsulfonaten. Als Katalysator dienten 10 mol% $NiCl_2$(dppf) in Gegenwart von 1.7 Äquivalenten Zinkpulver als Reduktionsmittel. In den Folgejahren beschrieben Miyaura *et al.* weiterhin auch die Umsetzung von Arylmesylaten mit Buthyllithium als Reduktionsmittel.[142] Die Kupplung von Aryltosylaten (**2.2.4–2**) erfolgte durch Monteiro *et al.* mit 1.5–3 mol% $NiCl_2(PCy_3)_2$ und 6–12 mol% PCy_3 bei 130 °C auch ohne externes Reduktionsmittel.[135] Die Generierung der Ni(0)–Spezies erfolgt dabei durch Transmetallierung der Boronsäure (**2.2.4–1**) mit der Nickel–Vorstufe und anschließender reduktiver Eliminierung des Homokupplungsprodukts. Ausgehend von diesen Arbeiten entwickelten Hu und Tang schließlich ein sehr mildes Kupplungsverfahren, bei dem das aktive Katalysatorsystem aus 3 mol% $Ni(cod)_2$ und 12 mol% PCy_3 gebildet wird (Schema 27).[136,143]



Schema 27: Nickel–katalysierte Suzuki–Miyaura–Kupplung von Aryltosylaten.

Einer der größten Vorteile Nickel–basierter Systeme ist aber die Fähigkeit zur C(Aryl)–O–Bindungsaktivierung ansonsten inerter Phenolderivate, etwa Arylether, –ester, –carbonate, –carbamate und –sulfamate. Besonders nachhaltig ist die Verwendung von Arylestern als Kohlenstoffelektrophile, da diese durch einfache Veresterung leicht verfügbarer Substrate zugänglich sind und bei einer Übergangsmetall–katalysierten Kupplung lediglich organische Carboxylate freisetzen. Das Problem dieses Konzepts liegt in der selektiven C–O Aktivierung der Arylester, da die Bindungsdissoziationsenergie der C(Aryl)–O Bindung (106 kcal/mol) deutlich über der einer C(Acyl)–O Bindung (80 kcal/mol) liegt.[137] Bereits 1980 erfolgten erste Pionierarbeiten durch Yamamoto *et al.* zur selektiven Spaltung von Arylcarboxylaten. Dabei konnte gezeigt werden, dass die Selektivität der Nickel(0)–Insertion in gewissem Maße durch die Wahl der Reaktionsbedingungen gesteuert werden kann.[144] Basierend auf diesen Arbeiten entwickelten die Arbeitsgruppen um Shi und Garg schließlich 2008 unabhängig voneinander Protokolle zur Nickel–katalysierten

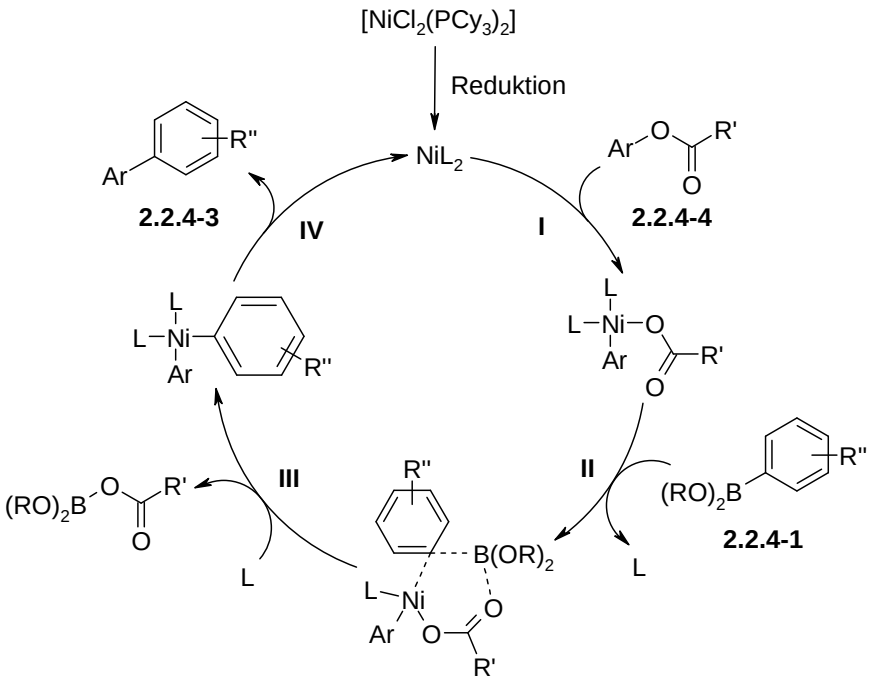
Suzuki–Miyaura Kreuzkupplung von Arylestern (**2.2.4–4**) mit Arylboronsäuren (Schema 28).[33,34]



Schema 28: Nickel–katalysierte Kreuzkupplung von Arylpivalaten mit Arylboronsäuren.

Während sich die Arbeiten von Garg auf Arylpivalate beschränken, beschreibt Shi die Aktivierung verschiedener Carboxylate, wobei das Pivalat ebenfalls die besten Ausbeuten ermöglicht. In beiden Protokollen werden die Ester mit Arylboronsäuren in Gegenwart von 5–10 mol% $NiCl_2(PCy_3)_2$ und K_3PO_4 oder K_3PO_4 als Base in Toluol oder Dioxan bei 80–130 °C umgesetzt. Einzig der verwendete PCy_3 Ligand ermöglichte dabei hohe Umsätze, andere Phosphane führten zu nicht annähernd guten Ausbeuten.

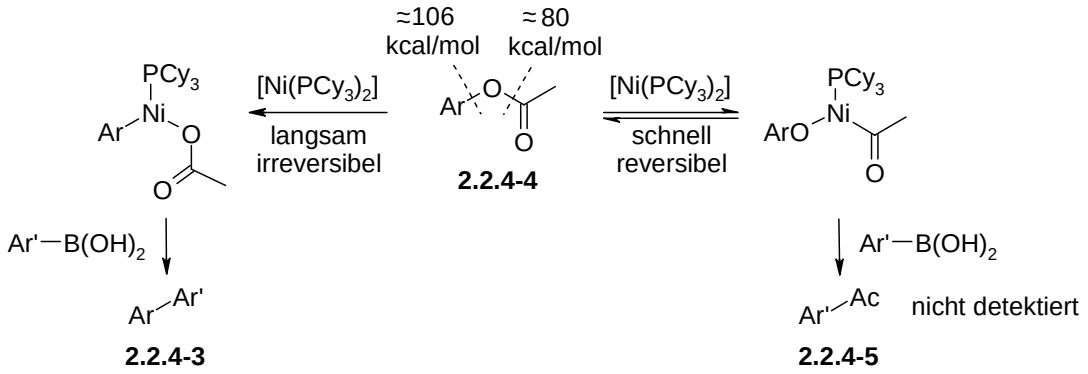
Der vorgeschlagene Mechanismus startet mit der Reduktion der Nickel(II)–Quelle zur aktiven Nickel(0)–Spezies (Schema 29). Die oxidative Addition des Arylcarboxylats **2.2.4–4** bildet ein Aryl–Nickel(II)carboxylat (**I**), das durch eine Transmetallierung mit der Boronsäure (**II** & **III**) in eine Diaryl–Nickel(II)–Verbindung übergeht. Die reduktive Eliminierung setzt das Kupplungsprodukt **2.2.4–3** frei und regeneriert den Nickel(0)–Katalysator (**IV**).



Schema 29: Mechanismus der Kreuzkupplung von Arylpivalaten mit Arylboronsäuren.

Wie auch schon bei früheren Arbeiten von Wenkert,[145] Dankwardt[146] und Tobisu[147] zur selektiven Aktivierung von Arylmethylethern zeigen 1– und 2–Naphtholderivate eine besonders hohe Aktivität. Diese könnte darin begründet sein, dass die C–O Aktivierung über ein dearomatisiertes Intermediat, etwa einen η^2–Komplex oder einen Meisenheimer–analogen Komplex, verläuft.[147] In beiden Fällen ist die Aktivierung der Naphthalinderivate gegenüber Benzolderivaten begünstigt, da die Aromatizität des Substrats teilweise erhalten bleibt.

Kurz nach Veröffentlichung dieser Arbeiten folgten auch die ersten mechanistischen Untersuchungen durch Liu *et al*.[148] Diese zeigen, dass die oxidative Addition einer Nickel(0)–Spezies in die C(Acyl)–O Bindung viel leichter erfolgt als in die C(Aryl)–O Bindung. Berechnungen deuten aber darauf hin, dass die Barriere der Rückreaktion energetisch sehr niedrig ist und der erhaltene Acyl–Nickel–Komplex nur schlecht mit der Boronsäure transmetalliert (Schema 30). Im Gegensatz dazu ist die C(Aryl)–O Aktivierung irreversibel, da die Rückreaktion energetisch nicht möglich ist. Zudem erfolgt die Transmetallierung des Aryl–Nickel(II)carboxylats mit den Boronsäuren leichter, wodurch die Reaktion schließlich zu den gewünschten Biarylen führt.



Schema 30: Selektivität der Nickel–katalysierten C–O Aktivierung von Arylcarboxylaten.

3. Aufgabenstellung

Die Zielsetzung dieser Arbeit bestand in der Entwicklung neuer, katalytischer Transformationen zur nachhaltigen, regioselektiven C–C Bindungsknüpfung. Als Substrate sollten ubiquitäre Carbonsäureester dienen, die durch einfache Veresterungsprozesse verfügbar sind. Für diese Verbindungen sollten geeignete Katalysatorsysteme zur selektiven C–O Bindungsaktivierung, Decarboxylierung und anschließenden effizienten C–C Bindungsknüpfung entwickelt werden, sodass lediglich CO_2 als flüchtiges Nebenprodukt freigesetzt wird. Das Reaktionskonzept selbst konnte bereits erfolgreich an besonders aktivierten β–Ketocarbonsäureallylestern demonstriert werden,[37] bei denen ein Palladium(0)–Katalysator sehr rasch in die C(Allyl)–O Bindung insertiert, die aktivierten β–Ketocarboxylate decarboxyliert und schließlich die C–C Bindungsknüpfung ermöglicht.

Aufbauend auf meiner Diplomarbeit sollte zunächst die decarboxylierende Allylierung von α–Ketocarbonsäureallylestern weiter untersucht und die Anwendungsbreite der Reaktion bestimmt werden. Anschließend sollte geprüft werden, ob diese decarboxylierende Funktionalisierung auch auf andere nicht aktivierte Substrate, etwa Oxalsäureester oder Benzoesäureester, übertragen werden kann. Dabei sollten neben Allylierungsreaktionen auch Benzylierungen untersucht werden.

Die Kombination aus selektiver C(Aryl)–O Aktivierung und Decarboxylierung leicht verfügbarer Benzoesäurearylester könnte weiterhin zur regioselektiven Biarylsynthese und damit zur atomökonomischen und salzfreien Alternative zu traditionellen, abfallintensiven Kreuzkupplungsreaktionen führen. Da solche C(Aryl)–O Bindungen bisher nur mit speziellen Nickel(0)–Katalysatoren aktiviert und funktionalisiert werden konnten, sollte die Reaktivität dieser Nickel–Verbindungen nun auch in decarboxylierenden Kupplungen evaluiert werden.

Im Erfolgsfall sollte jeweils auch untersucht werden, ob die Reakionen direkt ausgehend von Alkoholen und den freien Carbonsäuren erfolgen können. Eine vorgelagerte, reversible Veresterung sollte die Ester *in situ* zumindest in geringen Mengen bilden und durch die selektive Palladium– oder Nickelinsertion zum Metallcarboxylat führen, welches irreversibel decarboxyliert und zum Produkt gekuppelt wird.

In einem weiteren Teilprojekt sollten neue Syntheseverfahren trifluormethylierter Verbindungen entwickelt werden. Basierend auf den Ergebnissen der Nickel–katalysierten

Decarboxylierung sollte eine decarboxylierende Kupplung von Trifluoracetaten mit Arylelektrophilen entwickelt werden. Unabhängig davon sollte aufbauend auf der Kupfer–katalysierten Trifluormethylierung von Aryliodiden auch weiterhin ein Sandmeyer–analoges System zur Funktionalisierung von Aryldiazoniumsalzen realisiert werden. Diese beiden Verfahren haben nicht nur präparative Vorteile gegenüber etablierten Transformationen, sondern ermöglichen darüber hinaus auch einen neuen synthetischen Zugang zu pharmakologisch relevanten Verbindungen.

Weiterhin kam es im Laufe der Arbeit zu einer Kooperation mit Umicore, die an neuen, effizienten Kreuzkupplungskatalysatoren interessiert sind. Daraus entstand ein gemeinsames Projekt, dessen Ziel die Entwicklung eines Katalysators zur hochselektiven Monoarylierung primärer Amine war. Im Hinblick auf eine technische Nutzung zur Synthese von OLED–Materialien sollten dabei äquimolare Substratmengen in einer konzentrierten Reaktionslösung umgesetzt werden. Ausgehend vom etablierten Syntheseverfahren solcher Verbindungen sollte nicht nur die benötigte Katalysatormenge stark reduziert, sondern auch die als Nebenreaktion stattfindende doppelte Arylierung komplett unterdrückt werden. Abschließend sollte die Anwendungsbreite der Reaktion anhand representativer Verbindungen bestimmt werden.

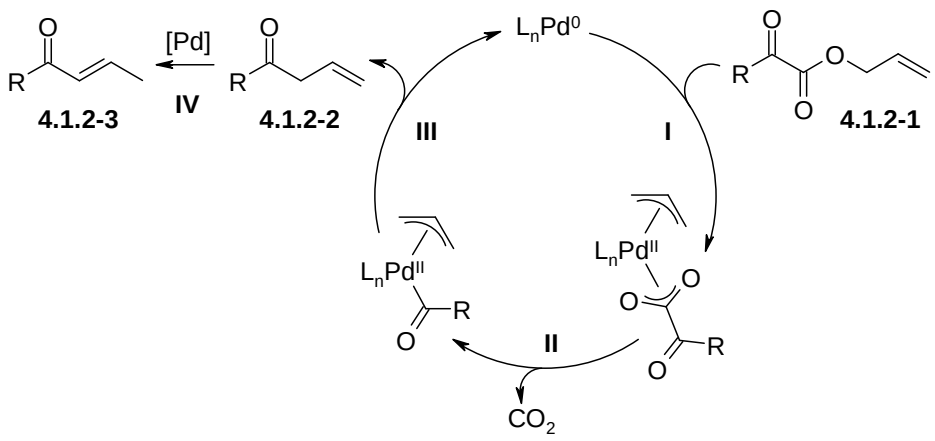
4. Ergebnisse und Diskussion

4.1. Nachhaltige Transformationen von Carbonsäuren und ihren Derivaten

4.1.1. Hintergrund

Im Rahmen meiner Diplomarbeit erfolgten bereits erste Untersuchungen, ob Palladium–katalysierte decarboxylierende Allylierungsreaktionen lediglich auf Allyl–β–ketoester und β–keto–ähnliche Systeme beschränkt sind, oder ob das Konzept auch auf andere, nicht aktivierte Substrate übertagen werden kann. Unser Interesse richtete sich dabei zunächst auf die Umsetzung von α–Ketosäuren, die decarboxylierend in hochreaktive Acylanionen überführt und mit Kohlenstoffelektrophilen gekuppelt werden können.[28] Dieses Reaktionskonzept stellt eine Alternative zu klassischen Umpolungsreaktionen dar, bei denen eine Carbonylfunktion in ein Cyanhydrin, Acetal, Thioacetal oder Hydrazon überführt werden muss.[127–130] Durch die decarboxylierende Generierung der Acylanionen entfallen solche Schutzgruppen und die damit verbundenen zusätzlichen Derivatisierungs– und Hydrolyseschritte.

Während Palladium(0)–Katalysatoren bereits bei milden Temperaturen in C(Allyl)–O Bindungen insertieren und β–Ketosäuren decarboxylieren können,[37] verläuft die Kupfer–katalysierte Decarboxylierung von Phenylglyoxylaten allerdings nur bei sehr hohen Temperaturen.[28] Anhand der Umsetzung präformierter Allylester sollte nun ein effizientes, monometallisches Palladium–Katalysatorsystem zur decarboxylierenden Allylierung von Phenylglyoxylaten entwickelt werden.



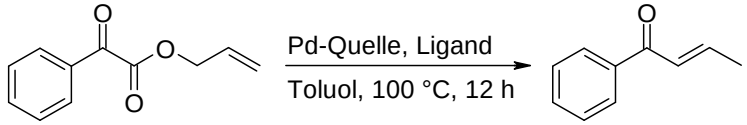
Schema 31: Mechanismus der decarboxylierenden Allylierung von Phenylglyoxylaten.

Bei einer solchen Reaktion sollte der Palladium(0)–Katalysator zunächst in die C(Allyl)–O Bindung des Allylesters insertieren und damit ein π–Allyl–Palladium(II)carboxylat bilden (Schema 31, **I**). Die Decarboxylierung führt zur Acyl–Palladium(II)–Spezies (**II**), die das β,γ–ungesättigte Keton reduktiv eliminiert und den Palladium(0)–Katalysator regeneriert (**III**). Unter den gegebenen Reaktionsbedingungen sollte die isolierte Doppelbindung rasch in die konjugierte Position isomerisieren, wodurch es zur Bildung des entsprechenden Vinylketons kommt (**IV**). Als einziges Nebenprodukt der Reaktion wird lediglich CO_2 freigesetzt.

4.1.2. Decarboxylierende Allylierung präformierter Phenylglyoxylsäureester

Zur Entwicklung eines effizienten Katalysatorsystems wurde der Allylester der Phenylglyoxylsäure als Modellsubstrat gewählt. Die Reaktivität dieser Verbindung wurde unter den typischen Reaktionsbedingungen zur decarboxylierenden Allylierung von Allyl–β–ketoestern näher untersucht. Dabei zeigte sich, dass der in Toluol gelöste Ester nach 12 h bei 100 °C und in Gegenwart von 2.5 mol% $Pd_2(dba)_3$ und 10 mol% PPh_3 in 14% Ausbeute zum α,β–ungesättigten Keton umgesetzt werden konnte (Tabelle 1, Eintrag 2).

Tabelle 1: Ligandeneinfluss auf die Palladium–katalysierte decaboxylierende Allylierung.



4.1.2-1aa **4.1.2-3aa**

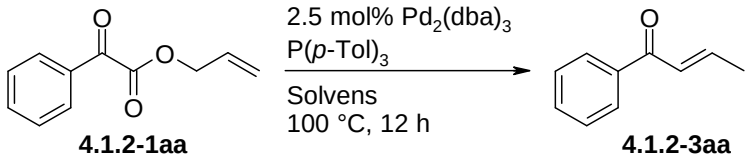
Eintrag	Pd–Quelle	Ligand	4.1.2–1aa [%]	4.1.2–3aa [%]
1	$Pd_2(dba)_3$	–	quant.	–
2	"	PPh_3	68	14
3	"	P(*p*–Tol)$_3$	56	21
4	"	P(*p*–CF_3–Ph)$_3$	79	7
5	"	P(*o*–Tol)$_3$	98	2
6	"	dppm	94	–
7	"	dppp	39	1
8	"	XantPhos	75	2
9	$Pd(P^tBu_3)_2$	–	73	4

Reaktionsbedingungen: 0.50 mmol Allylester, 5 mol% Palladium, 10 mol% eines monodentaten Liganden bzw. 5 mol% eines bidentaten Liganden, 2 mL Toluol, 100 °C, 12 h. Ausbeuten wurden gaschromatographisch mit *n*–Dodecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

Es folgte die rationale Katalysatoroptimierung, bei der zunächst die Effekte elektronisch und sterisch unterschiedlicher Phosphanliganden untersucht wurden. Dabei führte das elektronenreichere, monodentate P(*p*–Tol)$_3$ zu deutlich höheren Produktausbeuten (Tabelle 1, Eintrag 3), während elektronenärmere Liganden nur einen geringeren Umsatz ermöglichen (Eintrag 4). Weiterhin erfolgt die Produktbildung mit sterisch anspruchsvollen oder bidentaten Liganden nur in sehr geringen Ausbeuten (Einträge 5–9).

Lösungsmittel, die in decarboxylierenden Biarylsynthesen meist sehr hohe Umsätze ermöglichen, zeigten bei dieser Reaktion keinen besonderen Effekt und führten eher zu schlechteren Ausbeuten (Tabelle 2, Einträge 2 & 3). Erhöht man die Menge des Phosphanliganden auf 25 mol%, steigt die Produktausbeute auf 63% an (Eintrag 6). Die Verdünnung des Reaktionsgemischs ermöglichte schließlich eine quantitative Umsetzung des Startmaterials (Eintrag 8).

Tabelle 2: Optimierung der decarboxylierenden Allylierungsreaktion.



4.1.2-1aa **4.1.2-3aa**

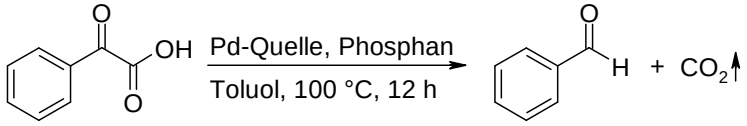
Eintrag	Solvens	Ligandenmenge	Solvensmenge	4.1.2–1aa [%]	4.1.2–3aa [%]
1	Toluol	10 mol%	2 mL	61	11
2	NMP	"	"	71	11
3	DMF	"	"	96	2
4	Toluol	15 mol%	"	40	29
5	"	20 mol%	"	2	49
6	"	25 mol%	"	5	63
7	"	"	3 mL	–	78
8	"	"	4 mL	–	quant.

Reaktionsbedingungen: 0.50 mmol Allylester, 5 mol% Palladium, P(*p*–Tol)$_3$, Solvens, 100 °C, 12 h. Ausbeuten wurden gaschromatographisch mit *n*–Dodecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

Um die besondere Rolle des Phosphans näher zu untersuchen und um zu klären, ob es sich, wie bei der enzymatischen Pyruvatdecarboxylierung, um eine organokatalytische Reaktion handelt (vgl. Schema 5, S. 9), folgten Protodecarboxylierungsstudien der freien

Phenylglyoxylsäure (Tabelle 3). Diese bestätigten, dass die Decarboxylierung keineswegs durch das Palladium erfolgt, sondern allein vom Phosphan katalysiert wird (Eintrag 4).

Tabelle 3: Protodecarboxylierung der Phenylglyoxylsäure.



4.1.2-4a **4.1.2-5a**

Eintrag	Pd–Quelle	Phosphan	4.1.2–5a [%]
1	$Pd(OAc)_2$	–	–
2	$Pd_2(dba)_3$	–	–
3	"	P(*p*–Tol)$_3$	26
4	–	"	56

Reaktionsbedingungen: 0.50 mmol Phenylglyoxylsäure, 5 mol% Palladium, 25 mol% P(*p*–Tol)$_3$, Toluol, 100 °C, 12 h. Ausbeuten wurden gaschromatographisch mit *n*–Dodecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

Alle Optimierungsarbeiten zur decarboxylierenden Allylierung präformierter Allylester, sowie die Untersuchungen zur Anwendungsbreite und zum Reaktionsmechanismus sind in der nachfolgenden Publikation aufgeführt. Die Entwicklung des Katalysatorsystems führte ich zum Großteil eigenständig im Rahmen meiner Diplomarbeit durch und erfolgte erst gegen Ende unter Aufsicht von Dr. Nuria Rodríguez Garrido. Diese Ergebnisse wurden bereits in meiner Diplomarbeit niedergeschrieben. Während meines Industriepraktikums bei Novartis Pharma in Basel erfolgten durch Herrn Dr. Costa mechanistische Untersuchungen zur Protodecarboxylierung und auch die ersten Reaktionen von Kaliumcarboxylaten mit Allylhalogeniden. Die „cross–over"–Experimente wurden schließlich wieder von mir durchgeführt. Die Isolierung der synthetisierten *α,β*–ungesättigten Ketone erfolgte zu gleichen Teilen durch die Arbeit von Herrn Dr. Costa und mir.

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Synthesis of α,β-Unsaturated Ketones by Pd-Catalyzed Decarboxylative Allylation of α-Oxocarboxylates

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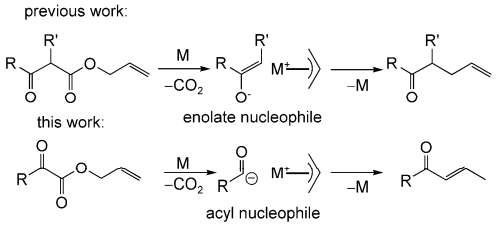
Within recent years, the field of decarboxylative allylation reactions has undergone tremendous development, with innovative contributions that have attracted considerable attention within the chemical community.[1] The foundations for this area were laid by Carroll in 1940 with his report that allyl β-oxocarboxylates extrude carbon dioxide to give γ,δ-unsaturated alkyl ketones when heated in the presence of a base.[2] In the 1980s, palladium-catalyzed versions of this transformation that proceed under neutral conditions were discovered by Saegusa[3] and Tsuji (Scheme 1, top).[4] This



Scheme 1. Decarboxylative allylation of carbon nucleophiles.

concept was decisively advanced by Tunge[5] and Stoltz.[6] For example, Tunge et al. reported an asymmetric decarboxylative allylation of ketone enolates.[5] Stoltz et al. utilized decarboxylative allylations as the key step in enantioselective syntheses of complex target molecules such as (−)-cyanthiwigin F, (+)-carissone and (+)-cassiol. In all these cases, the carbon nucleophiles generated in the decarboxylation step of the allylation process are highly stabilized carbanions,[3] that is, enolates, benzyl, α-iminoyl,[7] α-cyano-,[3] α-sulfonyl-,[8] nitronate-,[9] or nitrotolyl-anions.[5d]

Another major step in the development of this reaction class would undoubtedly be its extension to carboxylates for which the decarboxylation step would lead to non-stabilized or even destabilized carbon nucleophiles. Examples of the latter are acyl anions, generated by extrusion of carbon dioxide from α-oxocarboxylates. The proverbial instability of these species normally precludes their use in organic synthesis. Instead, synthetic equivalents to acyl anions usually have to be generated within multistep procedures, for example, through umpolung of aldehydes by reaction with dithiols and subsequent deprotonation with strong bases.[10]

α-Oxocarboxylic acid are attractive sources of acyl anions as they are stable and easy to access.[11] Some derivatives serve as intermediates in the synthesis of α-amino acids and are commercially available. Others are accessible by double carbonylations of aryl halides with CO using Pd,[12] Co,[13] or Cu catalysts,[14] by Friedel–Crafts acylations with oxalyl chlorides,[15] additions of arylmetal reagents to oxalates,[16] or oxidations of acetophenones.[17]

We herein report the Pd/phosphine-catalyzed decarboxylative allylation of allyl α-oxocarboxylates as the first example of a decarboxylative allylation involving destabilized carbon nucleophiles (see Scheme 1, bottom). This reaction provides an expedient synthetic entry to α,β-unsaturated ketones as privileged structures in biologically active natural products.[18] Such compounds are traditionally synthesized, for example, by using aldol condensations, Meyer–Schuster rearrangement of propargylic alcohols,[19] or the hydroacylation of alkynes.[20]

In the course of our work on redox-neutral decarboxylative cross-couplings of aryl and vinyl halides with bimetallic catalysts,[21] we successively extended the substrate scope from heterocyclic and *ortho*-substituted benzoic acids[22] to nonactivated aromatic carboxylic acids[23] and finally to α-imino-[24] and α-oxocarboxylic acids.[25] α-Oxocarboxylate salts proved to be particularly unreactive, extruding CO_2 only at 170 °C within the coordination sphere of special copper catalysts. Oxidative decarboxylative couplings of α-oxocarboxylatic acids proceed at lower temperatures, but these reactions involve stable electrophilic rather than labile nucleophilic acyl intermediates.[26]

As can be seen in Scheme 2, the targeted decarboxylative allylation would have to proceed through a different mechanism than bimetallic decarboxylative cross-coupling reactions.[1] Coordination and subsequent oxidative addition of the substrate to a Pd^0 precursor (**A**) lead to the formation of covalent or ionic π-allyl-Pd-carboxylate complexes (**B**). Our initial plan was to tune the ligand environment of palladium complex **A** in a way that the next step, an extrusion of CO_2 with formation of the acyl π-allyl-Pd complex **C**, would become possible. Reductive elimination would then give the allyl ketone **2**, which can be expected to rapidly isomerize

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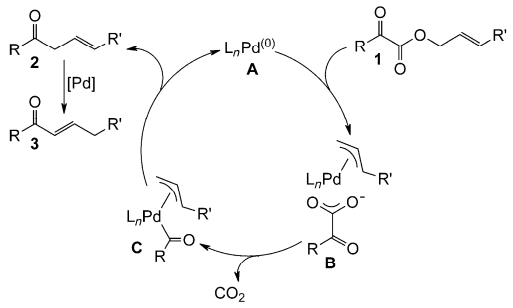
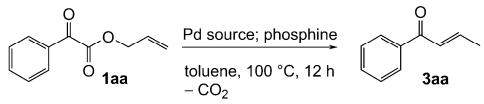


Scheme 2. Postulated mechanism for the synthesis of α,β-unsaturated ketones through decarboxylative coupling.

to the conjugated vinyl ketone **3** in the presence of palladium.[27]

The carboxylates that so far had been employed in decarboxylative allylations lose CO_2 under very mild conditions even in the absence of a catalyst.[1] In contrast, the redox-neutral decarboxylation of α-oxocarboxylates requires much higher temperatures.[22] We were thus surprised to detect 15% of crotonophenone (**3aa**) when heating our model substrate allyl 2-oxophenylacetate (**1aa**) in the presence of Pd(PPh_3)$_4$ (5 mol%) in toluene to only 100°C (Table 1, entry 1). Among the side products were benzoic acid and polyenes resulting from oligomerization reactions of the allyl residue.

Table 1. Development of the catalytic system.[a]

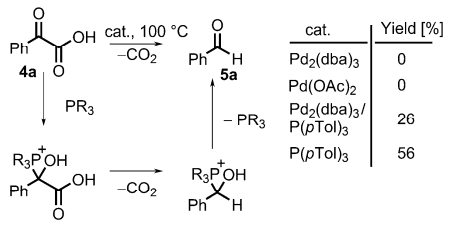


Entry	Pd Source	Phosphine	Yield [%]
1	$Pd(PPh_3)_4$	–	15
2	$Pd_2(dba)_3$	PPh_3	29
3	$Pd_2(dba)_3$	P(*p*Tol)$_3$	37
4	$Pd_2(dba)_3$	BINAP	0
5	$Pd_2(dba)_3$	PCy_3	0
6[b]	$Pd_2(dba)_3$	P(*p*Tol)$_3$	59
7[c]	$Pd_2(dba)_3$	P(*p*Tol)$_3$	79

[a] Reaction conditions: allyl-2-oxo-phenylacetate (**1aa**; 0.50 mmol), palladium (5 mol%), phosphine (15 mol%; 7.5 mol% for bidentate phosphines), toluene (4.0 mL), 12 h. Yields were determined by GC analysis using *n*-dodecane as the internal standard; [b] P(*p*Tol)$_3$; [c] P(*p*Tol)$_3$ (25 mol%). BINAP = (2,2'-bis(diphenylphosphino)-1,1'–binaphthyl.

We systematically screened various catalysts generated in situ from palladium precursors and phosphines (Table 1).[28] The choice of the phosphine ligand had a particularly strong impact on the reaction outcome. The highest yields were obtained with a catalyst generated from tri-*p*-tolylphosphine (P(*p*Tol)$_3$) and tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3) (entry 3). Bidentate (entry 4) and sterically more demanding phosphines such as tricyclohexylphosphine (entry 5) were almost ineffective. The decisive step towards higher yields was to add the phosphine ligand in excess (entries 6–7). When heating the allyl ester **1aa** in the presence of Pd_2dba_3 (2.5 mol%) and P(*p*Tol)$_3$ (25 mol%) to 100°C for 12 h, the product **3aa** was isolated in almost quantitative yields. Control experiments showed no conversion when leaving out either the palladium or the phosphine.

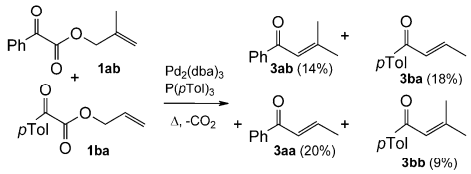
It did not appear plausible that simple Pd catalysts could promote the decarboxylation of α-oxocarboxylic acids at such low temperatures, as only particularly activated carboxylic acids decarboxylate at Pd catalysts.[29] Moreover, these results are in sharp contrast to findings for Pd-catalyzed cross-couplings in which such high phosphine-to-palladium ratios would be disadvantageous.[30] To obtain a better understanding of the decarboxylation step, we heated a toluene solution of phenylglyoxylic acid (**4a**) with various catalysts (Scheme 3). Neither palladium(II) salts nor phosphine-free Pd^0 complexes catalyzed the protodecarboxylation of **4a**.



Scheme 3. Protodecarboxylation of α-oxocarboxylic acids.

In the presence of Pd_2dba_3 and P(*p*Tol)$_3$, benzaldehyde was formed in moderate yields. The most effective decarboxylation catalyst, however, was tri-*p*-tolylphosphine alone. This confirms that the phosphine has a dual function in the decarboxylative allylation: It acts as an organocatalyst for the decarboxylation step, and also stabilizes the palladium cross-coupling catalyst.[31] An organocatalytic decarboxylation step is plausible in the light of the enzymatic pyruvate decarboxylation mechanism, which also involves the temporary addition of a nucleophilic group to the carbonyl carbon.[32] An analogous mechanism for the phosphine-catalyzed decarboxylation is outlined in Scheme 3.

We also performed a cross-over experiment in which a mesitylene solution of two different allyl α-oxocarboxylates was heated to 150°C in the presence of the optimized catalyst system (Scheme 4).[28] A higher reaction temperature was employed to ensure full conversion even of the less re-



Scheme 4. Decarboxylative allylation cross-over studies.

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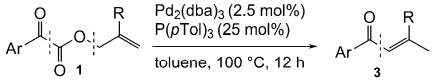
active, branched allyl ester **1ab**. The fact that all possible products were formed in comparable quantities shows that after the oxidative addition step, the carboxylate ions can dissociate and exchange with other salts, even in the nonpolar solvent toluene.[33] A control experiment performed in the absence of catalyst did not show any transesterification, confirming that the exchange takes place after oxidative addition. It remains unclear whether the phosphine-mediated decarboxylation in decarboxylative allylations proceeds within or outside the coordination sphere of the palladium.

The scope of the new reaction is illustrated by the examples in Table 2. Many α-oxocarboxylic acid derivatives were converted into the corresponding α,β-unsaturated ketones in high yields. Substrates with electron-withdrawing substituents reacted particularly well, but **3ba** and **3la**, which represent moderately electron-rich α-oxocarboxylates, also gave reasonable yields. Various functional groups were tolerated, and some heterocyclic derivatives could also be converted. The reaction also gave a high yield when conducted on gram-scale for compound **3aa**. If the allyl group bears an additional substituent in the 2-position, the reaction still works, albeit at a higher temperature (**3ab**). However, this prototype system gives unsatisfactory yields with allyl esters substituted in the 3-position.

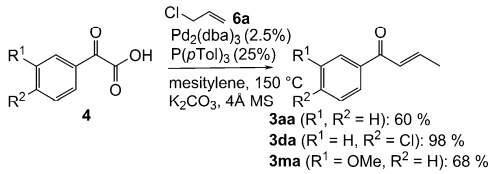
Table 2. Decarboxylative synthesis of α,β-unsaturated ketones.[a]



Product	Yield [%]	Product	Yield [%]
3aa	99	**3ca**	94
3da (Cl)	98	**3ea** (NC)	97
3ba	62	**3fa** (F_3C)	78
3ga (Ph)	99	**3ha**	66
3ia (F)	82	**3ja** (CF_3)	97
3ka	88	**3la**	77
3ab	92[b]	**3ac** (Ph)	20[c]
3ad	traces	**3ae** (Ph)	traces

[a] Reaction conditions: allyl α-oxocarboxylate (**1**; 1.00 mmol), $Pd_2(dba)_3$ (2.5 mol%), P(*p*Tol)$_3$ (5 mol%), toluene (8.0 mL), 12 h, 100°C, isolated product yields. [b] in mesitylene at 150°C. [c] Yield was determined by GC analysis using *n*-dodecane as the internal standard.

Analogous decarboxylative allylations can also be performed starting from α-oxocarboxylic acids, allyl chlorides and potassium carbonate as the base (Scheme 5). In situ spectroscopic studies confirmed that under the conditions of this reaction variant, allyl esters are rapidly formed and



Scheme 5. Decarboxylative coupling of α-oxocarboxylic acids with allyl halides.

then slowly decarboxylate.[28] Further experiments revealed that the carbonate base required in this reaction variant retards the decarboxylation of the allyl α-oxocarboxylates, which is why higher temperatures are required. Presumably, the α-oxocarboxylate has to compete with the carbonate anion for a coordination site at the palladium.

Ongoing work is directed towards combining the phosphine-catalyzed decarboxylation of α-oxocarboxylates with other synthetic transformations that require acyl anion equivalents. Ultimately, this strategy may become a general alternative to established syntheses involving the umpolung of aldehydes.

Experimental Section

Standard procedure for the synthesis of α,β-unsaturated ketones: A 20 mL crimp cap vessel was charged with tris(dibenzylideneacetone)dipalladium(0) (5.72 mg, 0.006 mmol) and tri-*p*-tolylphosphine (19.4 mg, 0.062 mmol). After the vessel was flushed with alternating vacuum and nitrogen purge cycles, a solution of **1** in toluene (4 mL) was added through a syringe. The reaction mixture was stirred at 100°C for 12 h and then cooled to room temperature. The solvent was removed by Kugelrohr distillation (6×10^{-2} mbar) at 30–35°C. The residue was further purified by flash chromatography (SiO_2, ethyl acetate/hexane (1:10)), yielding the corresponding products **3** in 62–99%.

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Keywords: allylation · decarboxylation · ketones · organocatalysis · palladium

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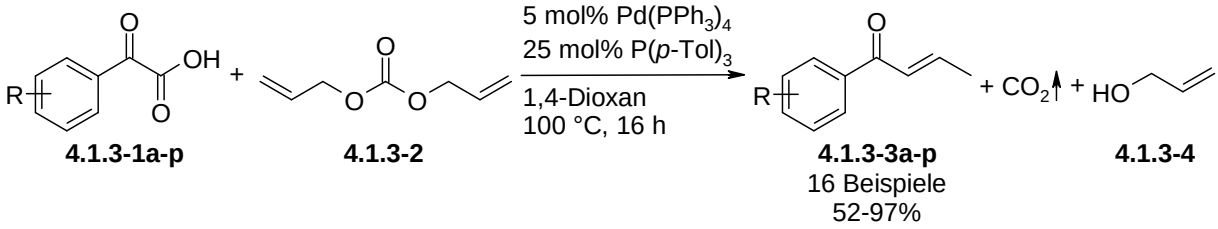
4.1.3. Decarboxylierende Allylierung mit Diallylcarbonat

Ein verbleibender Nachteil des Allylierungsprotokolls ist, dass die Präformierung der Allylester in einem zusätzlichen Reaktionsschritt stattfindet und bei einigen Arylglyoxylsäuren zudem Kupplungsreagenzien benötigt werden. Aus diesem Grund erfolgten weitere Arbeiten an einer intermolekularen Reaktionsvariante. Erste Reaktionen zeigten, dass die Ester in Gegenwart von Kaliumcarbonat auch *in situ* aus der Phenylglyoxylsäure und Allylhalogeniden erzeugt und dann weiter umgesetzt werden können. Da der Decarboxylierungsschritt allerdings durch die Anwesenheit des Kaliumcarbonats behindert wird, musste die Reaktionstemperatur auf 150 °C erhöht werden. Um dies und die Bildung anorganischer Salze zu umgehen, kamen im Zuge dieser Untersuchungen auch andere, einfache Allylester als Kohlenstoffelektrophile zum Einsatz.

Mechanistisch sollte der Palladium(0)–Katalysator bei einer solchen intermolekularen Reaktion zunächst in die C(Allyl)–O Bindung der Allylquelle insertieren und das Carboxylat in einem Metatheseschritt gegen das Arylglyoxylat austauschen. Die anschließenden Reaktionsschritte sollten danach analog zur Umsetzung präformierter Allylglyoxylate ablaufen. Während der Einsatz von Allylacetat neben dem α,β–ungesättigten Keton auch stets zur Protodecarboxylierung führte, ermöglichte das Diallylcarbonat eine selektive Produktbildung. Mit dem Wechsel von Toluol zu 1,4–Dioxan konnten so nahezu quantitative Produktausbeuten erzielt werden.



Schema 32: Decarboxylierende Allylierung mit Diallylcarbonat.

Alle Optimierungsarbeiten und die Untersuchungen zur Anwendungsbreite sind in der nachfolgenden Publikation aufgeführt. Diese Arbeit basiert auf Erkenntnissen, die unter Aufsicht von Dr. Nuria Rodríguez Garrido und in Zusammenarbeit mit Dr. Filipe Costa gewonnen wurden. Die Entwicklung der Kupplung freier Carbonsäuren mit Allylhalogeniden und Allylcarbonaten erfolgte in Zusammenarbeit mit Herrn Dr. Costa. Die

Katalysatoroptimierung und die Isolierung der Produkte erfolgten durch Herrn Dr. Costa alleine. Das Manuskript und die Supporting Information verfassten wir gemeinsam.

Die hier gezeigten Resultate wurden 2012 im European Journal of Organic Chemistry, 4680–4683 veröffentlicht. Die Publikation wurde für dieses Manuskript angepasst und mit Erlaubnis der John Wiley & Sons, Inc. beigefügt.

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Decarboxylative Allylation of Glyoxylic Acids with Diallyl Carbonate

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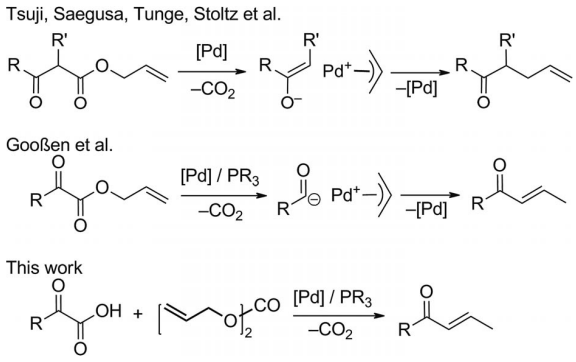
Keywords: Allylation / C–C bond formation / Decarboxylation / Palladium / Organocatalysis

A catalyst system consisting of $Pd(PPh_3)_4$ and $P(pTol)_3$ was found to effectively promote the intermolecular decarboxylative coupling of α-oxocarboxylic acids with diallyl carbonate to give α,β-unsaturated ketones. The key advantage of the new reaction protocol is that preformation of the allyl esters is not required. The reaction is believed to proceed via phosphane-mediated decarboxylation of the α-oxocarboxylates, leading to acyl anion equivalents that are allylated within the coordination sphere of the palladium catalyst. Under the reaction conditions, the double bond then migrates into conjugation with the carbonyl group.

Introduction

Carbon–carbon bond-forming reactions belong to the most fundamental transformations in organic synthesis, and new concepts for regiospecific couplings are constantly sought. In this context, decarboxylative couplings have recently emerged as valuable alternatives to cross-couplings of organometallic reagents.[1,2] Among them, decarboxylative allylations of allyl β-ketocarboxylate derivatives to give γ,δ-unsaturated ketones have received particular attention.[3] This catalytic version of the Carroll rearrangement[4] was first described by Tsuji[5] and Saegusa[6] and has further been developed by Tunge[7] and Stoltz.[8] However, the scope of such waste-minimized C–C bond-forming reactions extends only to allyl esters of carboxylic acids that – upon extrusion of carbon dioxide – form highly stable carbanions, for example, enolate, benzyl,[9] α-cyano,[6] or nitronate anions.[10] All described methods start from preformed allyl esters (Scheme 1).

We have recently shown that decarboxylative allylations can also be performed with carboxylates for which the extrusion of CO_2 leads to non-stabilized carbon nucleophiles.[11] In the presence of a bifunctional catalyst consisting of a palladium complex and an excess amount of $P(pTol)_3$, allyl α-oxocarboxylates were converted into α,β-unsaturated ketones via a decarboxylative allylation/double-bond migration cascade. In this protocol, the decarboxylation step is promoted by the phosphane as an organocatalyst, whereas the C–C bond formation takes place



Scheme 1. Approaches to generate acyl anions via decarboxylation.

inside the coordination sphere of the palladium. This reaction is of considerable interest because it is a rare example of a C–C bond-forming reaction involving unstable acyl anions as carbon nucleophiles.[12] It constitutes an alternative to traditional syntheses of α,β-unsaturated compounds, such as aldol condensations, Wittig or Horner–Wadsworth–Emmons olefinations,[13] or the Meyer–Schuster rearrangement of propargylic alcohols.[14] However, from a practical standpoint, the prototype protocol was limited by the rather troublesome synthesis of the allyl esters. High yields were achieved only when using expensive coupling reagents. Attempts to generate the esters in situ from α-oxocarboxylate salts and allyl halides led to the formation of large quantities of halide salts that inhibited the reaction, so that the temperature had to be increased to 150 °C.[11]

We herein describe how this limitation was overcome by employing diallyl carbonate as the allyl source in an intermolecular decarboxylative coupling with α-oxocarboxylic acids.

According to the proposed mechanism (Scheme 2), a key intermediate in decarboxylative allylations is believed to be allylpalladium(II) α-oxocarboxylate complex **C** formed by

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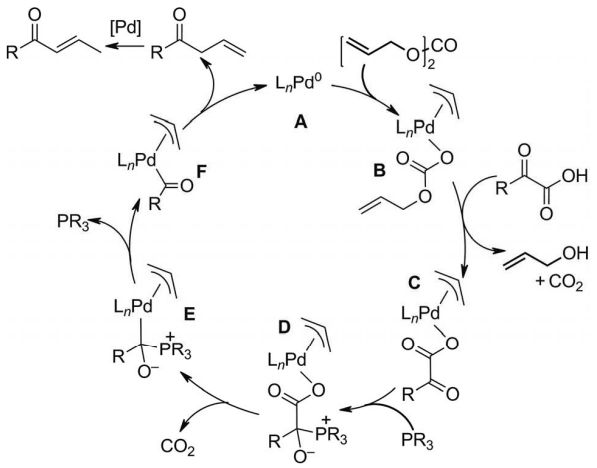
oxidative addition of the ester to palladium(0) species **A**. We reasoned that such species could also be generated by reaction of allylpalladium(II) allyl carbonate species **B** formed via the analogous oxidative addition of allyl carbonate to palladium(0) in the presence of an α-oxocarboxylic acid.[15] The release of CO_2 gas along with allyl alcohol would render this step irreversible. The decarboxylation of the α-oxocarboxylate, which was previously shown to be mediated by an excess amount of phosphane, should give rise to acylpalladium(II) allyl complex **E**. The allyl ketone would then be liberated via reductive elimination and isomerize into the α,β-unsaturated compound under the reaction conditions. Even without auxiliary base, competing protodecarboxylation should be comparatively slow, as the allyl alcohol should not be sufficiently acidic to promote protodeacylation of **E** with formation of the corresponding aldehyde and an allyl ether. If this mechanistic concept is viable, it should be possible to convert α-oxocarboxylic acids into α,β-unsaturated ketones by reaction with diallyl carbonate in the presence of a palladium/phosphane catalyst.



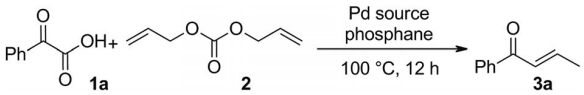
Scheme 2. Proposed decarboxylative allylation mechanism.

Results and Discussion

To search for an effective catalyst system, we chose the reaction of phenylglyoxylic acid with diallyl carbonate as a test system and began with the optimized conditions for the intramolecular decarboxylative allylation of allyl-2-oxoacetate. In the presence of a combination of $Pd_2(dba)_3$ and P(*p*Tol)$_3$ in toluene at 100 °C, the desired product was indeed formed, albeit in modest yields (Table 1, entry 1).

Systematic studies revealed that the solvent had a profound influence on the reaction outcome. Whereas non-polar solvents gave unsatisfactory yields (Table 1, entries 1 & 2), the use of moderately polar, coordinating solvents and 1,4-dioxane in particular, were substantially more effective (Table 1, entries 3–5). Strongly polar aprotic (Table 1, entries 6 & 7) or protic solvents (Table 1, entry 8) also led to low conversions. The beneficial effect of 1,4-dioxane may consist in assisting the coordination of carbon residues, as reported for Pd-enolates.[3,16]

Table 1. Development of the catalyst system.[a]



Entry	Catalyst	Phosphane	Solvent	Yield [%][b]
1	$Pd_2(dba)_3$	P(*p*Tol)$_3$	toluene	7
2	$Pd_2(dba)_3$	P(*p*Tol)$_3$	mesitylene	4
3	$Pd_2(dba)_3$	P(*p*Tol)$_3$	1,4-dioxane	77
4	$Pd_2(dba)_3$	P(*p*Tol)$_3$	diglyme	22
5	$Pd_2(dba)_3$	P(*p*Tol)$_3$	DMPU	39
6	$Pd_2(dba)_3$	P(*p*Tol)$_3$	DMF	13
7	$Pd_2(dba)_3$	P(*p*Tol)$_3$	DMSO	5
8	$Pd_2(dba)_3$	P(*p*Tol)$_3$	ethanol	0
9	$Pd(acac)_2$	P(*p*Tol)$_3$	1,4-dioxane	44
10	$Pd(OAc)_2$	P(*p*Tol)$_3$	1,4-dioxane	33
11	$[(cinnamyl)PdCl]_2$	P(*p*Tol)$_3$	1,4-dioxane	17
12	$Pd(PPh_3)_4$	P(*p*Tol)$_3$	1,4-dioxane	97
13	$Pd(PPh_3)_4$	PPh_3	1,4-dioxane	63
14	$Pd(PPh_3)_4$	P(*p*-F-C_6H_4)$_3$	1,4-dioxane	33
15	$Pd(PPh_3)_4$	PCy_3	1,4-dioxane	42
16	$Pd(PPh_3)_4$	BINAP	1,4-dioxane	29
17[c]	$Pd(PPh_3)_4$	P(*p*Tol)$_3$	1,4-dioxane	95
18[d]	$Pd(PPh_3)_4$	P(*p*Tol)$_3$	1,4-dioxane	89
19	$Pd(PPh_3)_4$	–	1,4-dioxane	36
20	$Pd_2(dba)_3$	–	1,4-dioxane	0
21	–	P(*p*Tol)$_3$	1,4-dioxane	0

[a] Reaction conditions: phenylglyoxylic acid (**1**, 1.00 mmol), diallyl carbonate (**2**, 1.00 mmol), catalyst (5 mol-%), phosphane (25 mol-%), solvent (8.0 mL), 12 h, 100 °C. [b] Yield determined by GC analysis using *n*-dodecane as an internal standard. [c] 4 h. [d] 80 °C.

A test of various palladium sources revealed that palladium(0) complexes displayed higher yields than palladium(II) salts. Almost quantitative conversion was reached with $Pd(PPh_3)_4$. This may in part be due to an increase in phosphane concentration, as the decarboxylation is mediated by the phosphane. The use of PPh_3 instead of P(*p*Tol)$_3$ led to lower yields (Table 1, entry 13). Further experiments with various phosphanes confirmed that P(*p*Tol)$_3$ is the optimal decarboxylation catalyst (Table 1, entry 12), whereas triaryl phosphanes with different electronic properties (Table 1, entry 14), trialkyl phosphanes (Table 1, entry 15), or bidentate phosphanes (Table 1, entry 16) gave inferior yields. Further studies revealed that almost full conversion could be reached within 4 h at 100 °C (Table 1, entry 17), and that the yields are only marginally lower at 80 °C (Table 1, entry 18). With $Pd(PPh_3)_4$, modest yields were achieved (Table 1, entry 19), presumably due to a partial dissociation of phosphanes from the complex. This was confirmed by a control experiment in which a phosphane-free palladium catalyst was used and no additional phosphane was added (Table 1, entry 20). Without palladium, no conversion was observed (Table 1, entry 21).

We next investigated the scope of the optimized intermolecular decarboxylative allylation protocol. The scope and limitations (Table 2) are very similar to those observed for reactions starting from preformed allyl esters.[11] Arylglyoxylic acids with common functionalities such as halides, cy-

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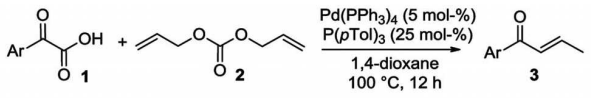
ano and methoxy groups, as well as heterocyclic derivatives were converted in good yields into the corresponding α,β-unsaturated ketones. Arylglyoxylic acids bearing electron-poor nitro substituents were converted in only 10% yield. The reason for this low yield could not yet be elucidated. As observed also for intramolecular reactions, the intermolecular version does not yet allow the conversion of alkylglyoxylic acids.

Table 2. Scope of the intermolecular decarboxylative allylation.[a]



Product	Yield [%]	Product	Yield [%]
3a	96	3b	79
3c	94	3d	97
3e	73	3f	71
3g	80	3h	57
3i	75[b]	3j	83
3k	85	3l	83
3m	71	3n	52[b]
3o	79	3p	83
3q	10[c]	3r	trace

[a] Reaction conditions: arylglyoxylic acid **1** (1.00 mmol), diallyl carbonate (**2**, 1.00 mmol), $Pd(PPh_3)_4$ (5 mol-%), P(*p*Tol)$_3$ (25 mol-%), 1,4-dioxane (8.0 mL), 12 h, 100 °C, isolated yields. [b] 35 mol-% P(*p*Tol)$_3$. [c] Yield determined by GC analysis using *n*-dodecane as an internal standard.

Conclusions

An intermolecular decarboxylative allylation of arylglyoxylic acids with diallyl carbonate has been developed as an expedient synthetic entry to α,β-unsaturated ketones. The new protocol is similarly effective as related couplings of allyl esters, but obviates the laborious synthesis and purification of these substrates. It is broadly applicable to arylglyoxylic acid bearing various functional groups. Present work is directed towards extending this decarboxylative allylation strategy to other carboxylic acid substrate classes.

Experimental Section

Standard Procedure for the Synthesis of α,β-Unsaturated Ketones from α-Oxocarboxylic Acids: A 20-mL crimp cap vessel was charged with tetrakis(triphenylphosphane)palladium(0) (57.6 mg, 0.05 mmol) and tri-*p*-tolylphosphane (77.6 mg, 0.25 mmol). A solution of the α-oxocarboxylic acid (1.00 mmol) in 1,4-dioxane (8 mL) and diallyl carbonate (**2**; 144 μL, 1.00 mmol) were added via syringe. The reaction mixture was stirred at 100 °C for 12 h and then cooled to room temperature. The solvent was removed in vacuo (40 °C, 107 mbar), and the remaining residue was further purified by flash chromatography (SiO_2; ethyl acetate/hexane, 1:10) to yield products **3a**–**p** (52–99%).

Synthesis of (*E*)-1-Phenylbut-2-en-1-one (3a): Compound **3a** [CAS: 495-41-0] was prepared following the standard procedure, starting from phenylglyoxylic acid (**1a**; 150 mg, 1.00 mmol). After purification, **3a** was isolated as a yellow oil (145 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (m, 2 H), 7.56 (m, 1 H), 7.45 (m, 2 H), 7.07 (m, 1 H), 6.93 (dq, J = 1.6 Hz, 1 H), 1.99 (dd, J = 6.8, 1.6 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 190.7, 144.9, 137.8, 132.5, 128.4 (4 C), 127.5, 18.5 ppm. $C_{10}H_{10}O$ (146.19): calcd. C 82.16, H 6.19; found C 82.19, H 6.22.

Supporting Information (see footnote on the first page of this article): Characterization data for all compounds, copies of the ^{1}H NMR and ^{13}C NMR spectra.

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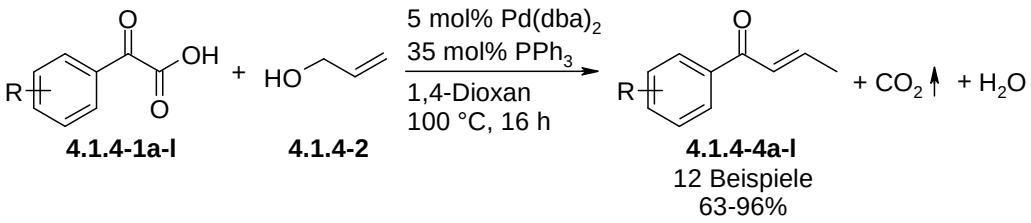
4.1.4. Decarboxylierende Allylierung mit Allylalkohol

In weiterführenden Studien sollte nun untersucht werden, ob der benötigte Arylglyoxylsäureallylester unter den gegebenen Reaktionsbedingungen auch direkt *in situ* durch eine reversible Veresterung der freien Arylglyoxylsäure mit Allylalkohol gebildet werden kann. Selbst geringe Mengen des Esters sollten oxidativ an den Palladium(0)–Katalysator addieren und das gewünschte Produkt nach dem irreversiblen Decarboxylierungsschritt freisetzen, sodass lediglich Wasser und CO_2 als Nebenprodukte gebildet werden.

Auf der Suche nach einem effektiven Katalysatorsystem wurden die Modellverbindungen Phenylglyoxylsäure und Allylalkohol mit $Pd(dba)_2$ und P(*p*–Tol)$_3$ in Toluol für 16 h auf 100 °C erhitzt. Unter diesen Bedingungen wurde allerdings nur die Protodecarboxylierung der Säure beobachtet. Es folgte ein umfangreiches Lösungsmittelscreening, bei dem nur 1,4–Dioxan eine Produktbildung ermöglichte. Weitere Reihenversuche zeigten, dass ein *in situ* aus 5 mol% $Pd(dba)_2$ und 35 mol% PPh_3 gebildetes Katalysatorsystem zu den besten Produktausbeuten führt (Schema 33).



Schema 33: Decarboxylierende Allylierung mit Allylalkohol.

Alle Resultate der Katalysatoroptimierung und die Untersuchungen zur Anwendungsbreite sind in der nachfolgenden Publikation aufgeführt. Diese wurde 2013 im Journal of Organometallic Chemistry, Vol. 744, 140–143 veröffentlicht, für dieses Manuskript angepasst und mit Erlaubnis von Elsevier beigefügt.

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Decarboxylative allylation of arylglyoxylic acids with allyl alcohol

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ABSTRACT

A decarboxylative allylation of arylglyoxylic acids with allyl alcohol has been developed. In the presence of catalytic amounts of $Pd(dba)_2$ and PPh_3, the substrates are in an esterification equilibrium with the allyl arylglyoxylates, which are continuously decarboxylated to give α,β-unsaturated ketones along with CO_2 and water as the only byproducts.

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1. Introduction

Within the last decade, decarboxylative cross-coupling reactions have evolved into effective tools for C–C and C–heteroatom bond formation [1,2]. This reaction concept compares favourably to traditional cross-coupling reactions in that it involves using easily available carboxylic acids as carbon nucleophiles in place of organometallic reagents. Decarboxylative allylations, in which allyl esters of activated carboxylic acids extrude CO_2, are particularly efficient [3]. Carroll was the first to describe the thermal rearrangement of allyl β-ketocarboxylates into the corresponding γ,δ-unsaturated ketones [4]. Tsuji [5] and Saegusa [6] disclosed a catalytic version of the Carroll reaction which proceeds under mild, neutral conditions. This concept was extended to various other substrates and led to synthetic maturity by Tunge [7], Stoltz [8] and others [9]. However, in all these cases, the substrates employed are esters of carboxylic acids that decarboxylate with the formation of highly stabilized carbanions such as enolate, benzyl [10], α-cyano [6], or nitronate species [9a] (Scheme 1).

The first example of a decarboxylative allylation of non-activated allyl carboxylates was the Pd/phosphine-catalyzed conversion of arylglyoxylic acid allyl esters to allyl ketones, which immediately isomerize to give the α,β-unsaturated ketones [11]. The decarboxylation of the arylglyoxylates leads to an intermediate formation of synthetic equivalents to unstable acyl anion equivalents and is promoted by tri(*p*-tolyl)phosphine. These are then allylated within the coordination sphere of the palladium.

We have also shown that the allyl ester substrates can be generated *in situ* from arylglyoxylic acids and diallyl carbonate [12]. Liu et al. have recently disclosed the decarboxylative allylation of silver benzoates with allyl halides in the presence of a complex palladium/copper catalyst system, which is another example of a catalytic allylation of non-activated carboxylic acids [13].

In continuation of our search for concepts for the activation of carboxylic acids for catalytic coupling reactions [14], we herein present the decarboxylative allylation of arylglyoxylic acids with allyl alcohol as a new, sustainable allylation method. In this intermolecular C–C-bond forming process, the allyl ester substrates are generated *in situ* via esterification, so that CO_2 and water are the only byproducts.

2. Results and discussion

A combination of an esterification process and a decarboxylative coupling of the resulting allyl ester should be possible following the mechanistic hypothesis outlined in Scheme 2. Upon mixing an arylglyoxylic acid **1** with allyl alcohol **2**, at least small quantities of the allyl ester should form in a reversible esterification. Once formed, the allyl esters should oxidatively add to the palladium(0) species **A** with formation of an allylpalladium(II) α-oxocarboxylate

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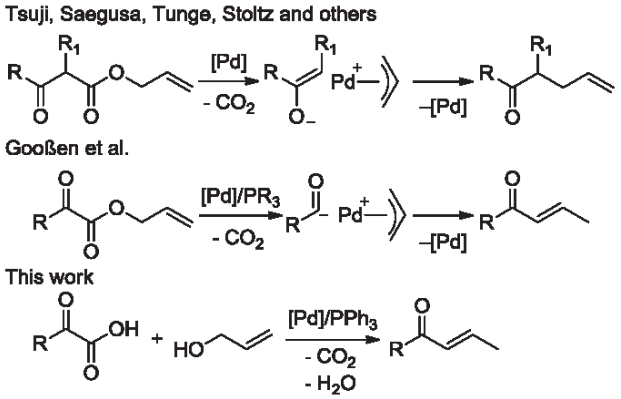
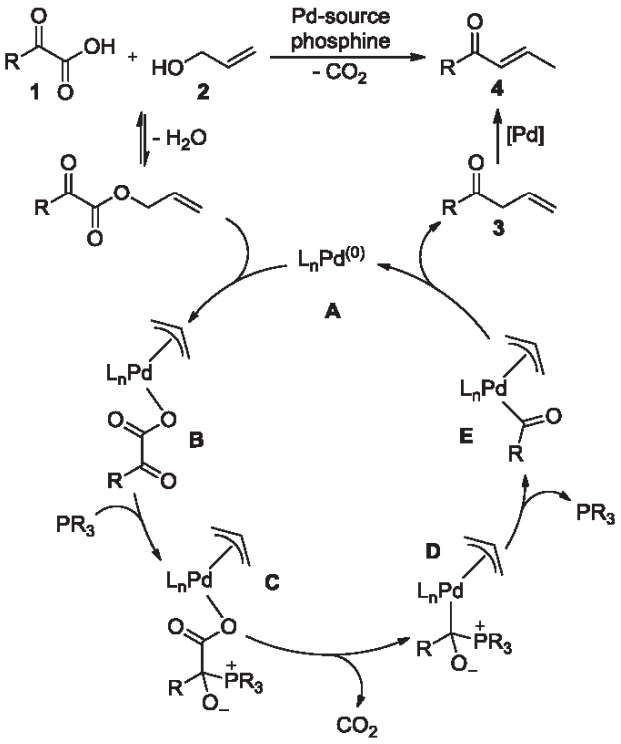


Scheme 1. Decarboxylative allylations.

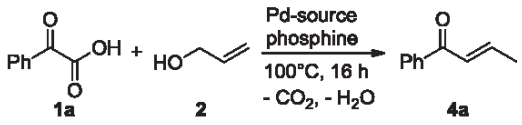
complex **B**. The phosphine should then add to the carbonyl group of the arylglyoxylate (**C**), promoting the extrusion of CO_2 with the formation of the acyl palladium complex **D**. In a reductive elimination step, the allylketone **3** would be released, regenerating the initial palladium(0) complex **A**. The product would then immediately isomerize to the stabilized (*E*)-configured α,β-unsaturated ketone (**4**).

In search for an effective catalyst system, we used phenylglyoxylic acid and allyl alcohol as the model reaction and evaluated various palladium complexes in combination with several phosphines [11,12]. Under the optimal reaction conditions for the conversion of preformed allyl esters ($Pd(dba)_2$/P(*p*Tol)$_3$, toluene, 100 °C, 16 h), only protodecarboxylation of the phenlglyoxylic acid was observed (Table 1, entry 1). A screening of various solvents revealed that 1,4-dioxane was uniquely effective for the desired



Scheme 2. Proposed mechanism of the decarboxylative allylation.

Table 1
Optimization of the reaction conditions.[a]



Entry	Pd source	Phosphine	Solvent	Yield [%][b]
1	$Pd(dba)_2$	P(*p*Tol)$_3$	Toluene	0
2	$Pd(dba)_2$	P(*p*Tol)$_3$	1,4-Dioxane	50
3	$Pd(dba)_2$	P(*p*Tol)$_3$	Anisole	0
4	$Pd(dba)_2$	P(*p*Tol)$_3$	Diglyme	0
5	$Pd(dba)_2$	P(*p*Tol)$_3$	NMP	0
6	$Pd(dba)_2$	P(*p*Tol)$_3$	DMF	0
7	$Pd(dba)_2$	P(*p*Tol)$_3$	DMSO	0
8	$Pd(PPh_3)_4$	P(*p*Tol)$_3$	1,4-Dioxane	79
9	$PdCl_2$	P(*p*Tol)$_3$	1,4-Dioxane	0
10	$Pd(OAc)_2$	P(*p*Tol)$_3$	1,4-Dioxane	23
11	$Pd(acac)_2$	P(*p*Tol)$_3$	1,4-Dioxane	29
12	$Pd(dba)_2$	PPh_3	1,4-Dioxane	84
13	$Pd(dba)_2$	P(*p*-F-C_6H_4)$_3$	1,4-Dioxane	64
14	$Pd(dba)_2$	P(*p*-OMe-C_6H_4)$_3$	1,4-Dioxane	0
15	$Pd(dba)_2$	P(*o*-Tol)$_3$	1,4-Dioxane	0
16	$Pd(dba)_2$	P(fur)$_3$	1,4-Dioxane	0
17	$Pd(dba)_2$	PCy_3	1,4-Dioxane	0
18	$Pd(dba)_2$	JohnPhos	1,4-Dioxane	0
19[c]	$Pd(dba)_2$	PPh_3	1,4-Dioxane	89

[a] Reaction conditions: phenylglyoxylic acid (**1a**) (0.50 mmol), allyl alcohol (**2**) (0.75 mmol), Pd-source (5 mol%), ligand (30 mol%), 4 mL solvent, 100 °C, 16 h.
[b] Yields were determined by GC analysis, with *n*-tetradecane as an internal standard.
[c] 35 mol% PPh_3.

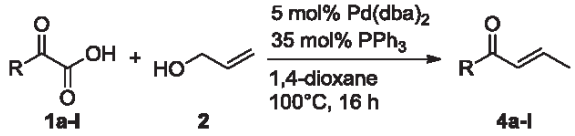
process. Whereas in this solvent, product **4a** was obtained in an encouraging 50% yield (entry 2), product formation was observed neither in less polar nor in strongly polar solvents (entries 3–7). Among the palladium precursors tested, the Pd(0) complex $Pd(PPh_3)_4$ gave the best result (entry 8), and almost no conversion was achieved for palladium(II) complexes (entries 9–11). The screening of various phosphines revealed that simple PPh_3 is the most active cocatalyst, with optimal donating ability and steric demand (entries 12–18). This is an interesting finding, since for other protocols P(*p*Tol)$_3$ was by far the most effective phosphine cocatalyst. Using a catalyst generated *in situ* from 5 mol% $Pd(dba)_2$ and 35 mol% of PPh_3, the desired product was finally obtained in 89% yield when stirring a mixture of the phenylglyoxylic acid and 1.5 equivalents of allyl alcohol in 1,4-dioxane at 100 °C for 16 h (entry 19).

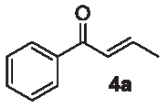
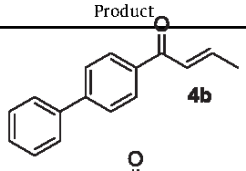
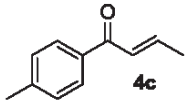
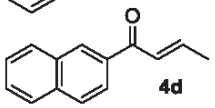
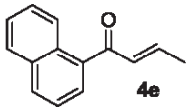
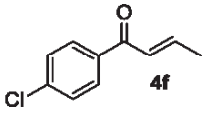
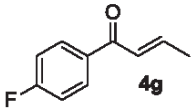
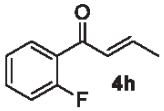
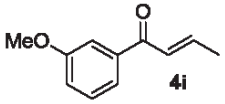
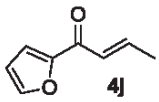
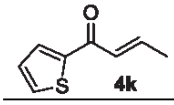
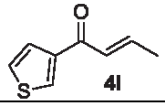
Having thus found an efficient reaction protocol, we next investigated the scope of the new transformation. As can be seen from the examples in Table 2, various aromatic and heteroaromatic glyoxylic acids were converted in good yields into the corresponding α,β-unsaturated ketones. Several functional groups, e.g., methoxy-, chloro- and fluoro-groups were tolerated. The reaction is not yet applicable to alkylglyoxylic acids, to particularly sterically demanding aromatic substrates such as mesitylglyoxylic acid, and to arylglyoxylic acids bearing strongly electron-withdrawing substituents such as nitro-groups in *para*-position.

3. Conclusion

In conclusion, a decarboxylative cross-coupling of arylglyoxylic acids with allyl alcohol was developed. It constitutes the first example of a C–C bond forming reaction starting from carboxylic acids and alcohols. The simplicity of the catalyst system, which is

Table 2
Scope of the reaction.[a]



Product	Yield [%]	Product	Yield [%]
 4a	88	 4b	85
 4c	81	 4d	86
 4e	87	 4f	86
 4g	96	 4h	82
 4i	77	 4j	80
 4k	73	 4l	63

[a] Reaction conditions: arylglyoxylic acid (1.00 mmol), allyl alcohol (1.50 mmol), $Pd(dba)_2$ (5 mol%), PPh_3 (35 mol%), 8 mL 1,4-dioxane, 100 °C, 16 h.

formed *in situ* from easily available $Pd(dba)_2$ and PPh_3, as well as the mild reaction conditions are particular advantages of this reaction protocol. This is a first step towards a new generation of salt-free cross-coupling reactions, in which the substrates are generated in an equilibrated esterification process that releases only water as byproduct, combined with a regiospecific coupling reaction, in which only CO_2 is released. If this concept could be extended, e.g., to biaryl couplings, the sustainability of such processes could dramatically be improved (Scheme 3).

4. Experimental section

4.1. General methods

All reactions were performed in oven-dried vessels equipped with teflon-coated stirrer bars and septa using degassed solvents under a nitrogen atmosphere. 1,4-Dioxane was used without further purification. All reactions were monitored by GC using *n*-tetradecane as an internal standard. Response factors of the products with regard to *n*-tetradecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP-5 capillary column (phenyl methyl siloxane, 30 m|320|0.25, 100/2.3–30–300/3) and a time program beginning with 2 min at 60 °C followed by 30 °C/min ramp to 300 °C, then 3 min at this temp. Column chromatography was performed using a Combi Flash Companion-Chromatography-System (Isco-Systems) and Grace Reveleris packed flash columns (12 g). Melting points were determined with a Mettler FP61. NMR spectra were obtained on a Bruker AMX 400 system using $CDCl_3$ as solvent, with proton and carbon resonances at 400 MHz and 101 MHz, respectively. Infrared spectra were recorded on a Perkin Elmer Fourier transform spectrometer. Mass spectral data were acquired on a GC–MS Saturn 2100 T (Varian). CHN–elemental analysis was performed with a Hanau Elemental Analyzer vario Micro cube. Compounds **1b** [CAS: 5449-21-8], **1c** [CAS: 7163-50-0], **1d** [CAS: 14289-45-3], **1e** [CAS: 26153-26-4], **1f** [CAS: 7099-88-9], **1g** [CAS: 2251-76-5], **1h** [CAS: 79477-86-4], **1i** [CAS: 26767-10-2] and **1l** [CAS: 39684-36-1] were synthesized in 61–98% yield following known synthetic procedures [2a,15]. All other compounds were commercially available and used without further purification.

4.2. Standard procedure for the synthesis of α,β-unsaturated ketones from α-oxocarboxylic acids

A 20 mL crimp-cap vessel was charged with bis(dibenzylideneacetone)palladium(0) (28.8 mg, 0.05 mmol) and triphenylphosphine (91.8 mg, 0.35 mmol). A solution of the α-oxocarboxylic acid (**1a–l**) (1.00 mmol) in 1,4-dioxane (8 mL) and allyl alcohol (**2**) (104 μL, 1.50 mmol) were added via syringe. The reaction mixture was stirred at 100 °C for 16 h and was then cooled to room temperature. The solvent was removed in vacuo (40 °C, 100 mbar) and the remaining residue was further purified by flash chromatography (SiO_2, ethyl acetate/hexane (1:10)), yielding the corresponding ketones **4a–l** (63–96%).

4.2.1. Synthesis of (E)-1-phenylbut-2-en-1-one (*4a*) [CAS: 495-41-0]

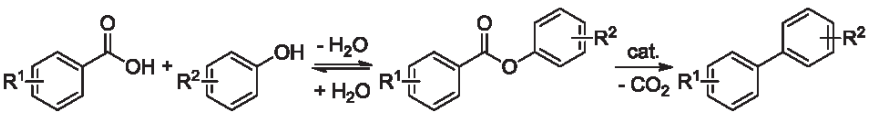
Compound **4a** was prepared following the standard procedure, starting from phenylglyoxylic acid (**1a**) (155 mg, 1.00 mmol). After purification, **4a** was isolated as colourless oil (129 mg, 88%). The spectroscopic data matched those reported in the literature.

4.2.2. Synthesis of (E)-1-([1,1′-biphenyl]-4-yl)but-2-en-1-one (*4b*) [CAS: 71823-67-1]

Compound **4b** was prepared following the standard procedure, starting from 4-biphenylglyoxylic acid (**1b**) (226 mg, 1.00 mmol). After purification, **4b** was isolated as beige solid (189 mg, 85%). The spectroscopic data matched those reported in the literature.

4.2.3. Synthesis of (E)-1-(4-tolyl)but-2-en-1-one (*4c*) [CAS: 3837-95-4]

Compound **4c** was prepared following the standard procedure, starting from 4-tolylglyoxylic acid (**1c**) (164 mg, 1.00 mmol). After purification, **4c** was isolated as colourless oil (129 mg, 81%). The spectroscopic data matched those reported in the literature.



Scheme 3. "Dream reaction" for biaryl synthesis.

*4.2.4. Synthesis of (E)-1-(naphthalen-2-yl)but-2-en-1-one (**4d**) [CAS: 128113-44-0]*

Compound **4d** was prepared following the standard procedure, starting from 2-napththylglyoxylic acid (**1d**) (200 mg, 1.00 mmol). After purification, **4d** was isolated as colourless solid (168 mg, 86%). The spectroscopic data matched those reported in the literature.

*4.2.5. Synthesis of (E)-1-(naphthalen-1-yl)but-2-en-1-one (**4e**) [CAS: 128113-46-2]*

Compound **4e** was prepared following the standard procedure, starting from 1-napththylglyoxylic acid (**1e**) (200 mg, 1.00 mmol). After purification, **4e** was isolated as yellow solid (170 mg, 87%). The spectroscopic data matched those reported in the literature.

*4.2.6. Synthesis of (E)-1-(4-chlorophenyl)but-2-en-1-one (**4f**) [CAS: 67864-02-2]*

Compound **4f** was prepared following the standard procedure, starting from 4-chlorophenylglyoxylic acid (**1f**) (185 mg, 1.00 mmol). After purification, **4f** was isolated as colourless solid (156 mg, 86%). The spectroscopic data matched those reported in the literature.

*4.2.7. Synthesis of (E)-1-(4-fluorophenyl)but-2-en-1-one (**4g**) [CAS: 28122-15-8]*

Compound **4g** was prepared following the standard procedure, starting from 4-flourophenylglyoxylic acid (**1g**) (168 mg, 1.00 mmol). After purification, **4g** was isolated as colourless oil (158 mg, 96%). The spectroscopic data matched those reported in the literature.

*4.2.8. Synthesis of (E)-1-(2-fluorophenyl)but-2-en-1-one (**4h**) [CAS: 79477-86-4]*

Compound **4h** was prepared following the standard procedure, starting from 2-fluorophenylglyoxylic acid (**1h**) (168 mg, 1.00 mmol). After purification, **4h** was isolated as colourless oil (135 mg, 82%). The spectroscopic data matched those reported in the literature.

*4.2.9. Synthesis of (E)-1-(3-methoxyphenyl)but-2-en-1-one (**4i**) [CAS: 1087399-25-4]*

Compound **4i** was prepared following the standard procedure, starting from 3-methoxyphenylglyoxylic acid (**1i**) (180 mg, 1.00 mmol). After purification, **4i** was isolated as yellow oil (135 mg, 77%). The spectroscopic data matched those reported in the literature.

*4.2.10. Synthesis of (E)-1-(furan-2-yl)but-2-en-1-one (**4j**) [CAS: 131323-45-0]*

Compound **4j** was prepared following the standard procedure, starting from furanyl-2-glyoxylic acid (**1j**) (140 mg, 1.00 mmol). After purification, **4j** was isolated as yellow solid (109 mg, 80%). The spectroscopic data (NMR, IR) matched those reported in the literature.

*4.2.11. Synthesis of (E)-1-(thiophen-2-yl)but-2-en-1-one (**4k**) [CAS: 13196-29-7]*

Compound **4k** was prepared following the standard procedure, starting from thiophenyl-2-glyoxylic acid (**1k**) (156 mg, 1.00 mmol). After purification, **4k** was isolated as yellow oil (111 mg, 73%). The spectroscopic data (NMR, IR) matched those reported in the literature.

*4.2.12. Synthesis of (E)-1-(thiophen-3-yl)but-2-en-1-one (**4l**) [CAS: 1308249-57-1]*

Compound **4l** was prepared following the standard procedure, starting from thiophenyl-3-glyoxylic acid (**1l**) (156 mg, 1.00 mmol). After purification, **4l** was isolated as colourless solid (95.5 mg, 63%). M.p. = 42.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 (dd, J = 2.8, 1.2 Hz, 1H), 7.58 (dd, J = 5.1, 1.3 Hz, 1H), 7.31 (dd, J = 5.1, 2.8 Hz, 1H), 7.08 (dq, J = 15.1, 6.8 Hz, 1H), 6.79 (dq, J = 15.3, 1.4 Hz, 1H), 1.97 ppm (dd, J = 6.8, 1.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 183.9, 144.0, 142.6, 131.8, 127.9, 127.3, 126.2, 18.3 ppm (2C; CH_3); IR ν = 3105 (s), 2909 (m), 1667 (vs), 1619 (vs), 1511 (m), 1443 (m), 1411 (m), 1291 (m), 1231 (m), 1179 cm ^{1} (m); MS (Ion trap, EI): m/z (%) = 152 (20), 151 (100), 136 (27), 91 (11), 69 (25), 45 (20), 41 (20); elemental analysis calcd (%) for C_8H_8OS: C 63.13, H 5.30, S 21.07; found: C 63.43, H 5.50, S 20.90.

Acknowledgements

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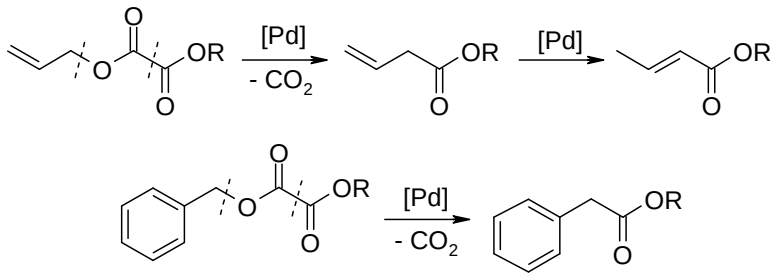
4.1.5. Decarboxylierende Benzylierung von Oxalaten

Das Konzept der reversiblen Veresterung mit anschließender decarboxylierender Kupplung sollte nun auch auf andere Substanzklassen erweitert werden. Dazu erfolgten zunächst Studien zur decarboxylierenden Benzylierung von Phenylglyoxylsäuren. Diese Reaktionen führten allerdings zu keiner Produktbildung, sondern lediglich zur Protodecarboxylierung der Carbonsäure.

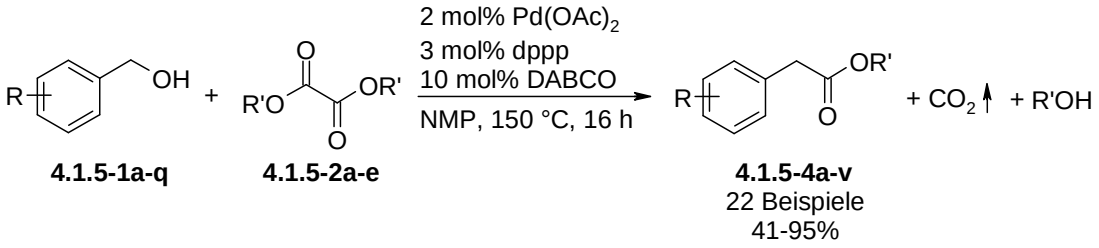
Es folgten Untersuchungen zur Reaktivität präformierter Allyl− und Benzyloxalate, die decarboxylierend einen neuen Zugang zu Acrylsäure− oder Phenylessigsäurederivaten ermöglichen könnten. Die oxidative Addition dieser Ester an einen Palladium(0)−Katalysator sollte Allyl− bzw. Benzylkomplexe bilden, die im irreversiblen Decarboxylierungsschritt zu Alkoxycarbonyl−Palladium(II)−Spezies führen. Die reduktive Eliminierung würde die entsprechenden Produkte bilden und den Palladium(0)−Katalysator regenerieren.



Schema 34: Decarboxylierende Allylierung und Benzylierung von Oxalaten.

Als Ausgangspunkt erster Testreaktionen wurden Reaktionsbedingungen gewählt, unter denen Fu und Liu Arylhalogenide mit Kaliumethyloxalat decarboxylierend kuppeln konnten.[30] Während die Allyloxalate keine Produktbildung zeigten, konnte das Benzylethyloxalat bei 150 °C mit 2 mol% $Pd(OAc)_2$ und 3 mol% dppp in NMP erfolgreich in 38% Ausbeute zum Phenylessigsäureethylester umgesetzt werden. Da nukleophile Additive bereits einen großen Effekt bei der Decarboxylierung von Arylglyoxylsäuren zeigten, wurde nun auch die Reaktivität verschiedener Lewis−Basen untersucht. Die Anwesenheit von DMAP ermöglichte dabei eine signifikante Ausbeutensteigerung auf 64%. Weitere Testreaktionen zeigten zudem, dass das gemeinsame Erhitzen von Diethyloxalat und Benzylalkohol bei 150 °C zur sehr raschen Bildung des Benzylethyloxalats führt.

Im Anschluss an diese Untersuchungen folgten nun Studien zur Kombination von Transesterifizierung und decarboxylierender Kupplung. Bei der Umsetzung von Diethyloxalat mit Benzylalkohol ermöglichte bereits der reine Palladium/Phosphan–Katalysator eine Produktausbeute von 11%. Auch hier zeigten Aminbasen einen besonderen Effekt, sodass die Ausbeute in Anwesenheit katalytischer Mengen DABCO sogar auf 89% gesteigert werden konnte (Schema 35). Kontrollreaktionen zeigten, dass bereits sehr geringe Mengen des freien Phosphans zur schnellen Equilibrierung der Startmaterialien führen und DABCO einen sehr starken Effekt auf die Decarboxylierung der Oxalate besitzt.



4.1.5-1a-q **4.1.5-2a-e** **4.1.5-4a-v**
22 Beispiele
41-95%

Schema 35: Synthese von Phenylessigsäureestern aus Benzylalkoholen und Oxalaten.

Die Anwendungsbreite wurde schießlich an zahlreichen Verbindungen mit unterschiedlichen funktionellen Gruppen demonstriert. Besonders Diphenyloxalat und Bis(2,2,2–trifluorethyl)oxalat ermöglichten sogar die Umsetzung sehr elektronenarmer und dadurch unreaktiver Benzylalkohole in guten Ausbeuten. Weiterhin wurde der Phenylessigsäureethylester auch im präparativen 50 mmol Maßstab in 95% Ausbeute dargestellt.

Alle Resultate der Katalysatoroptimierung und die Untersuchungen zum Mechanismus und zur Anwendungsbreite sind in der nachfolgenden Publikation aufgeführt. Diese wurde 2013 in Chemistry – A European Journal, Vol. 19, 7334–7337 veröffentlicht, für dieses Manuskript angepasst und mit Erlaubnis der John Wiley & Sons, Inc. beigefügt.

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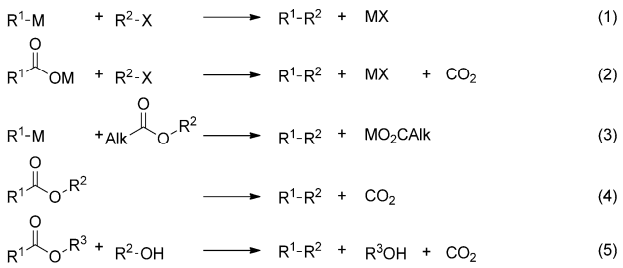
Synthesis of Arylacetates from Benzylic Alcohols and Oxalate Esters through Decarboxylative Coupling

Matthias F. Grünberg and Lukas J. Gooßen*[a]

The development of sustainable methodologies for carbon–carbon bond formation is among the key objectives in modern organic synthesis. Catalytic cross-coupling reactions have proven to be efficient and versatile tools for assembling even complex molecular structures.[1] In classical redox-neutral cross-coupling reactions, carbon electrophiles, for example, aryl halides [Eq. (1); X = halide], are regiospecifically coupled with carbon nucleophiles, for example, organometallic compounds (M = main-group metal). Along with the C–C coupling products, byproducts are formed resulting from the leaving groups, usually metal salts. Within the last decade, several strategies have been developed to overcome the major limitations of this concept, that is, the necessity to generate sensitive organometallic reagents in an extra reaction step, the use of environmentally questionable organohalides, and the formation of salt waste.



One of these strategies consists in replacing traditional with decarboxylative coupling reactions, which draw on carboxylate salts rather than organometallic reagents as the carbon nucleophiles [Eq. (2)].[2] This reaction type has found application, for example, in syntheses of biaryls[3] and arylketones[4] and for the introduction of either allyl or benzyl groups.[5] Another strategy involves using carboxylates in the place of organohalides in cross-coupling reactions with organometallic reagents [Eq. (3)].[6] A prominent example is the Tsuji–Trost allylation (R^2 = allyl).[7] The two above approaches are combined in catalytic decarboxylation reactions of allyl carboxylates [Eq. (4); R^2 = allyl].[8] The allyl carboxylate substrates provide both the electrophilic allyl group and the carbon nucleophile that is masked initially, but liberated at the Pd catalyst by extrusion of CO_2, which is the only byproduct generated in the overall process. This attractive reaction type was discovered by Saegusa and Tsuji et al.[9] and has been led to synthetic maturity by the research groups of Tunge,[10] Stoltz[11] and others.[8] Unfortunately, an extra step is required to preform the starting material, which often generates a lot of waste. Moreover, the reaction is known only for allylic and benzylic esters. However, recent reports by the research groups of both Garg and Shi, that aryl carboxylates (R^2 = aryl) can undergo oxidative additions to catalyst metals that are capable of mediating decarboxylative processes indicate that this attractive concept may soon become more generally applicable, maybe even to biaryl synthesis.[6,12]

To the best of our knowledge, there is still no example of a regiospecific intermolecular decarboxylative cross-coupling reaction between an alcohol and either a carboxylic acid or ester [Eq. (5); R^3 = H or alkyl].[13] We envisioned that this kind of C–C coupling should be achievable by combining a reversible transesterification between an alcohol and an appropriate alkyl carboxylate with a catalytic decarboxylation of the resulting ester. In the overall process, CO_2 and an alcohol would be the only byproducts. As a first example of such a process, we herein disclose a synthesis of α-arylacetic acid esters from benzylic alcohols and diethyl oxalate (Scheme 1).

α-Arylacetic acids are an important product class because many of its members possess unique biological and pharmaceutical activities (Figure 1).[14] Well-known representatives include the nonsteroidal anti-inflammatory drugs, diclofenac and indomethacin, and the antihistamine, olopatadine. Arylacetic acids are also versatile intermediates used, for example, in the synthesis of agrochemicals like spiromesifen and pinoxaden.

The overall reaction (Scheme 1, top), in which CO_2 and ethanol are the only byproducts, compares favorably with classical arylacetic acid syntheses such as the hydrolysis of benzyl cyanides and the transition metal catalyzed carbonylation of benzylic halides or alcohols.[15] It is also a valuable alternative to modern arylacetic acid syntheses, involving, for example, the oxidative carbonylation of toluene,[16] the

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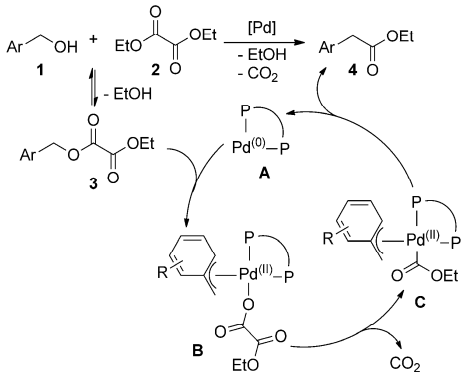


Scheme 1. Synthesis of α-arylacetates from benzylic alcohols.

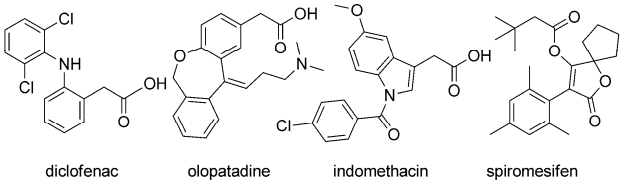


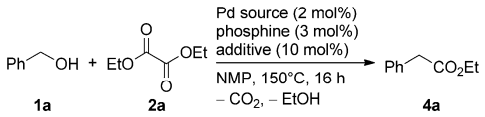
Figure 1. Biologically active arylacetic acid derivatives.

oxidation of terminal alkynes,[17] the electrocatalytic carboxylation of benzyl halides,[18] transition metal catalyzed cross-coupling reactions between aryl halides and enolates,[19] malonates,[20] cyanoacetates,[21] or acetoacetates,[22] carbene-transfer reactions from ethyl diazoacetate,[23] and coupling reactions of α-haloacetate esters,[24] each of which have their individual drawbacks.

The mechanistic concept for the development of the new cross-coupling process is outlined in Scheme 1, bottom. The benzylic alcohol substrate **1** undergoes reversible transesterification with diethyl oxalate (**2**) leading to the benzyl ethyl oxalate **3**, which oxidatively adds to the Pd(0) catalyst, **A**. The resulting benzyl complex, **B**, extrudes CO_2 to give acyl-palladium(II) species **C**. Arylacetic ester **4** is then liberated by reductive elimination, regenerating Pd species **A**.

As starting point for catalyst development, we chose reaction conditions similar to those used by Fu, Liu et al. for the decarboxylative coupling of potassium oxalate monoesters with aryl halides.[4c] When heating benzyl ethyl oxalate (**3a**) with 2 mol% $Pd(OAc)_2$ and 3 mol% 1,3-bis(diphenylphosphino)propane (dppp) to 150°C, ethyl phenylacetate (**4a**) was indeed obtained, albeit in low yield (38%). Because we had observed that the presence of nucleophilic additives had a profound effect on the related coupling of α-oxocarboxylates,[25] we screened various Lewis bases and found that the addition of 4-(dimethylamino)pyridine (DMAP) increased the yield to 64%. To confirm that under these reaction conditions, transesterification takes place at a reasonable rate, diethyl oxalate was heated with benzyl alcohol to 150°C. To our delight, the benzyl ester was detected within only a few minutes.

Table 1. Optimization of the reaction conditions.



Entry	Pd source	Phosphine	Additive	Yield [%]
1	$Pd(OAc)_2$	dppp	–	11
2	$Pd(OAc)_2$	dppp	DMAP	70
3	$Pd(OAc)_2$	dppp	*t*-butylamine	11
4	$Pd(OAc)_2$	dppp	diethylamine	14
5	$Pd(OAc)_2$	dppp	2,6-lutidine	18
6	$Pd(OAc)_2$	dppp	TMP	39
7	$Pd(OAc)_2$	dppp	DABCO	89
8	$Pd(OAc)_2$	dppp	$P(p\text{Tol})_3$	20
9[a]	$Pd(OAc)_2$	dppp	DABCO	75
10	$[Pd(dba)_2]$	dppp	DABCO	74
11	$[Pd(acac)_2]$	dppp	DABCO	71
12	$Pd(OAc)_2$	–	DABCO	0
13	$Pd(OAc)_2$	PPh_3	DABCO	0
14	$Pd(OAc)_2$	PCy_3	DABCO	0
15	$Pd(OAc)_2$	dppb	DABCO	36
16	$Pd(OAc)_2$	dppe	DABCO	75
17[b]	$Pd(OAc)_2$	dppp	DABCO	82
18[c]	$Pd(OAc)_2$	dppp	DABCO	69

Reaction conditions: 0.50 mmol **1a**, 0.60 mmol **2a**, 2 mol% Pd source, either 6 mol% monodentate or 3 mol% bidentate ligand, 10% additive, 1 mL NMP, 150°C, 16 h, GC yields with *n*-tetradecane as internal standard. [a] 0.55 mmol **2a**; [b] 140°C; [c] 2 mol% dppp. acac = Acetylacetonate, Cy = cyclohexyl, dba = dibenzylidene acetone, dppb = 1,2-bis(diphenylphosphino)butane, dppe = 1,2-bis(diphenylphosphino)ethane, NMP = *N*-methylpyrrolidine, TMP = 2,2,6,6-tetramethylpiperidine.

After these successful trial experiments, we systematically investigated the combined transesterification/decarboxylation process for the model reaction of benzyl alcohol (**1a**) with diethyl oxalate (**2a**) in the presence of various catalyst systems (Table 1). Using 2 mol% $Pd(OAc)_2$ and 3 mol% dppp as the catalysts, the desired product (**4a**) was obtained in only 11% yield (Table 1, entry 1). Whereas primary and secondary amines, sterically hindered pyridines, and phosphines had little effect on the reaction outcome, the addition of strongly nucleophilic tertiary amines led to a marked increase in conversion (Table 1, entries 2–8). The best results were obtained with the nontoxic inexpensive base, 1,4-diazabicyclo[2.2.2]octane (DABCO). The highest yields, based on benzyl alcohol, were obtained when diethyl oxalate was used in slight excess (1.2:1; Table 1, entries 7, 9).

Variation of the Pd source revealed that $Pd(OAc)_2$ is most effective (Table 1, entries 10–11). The properties of the phosphine ligands have a profound influence on the reaction outcome (Table 1, entries 12–16). In the absence of phosphine or when using monodentate ligands, the product is formed in trace amounts at best. Similar to other coupling reactions of oxalates,[4c] the reaction is effectively promoted only by using bidentate phosphines. The reason for this condition is unclear at this stage. Interestingly, the yields strongly depend on the bite angle, the yield being highest when using dppp. Phosphines bridged by either longer or shorter carbon chains are less effective. Lowering the temperature to 140°C still furnished the product in reasonable yield

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(Table 1, entry 17); below this temperature, the rate-determining decarboxylation of the palladium carboxylate no longer occurred and the reaction became sluggish.

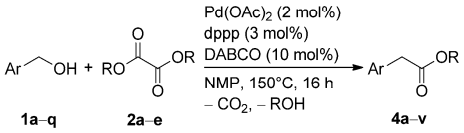
Further control experiments were conducted to elucidate the role of the individual components in the catalytic process.[26] The influence of $Pd(OAc)_2$ and the basic amine on the esterification step was found to be minimal. However, even the presence of small quantities of dppp accelerate the equilibration.[27] This observation explains why better results are obtained when the phosphine is added in an amount that is slightly in excess of that of Pd (Table 1, entries 7, 18). The amine additive strongly affected the decarboxylation of the oxalate. Both diethyl and benzyl ethyl oxalate decomposed with formation of CO_2 when stirred at 150 °C in the presence of DABCO, presumably through a reversible nucleophilic addition process. This result is in agreement with the observation that whereas the decarboxylative coupling is slow in the absence of the amine, in the presence of too much DABCO, the oxalate undergoes decarboxylation faster than it undergoes cross-coupling, thus causing unreacted benzyl alcohol to be left behind.

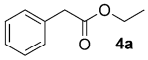
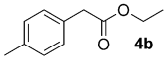
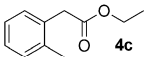
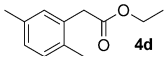
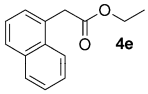
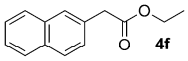
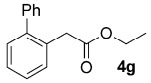
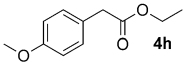
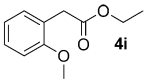
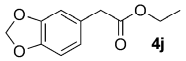
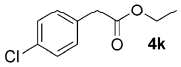
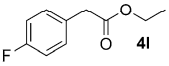
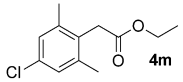
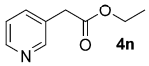
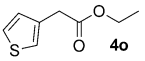
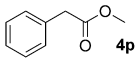
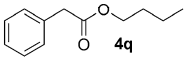
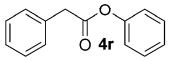
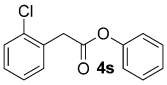
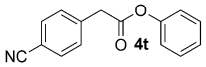
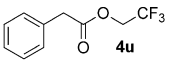
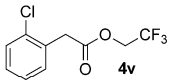
The scope of the new transformation was investigated using the optimized catalyst system, that is, $Pd(OAc)_2$ (2 mol %), dppp (3 mol %), and DABCO (10 mol %). As can be seen from the examples in Table 2, various benzylic alcohols with common functional groups, such as halides and methoxy groups, were converted in good yields into the corresponding arylacetic esters. Even alcohol **1m**, which contains two shielding methyl groups in *ortho* positions and an exposed chloro substituent in the *para* position, gave the desired ester **4m** in 56% yield. Heterocyclic derivatives were also successfully transformed.

Some benzylic alcohols with an electron-withdrawing group in the *para* position did not give satisfactory yields in the reaction with dialkyl oxalates; for example, the transformation of 4-cyanobenzylic alcohol (**1q**) led to less than 5% yield of the expected product. We attributed this result to the relatively low reactivity of such substrates in the transesterification step. Consequently, we replaced ethyl oxalate with the more activated derivatives, either diphenyl- or bis(2,2,2-trifluoroethyl) oxalate. This change did indeed lead to an increase in the efficiency of the process, so that 4-cyanobenzyl alcohol (**1q**) could also be converted into the corresponding arylacetate (**4t**). The reaction works reliably also on gram scale. Phenylacetic ester **4a** was synthesized in 95% yield on 50 mmol scale in concentrated solution (7.8 g product/50 g solvent) with only 1 mol % of the Pd catalyst. As expected, analogous reactions with either simple alkanols or phenol did not give C–C coupling products, although the mixed oxalate esters were formed. In the reaction with allyl alcohols, only decomposition products were detected. However, first results indicate that the transformation may be extendable to α-ketoacids.

In conclusion, a catalyst system consisting of $Pd(OAc)_2$/dppp and DABCO efficiently promotes the decarboxylation of benzyl oxalates to give arylacetates under reaction conditions allowing the continuous generation of these materials from benzylic alcohols and dialkyl oxalates. The overall process represents an intermolecular regiospecific C–C bond-forming reaction in which volatile alcohols and carbon dioxide are released as the only byproducts. This process may lead to the development of a new generation of salt-free cross-coupling reactions, for example, the dream reaction between alkyl benzoates and phenols to give the corresponding biaryl compound.

Table 2. Scope of the reaction.



Product	Yield [%]	Product	Yield [%]
 4a	95	 4b	93
 4c	88	 4d	81
 4e	59	 4f	58
 4g	85	 4h	82
 4i	75	 4j	66
 4k	74	 4l	90
 4m	56	 4n	41
 4o	55	 4p	84
 4q	88	 4r	42
 4s	70	 4t	54
 4u	75	 4v	81

Reaction conditions: 1.00 mmol benzylic alcohol, 1.20 mmol oxalate, 2 mol % $Pd(OAc)_2$, 3 mol % dppp, 10 mol % DABCO, 2 mL NMP, 150 °C, 16 h.

Experimental Section

Standard procedure for the synthesis of arylacetic esters: A crimp-cap reaction vessel was charged with palladium(II) acetate (4.58 mg, 0.02 mmol), 1,3-bis(diphenylphosphino)propane (12.4 mg, 0.03 mmol), and 1,4-diazabicyclo[2.2.2]octane (11.2 mg, 0.10 mmol). Under an inert

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atmosphere, a degassed solution of the benzylic alcohol (1.00 mmol) and the oxalate (1.20 mmol) in NMP (2 mL) was added using a syringe. The reaction mixture was stirred at 150 °C for 16 h and then cooled to room temperature. The slight pressure buildup caused by the partially dissolved CO_2 was carefully released by piercing the septum with a syringe needle before uncapping. Ethyl acetate (20 mL) was added and the mixture was washed with water (20 mL) and a saturated aqueous bicarbonate solution (20 mL). The organic layer was separated, dried over $MgSO_4$, and filtered, followed by removal of solvents in vacuo (40 °C, 200 mbar). The remaining residue was further purified by flash chromatography (SiO_2; ethyl acetate/hexane, 1:10), yielding the corresponding esters **4** (41–95 %).

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Keywords: arylacetic esters · decarboxylation · homogeneous catalysis · palladium · transesterification

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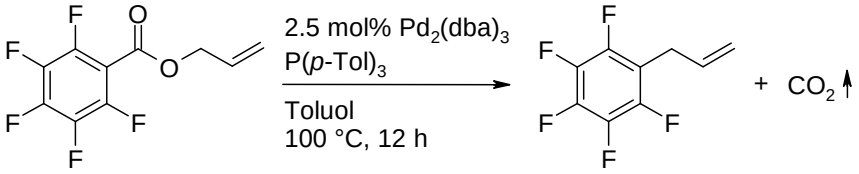
4.1.6. Decarboxylierende Allylierung von Allylbenzoaten

Während β–Ketocarbonsäuren aufgrund eines günstigen Übergangszustandes bereits thermisch[83] und α–Oxocarbonsäuren mithilfe eines Phosphans als Organokatalysator aktiviert und decarboxyliert werden können (siehe 4.1.2), ist die Extrusion von CO_2 aus Benzoesäurederivaten nur mit einem Metallkatalysator möglich (vgl. 2.2.1, S. 8). Da besonders aktivierte, bis–*ortho*–substituierte Benzoesäuren mit Palladium–Katalysatoren decarboxyliert werden können,[79,80,115] folgten im Anschluss an die Transformationen der Phenylglyoxylate auch erste Untersuchungen zur decarboxylierenden Allylierung von Benzoesäureestern.

4.1.6.1. Palladium–katalysierte Transformationen von Allylbenzoaten

In Anlehnung an Liu's Palladium–katalysierte decarboxylierende Kupplung von Pentafluorbenzoaten mit Arylhalogeniden und –triflaten[115] wurde der Pentafluorbenzoesäureallylester als Modellsubstrat gewählt und zunächst unter den Standardbedingungen der Phenylglyoxylsäureester umgesetzt (Tabelle 4).

Tabelle 4: Decarboxylierende Allylierung von Pentafluorbenzoesäureallylester.



4.1.6-1 **4.1.6-2**

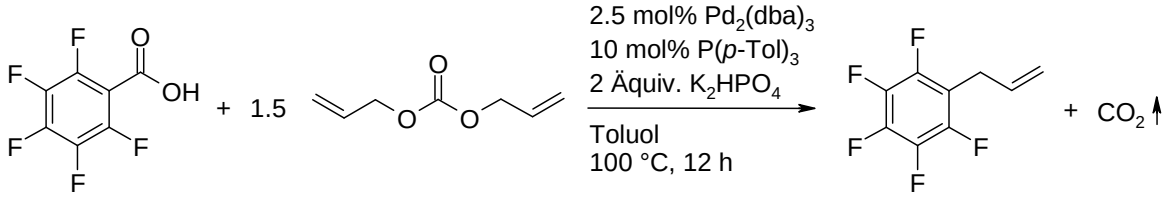
Eintrag	Ligand	4.1.6–2 [%]
1	50 mol% P(*p*–Tol)$_3$	4
2	25 mol% P(*p*–Tol)$_3$	10
3	10 mol% P(*p*–Tol)$_3$	27

Reaktionsbedingungen: 0.50 mmol des Esters, 5 mol% Palladium, 4 mL Toluol, 100 °C, 12 h. Ausbeuten wurden gaschromatographisch mit *n*–Tetradecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

Bereits unter diesen Reaktionsbedingungen erfolgte die Produktbildung des Allylbenzols in 10% Ausbeute (Eintrag 2). Da der Decarboxylierungsschritt vermutlich in der Koordinationssphäre des Palladiums und nicht organokatalytisch stattfindet, senkt ein Überschuss des freien Phosphans die Aktivität des Katalysators. Eine Verringerung der

Phosphanmenge auf 10 mol% führte hingegen zur deutlichen Ausbeutesteigerung auf 27% (Eintrag 3).

Neben diesen ersten Reaktionen präformierter Ester erfolgten zusätzlich auch Machbarkeitsstudien zur intermolekularen dearboxylierenden Allylierung der freien Pentafluorbenzoesäure mit Diallylcarbonat in Anwesenheit einer Base (Schema 36). Mit Dikaliumhydrogenphosphat konnte das Allylbenzol zwar nur in 5% Ausbeute gebildet werden, demonstriert aber auch mit dieser Methode die potentielle Möglichkeit zur Synthese von Allylbenzolen.



4.1.6-3 **4.1.6-4** **4.1.6-2** 5%

Schema 36: Intermolekulare decarboxylierende Allylierung von Pentafluorbenzoesäure.

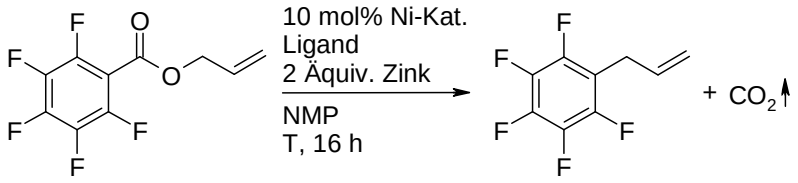
Im Rahmen seiner Diplomarbeit übernahm Herr Kai Pfister an dieser Stelle die weitere Optimierung der Reaktionsbedingungen. Dabei konnte er zeigen, dass eine weitere Verringerung der Phosphanmenge auf 2.5 mol% und der Wechsel auf das Lösungsmittel 1,4–Dioxan einen enorm positiven Einfluss auf die Produktbildung haben. Mit der Erhöhung der Reaktionstemperatur auf 110 °C konnte die Modellverbindung schließlich quantitativ in das Allylbenzol überführt werden. Die Anwendungsbreite konnte Herr Pfister an der Transformation von 16 Allylestern demonstrieren.

4.1.6.2. Nickel–katalysierte Transformationen von Allylbenzoaten

Da sich das frühe Übergangsmetall Nickel zusammen mit Palladium und Platin in der 10. Gruppe (früher 8. Nebengruppe) des Periodensystems der Elemente befindet, teilt es, aufgrund seiner Elektronenkonfiguration, viele Eigenschaften mit den anderen beiden Metallen. Nickel(0)–Verbindungen sind daher auch sehr effektive Katalysatoren in Kreuzkupplungsreaktionen und haben die Fähigkeit ansonsten inerte C–O Bindungen zu aktivieren (vgl. 2.2.4, S. 21).[137–141,149] Obwohl die Palladium–katalysierte Decarboxylierung von Benzoesäurederivaten bereits beschrieben wurde,[79,80,115] ist nur sehr wenig über Nickel–katalysierte Decarboxylierungen bekannt.[150,151] Im Rahmen der decarboxylierenden

Allylierung von Allylbenzoaten sollte nun die Aktivität von Nickel–Katalysatoren evaluiert werden.

Tabelle 5: Nickel–katalysierte decarboxylierende Allylierung von Pentafluorbenzoaten.



4.1.6-1a **4.1.6-2a**

Eintrag	**Ni–Quelle**	**Ligand**	**T [°C]**	**4.1.6–2a [%]**
1	$NiCl_2$	PPh_3	120	29
2	"	"	100	43
3	"	"	80	–
4[a]	"	"	100	5
5	"	P(*p*–Tol)$_3$	"	7
6	"	P(*p*–F–Ph)$_3$	"	42
7	"	P(*p*–CF_3–Ph)$_3$	"	50
8	"	P(2–Fur)$_3$	"	69
9	"	P(*o*–Tol)$_3$	"	–
10	"	dppe	"	60
11	"	dppp	"	19
12	"	BINAP	"	82
13	"	dppf	"	19
14	$NiBr_2$	BINAP	"	67
15	Ni(OAc)$_3$	"	"	60
16	Ni(acac)$_2$	"	"	55
17[b]	$NiCl_2$	"	"	**84**

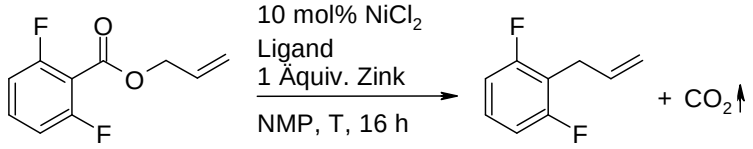
Reaktionsbedingungen: 0.50 mmol des Esters, 0.05 mmol der Nickelverbindung, 0.05 mmol eines bidentaten bzw. 0.10 mmol eines monodentaten Liganden, 1.00 mmol Zink, 2 mL NMP, 16 h. a) 4 mL NMP. b) 0.50 mmol Zink. Ausbeuten wurden gaschromatographisch mit *n*–Tetradecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

Analog zur Palladium–katalysierten Reaktion wurde der Pentafluorbenzoesäureallylester als Modellsubstrat gewählt, welcher zunächst mit $NiCl_2$, PPh_3 und dem Reduktionsmittel Zink

in verschiedenen Lösungsmitteln erhitzt wurde. Substanzielle Produktausbeuten wurden bei 120 °C lediglich in den polar–aprotischen Lösungsmitteln NMP (Tabelle 5, Eintrag 1) und DMF beobachtet. Eine Absenkung der Reaktiontemperatur auf 100 °C führte zur Ausbeutensteigerung auf 43% (Eintrag 2), wobei die Reaktion bei Temperaturen unter 100 °C komplett zum Erliegen kam (Eintrag 3).

Ein Ligandenscreening zeigte, dass elektronenreichere monodentate Liganden zu geringeren Ausbeuten führen (Eintrag 5) und Phosphane mit elektronenarmen Substituenten eine Steigerung auf 69% ermöglichen (Einträge 6–8). Sterisch gehinderte Phosphane blockierten die Reaktion und zeigten keine Produktbildung (Eintrag 9). Die besten Ausbeuten ermöglichte der bidentate Ligand BINAP mit 82% (Eintrag 12). Während andere Nickel(II)–Salze leicht schlechtere Ausbeuten ergaben (Einträge 14–16), konnte die Menge des Reduktionsmittels von 2 auf 1 Äquivalent verringert werden, ohne die Produktbildung negativ zu beeinflussen (Eintrag 17). Unter den optimalen Reaktionsbedingungen konnte das entsprechende Allylbenzol schließlich in 82% Ausbeute isoliert werden.

Tabelle 6: Nickel–katalysierte decarboxylierende Allylierung von 2,6–Difluorbenzoaten.



4.1.6-1d **4.1.6-2d**

Eintrag	Ligand	T [°C]	4.1.6–2d [%]
1	10 mol% BINAP	120	Spuren
2	"	150	10
3	"	170	14
4	10 mol% dppp	150	9
5	10 mol% dppe	"	**39**
6	10 mol% dppm	"	–
7	20 mol% P(*p*–Tol)$_3$	"	Spuren
8	20 mol% P(2–Fur)$_3$	"	–

Reaktionsbedingungen: 0.50 mmol des Esters, 10 mol% $NiCl_2$, 10 mol% eines bidentaten bzw. 20 mol% eines monodentaten Liganden, 0.50 mmol Zink, 1 mL NMP, 16 h. Ausbeuten wurden gaschromatographisch mit *n*–Tetradecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

Mit diesem Katalysatorsystem erfolgte nun auch die Umsetzung anderer Ester, darunter das 2,6–Difluorbenzoat, 2–Methoxybenzoat und das 2,6–Dimethoxybenzoat. Eine Produktbildung konnte allerdings bei keinem dieser Substrate beobachtet werden. Um dies näher zu untersuchen, folgten weitere Reihenversuche mit dem 2,6–Difluorbenzoesäure-allylester (Tabelle 6). Eine Erhöhung der Reaktionstemperatur führte bei 120 °C zu Produktspuren (Eintrag 1) und bei einer weiteren Steigerung auf 150 °C oder 170 °C zu Ausbeuten von 10% bzw. 14% (Einträge 2 & 3). Ein anschließendes Phosphanscreening resultierte in einer maximalen Ausbeute von 39% (Eintrag 5).

Diese Ergebnisse weisen deutlich darauf hin, dass die Pentafluorbenzoesäure aufgrund ihrer besonderen elektronischen Eigenschaften eine Sonderstellung unter den Benzoesäuren besitzt. Die fünf Fluorsubstituenten stellen dem aromatischen System eine hohe π–Elektronendichte zur Verfügung, während die elektronegativen Ringsubstituenten durch einen starken induktiven Effekt aber auch gleichzeitig eine Absenkung der Elektronendichte bewirken. Gegenüber der unsubstituierten Benzoesäure führt dies zur enormen Steigerung der Säurestärke (pK_s Benzoesäure = 4.2; pK_s Pentafluorbenzoesäure = 1.48)[152,153] und ermöglicht sowohl die Palladium– als auch die Nickel–katalysierte Decarboxylierung bereits bei 100 °C.

Weitere Einblicke über die Substituenteneffekte bieten Liu's Untersuchungen zur Palladium–katalysierten Kreuzkupplung von Polyfluorbenzoaten mit Arylhalogeniden und –triflaten (siehe Schema 20, S. 18).[115] Während das 2,6–Difluorbenzoat bei 130–160 °C decarboxylierend gekuppelt werden kann, ermöglicht das 2–Fluorbenzoat lediglich Produktspuren. Ein zusätzlicher Chlor– oder Trifluormethylsubstituent in der zweiten *ortho*–Position führt erneut zu guten Umsätzen und zeigt, dass ein gewisser σ–Elektronenzug zur effizienten Decarboxylierung benötigt wird.

Alle Ergebnisse zur Übergangsmetall–katalysierten decarboxylierenden Allylierung von Allylbenzoaten sind im nachfolgenden Manuskriptentwurf enthalten. Die Optimierung des Palladium–Katalysators und die Untersuchungen zur Anwendungsbreite erfolgten durch Herrn Pfister. Mein Beitrag bestand in den ersten Machbarkeitsstudien dieser Reaktion und der anschließenden Entwicklung des Nickel–Katalysators. Das Verfassen des Manuskripts erfolgte gemeinsam.

COMMUNICATION

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Synthesis of Allyl Arenes via Catalytic Decarboxylation of Allyl Benzoates

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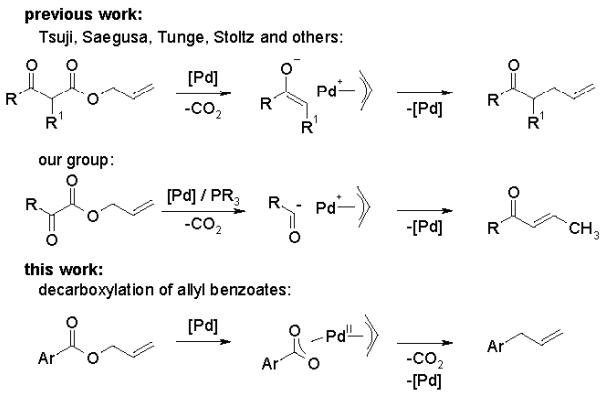
Abstract. A catalyst system consisting of $Pd_2(dba)_3$ and P(*p*-Tol)$_3$ was found to efficiently promote the decarboxylation of allyl benzoates with formation of allyl arenes. This catalytic C–O activation followed by extrusion of CO_2 and C–C bond formation represents a sustainable alternative to traditional waste-intensive cross-couplings. The scope of the transformation includes allyl and cinnamyl esters of various ortho-substituted benzoic acids. For particularly activated substrates, the palladium catalyst can optionally be replaced by an inexpensive nickel complex.

Keywords: allylation; decarboxylation; homogeneous catalysis; nickel; palladium

Over the past decades, transition metal-catalyzed cross-coupling reactions have become established as powerful tools for the regioselective formation of C–C bonds.[1] In redox-neutral transformations, coupling occurs between a carbon electrophile and a carbon nucleophile, usually an organometallic reagent. However, the synthetic value of such transformations depends on the availability and stability of the starting materials, which are normally synthesized in additional, waste-intensive steps. In recent years, the interest in sustainable and salt-free alternatives has grown considerably, and the use of cheap and easily available carboxylic acids as coupling partners has received tremendous attention.[2]

In decarboxylative couplings, organometallic reagents are replaced by simple carboxylates as the nucleophilic coupling partner. This concept has found application in the synthesis of biaryls[3] and aryl ketones,[4] and for introducing allyl and benzyl groups.[5] The catalytic activation of C–O bonds has allowed replacing ecologically questionable organohalides by ethers or carboxylates as the carbon electrophiles. Prominent examples include Tsuji-Trost allylations of allyl esters,[6] as well as Ni-catalyzed cross-couplings of anisoles or aryl pivalates with organometallic reagents.[7]

The two innovative concepts of C–O activation and decarboxylative coupling are combined in the catalytic decarboxylation of allyl carboxylates (Scheme 1, top). This reaction type was pioneered by the groups of Tsuji[8] and Saegusa,[9] and led to synthetic maturity by Tunge,[2c,10] Stoltz,[11] and others. However, its scope has long remained limited to activated structures that, upon decarboxylation, lead to stabilized carbanions, e.g. enolates.[9] Such carboxylate substrates, e.g. β-oxoesters or dialkyl malonates, readily extrude CO_2 even without a catalyst. Only recently, the reaction concept was extended to a class of non-activated carboxylates. Thus, a combination of palladium and nucleophilic organocatalysts was shown to catalyze the conversion of allyl α-oxocarboxylates into the corresponding α,β-unsaturated ketones in a decarboxylation/isomerization sequence (Scheme 1, center).[12]



Scheme 1. Decarboxylative allylation of allyl esters.

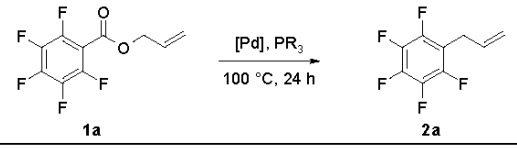
It would be highly desirable to use a related reaction concept also for the decarboxylative allylation of non-activated carboxylic acids, e.g. simple benzoic acids. The allyl benzene scaffold is a common structural motif,[13] and the allyl moiety is a versatile anchor for further derivatization.[14] However, the only example of an allyl arene

synthesis via decarboxylative coupling is the reaction of dimethoxybenzoates with allyl halides by Liu et al., which calls for an elaborate palladium/copper catalyst system and three equivalents of silver carbonate.[5a]

We herein present the first example of a decarboxylative allylation of benzoates that requires only a catalytic amount of metal and no stoichiometric additive, thus generating volatile CO_2 as the only byproduct.

We started the catalyst development by using allyl pentafluorobenzoate as a model substrate, since this benzoic acid decarboxylates easily in the presence of palladium catalysts that are also known to efficiently insert into allyl-C–O bonds.[15] With Liu's catalyst system, the allyl benzene was observed in only 31% yield, along with pentafluorobenzene. The monometallic palladium catalyst that had been employed in the decarboxylative allylation of α-oxocarboxylates (2.5 mol% $Pd_2(dba)_3$ / 25 mol% P(*p*-Tol)$_3$) gave only 7% yield (Table 1, entry 1).

Table 1. Optimization of the reaction conditions.[a]



1a **2a**

#	Catalyst	PR_3 (mol%)	Solvent	Yield [%][b]
1	$Pd_2(dba)_3$	P(*p*-Tol)$_3$ (25)	toluene	7
2	"	P(*p*-Tol)$_3$ (10)	"	29
3	"	P(*p*-Tol)$_3$ (5)	"	34
4	"	P(*p*-Tol)$_3$ (2.5)	"	42
5	"	-	"	29
6	$Pd(PPh_3)_4$	-	"	7
7	$Pd(OAc)_2$	P(*p*-Tol)$_3$	"	28
8	$PdCl_2$	"	"	0
9	$Pd(acac)_2$	"	"	0
10	$Pd_2(dba)_3$	"	anisole	50
11	"	"	1,4-dioxane	73
12	"	"	diglyme	34
13	"	"	NMP	43
14	"	"	DMSO	21
15	"	PPh_3	1,4-dioxane	35
16	"	P(*p*-F-C_6H_4)$_3$	"	27
17	"	P(*p*-MeO-C_6H_4)$_3$	"	25
18	"	P(2-furyl)$_3$	"	58
19	"	PCy_3	"	15
20	"	P(*t*Bu)$_3$	"	9
21[c]	"	P(*p*-Tol)$_3$	"	99
22[d]	"	"	"	13
23	-	P(*p*-Tol)$_3$	"	0

[a] Reaction conditions: **1a** (0.50 mmol), palladium (5 mol%), PR_3 (2.5 mol% unless specified), solvent (2.5 mL), N_2 atmosphere, 100 °C, 24 h. [b] Yields were determined by GC analysis using *n*-tetradecane as internal standard. [c] 110 °C. [d] 90 °C.

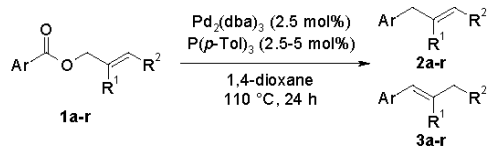
However, the yields increased when lowering the amount of P(*p*-Tol)$_3$, so that with 2.5 mol%, 42% of **2a** were obtained. Even lower phosphine amounts gave inferior results (Table 1, entries 1-5). Systematic variation of the Pd catalyst revealed that $Pd_2(dba)_3$ is optimal, although $Pd(PPh_3)_4$ and $Pd(OAc)_2$ are also active (Table 1, entries 6-9). Control experiments confirmed that the reaction does not take place in the absence of palladium (Table 1, entry 23).

Changing the solvent to 1,4-dioxane gave a decisive step-up in the yields, whereas other solvents were less effective (Table 1, entries 10-14). In comparison to other triaryl phosphines (Table 1, entries 15-18) and trialkyl phosphines (Table 1, entries 19-20), P(*p*-Tol)$_3$ gave the best results. The reaction temperature also has a profound influence on the reaction outcome. At the optimum temperature of 110 °C, **2a** was obtained in near-quantitative yield (Table 1, entry 21). It is remarkable that double-bond migration, as occurs quantitatively in the case of α-oxocarboxylates, is not observed.

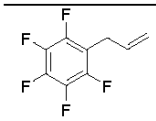
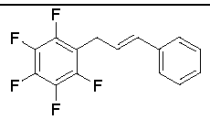
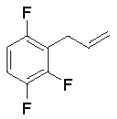
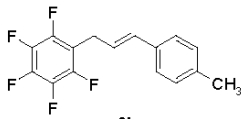
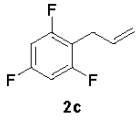
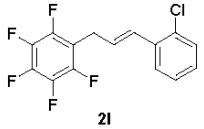
Having thus identified an efficient catalytic system, we next investigated the scope of the new reaction. As can be seen from Table 2, various substituted allyl benzoates could be converted to the corresponding allyl benzenes in good to excellent yields. It is not surprising that the scope with regard to the benzoic acids remains limited to substrates that can be easily decarboxylated with palladium catalysts.[15] *ortho*-Nitro benzoates and other substrates bearing only one substituent in the *ortho*-position were unreactive. Polyfluorinated arenes gave particularly high yields, and methoxy-substituted arenes were also smoothly converted (**2f, g**).

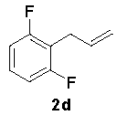
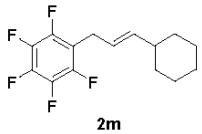
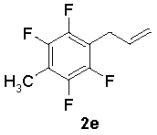
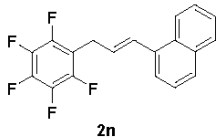
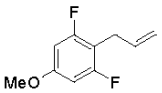
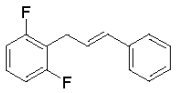
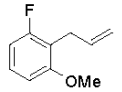
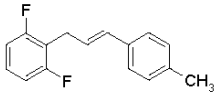
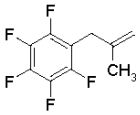
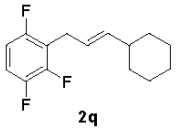
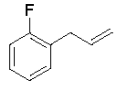
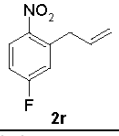
On the allyl side, several substituents were tolerated both in the 2- and 3-positions. Bulky substituents such as 3-cyclohexyl groups (**2m, q**) seem to hamper the reaction, whereas 3-phenyl groups lead to even better yields.

Table 2. Scope of the decarboxylation.[a]



1a-r **2a-r** **3a-r**

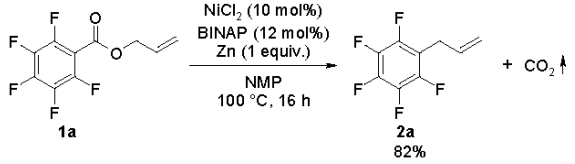
Product	Yield [%] (**2**:**3**)	Product	Yield [%] (**2**:**3**)
 **2a**	88 (>99:1)	 **2j**	99 (>99:1)
 **2b**	68[b] (>99:1)	 **2k**	97 (>99:1)
 **2c**	76[c] (97:3)	 **2l**	92 (99:1)

 2d	92 (98:2)	 2m	22 (96:4)
 2e	61[d] (99:1)	 2n	87 (>99:1)
 2f	99[b] (97:3)	 2o	99[f] (98:2)
 2g	66[e] (97:3)	 2p	97[f] (98:2)
 2h	87 (>99:1)	 2q	tr.[f]
 2i	0	 2r	0

[a] Reaction conditions: Allyl ester **1a-p** (1.00 mmol), $Pd_2(dba)_3$ (2.5 mol%), P(*p*-Tol)$_3$ (2.5 mol%), 1,4-dioxane (4 mL), N_2 atmosphere, 110 °C, 24 h, isolated yields, product ratios were determined by ^{19}F-NMR and GC analysis. [b] 4 mol% P(*p*-Tol)$_3$. [c] 5 mol% P(*p*-Tol)$_3$. [d] 3.75 mol% P(*p*-Tol)$_3$. [e] 5 mol% $Pd_2(dba)_3$, 5 mol% P(*p*-Tol)$_3$. [f] 130 °C.

Double-bond migration with formation of **3** was observed in less than 4% yield for substrate **2l**, which bears a cyclohexyl-substituted allyl group, and in even smaller amounts for all other products.

We next investigated whether this transformation is restricted to palladium catalysts only. Nickel(0) complexes appeared to be promising candidates, since they had successfully been used in C–O activation.[7] Indeed, a systematic survey revealed that allyl pentafluorobenzoate can efficiently be decarboxylated by a Ni^0 catalyst generated in situ from nickel(II) chloride, BINAP, and zinc powder (see the Supporting Information, Table S1). With this system, **2a** was obtained in 82% yield at 100 °C in NMP (Scheme 2).



Scheme 2. Nickel-catalyzed decarboxylative allylation of pentafluorobenzoates.

In conclusion, the advantageous concept of forming C–C bonds by catalytic ester decarboxylation was successfully employed for benzoic acid substrates. In the presence of a $Pd_2(dba)_3$ / P(*p*-Tol)$_3$ catalyst, various allyl arenes were synthesized in good yields, along with CO_2 as the only byproduct. Particularly activated substrates can also be converted by inexpensive nickel catalysts. Further catalyst development aiming at extending this sustainable transformation to the entire range of allyl benzoates is currently underway.

Experimental Section

General procedure for the palladium-catalyzed decarboxylative allylation: A 20 mL vessel was charged with $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol) and tri-*p*-tolylphosphine (7.76 mg, 0.025 mmol) and the vessel was brought under an atmosphere of dry nitrogen. 1,4-dioxane (4 mL) and allyl 2,3,4,5,6-pentafluorobenzoate (**1a**, 252 mg, 1.00 mmol) were added via syringe and the mixture was stirred at 110 °C for 24 h. After cooling to room temperature, the mixture was diluted with *n*-pentane (20 mL), washed with aqueous 1N NaOH (3 x 20 mL), water (20 mL) and brine (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed at ambient pressure and the products **2a-r** were isolated from the residue by flash column chromatography (SiO_2, Et_2O/*n*-pentane gradient).

Synthesis of allyl 2,3,4,5,6-pentafluorobenzene (2a): Following the general procedure, compound **2a** [CAS: 1736-60-3] was synthesized from allyl 2,3,4,5,6-pentafluorobenzoate (**1a**, 252 mg, 1.00 mmol). The product was obtained as a colorless liquid (183 mg, 879 µmol, 88 %). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.82 - 5.96 (m, 1 H), 5.03 - 5.16 (m, 2 H), 3.45 (dt, *J*=6.4, 1.7 Hz, 2 H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 145.1 (m), 139.8 (m), 137.2 (m), 132.9 (s), 116.8 - 117.2 (m), 112.8 - 113.4 (m), 26.3 (d, *J*=1.47 Hz) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -144.23 – -144.05 (m, 1 F), -157.73 – -157.38 (m, 1 F), -163.04 – -162.75 (m, 1 F) ppm. IR (NaCl) ν = 1655, 1643, 1503, 1443, 1415, 1315, 1299, 1219, 1123, 1011, 983, 911, 895, 752, 692, 624 cm^{-1}. HRMS-EI (TOF) m/z: [M$^+$] Calcd. for $C_9H_5F_5$: 208.0311. Found 208.0319. Anal. Calcd. for $C_9H_5F_5$: C, 51.94; H, 2.42. Found C, 52.20; H, 2.59.

Nickel-catalyzed decarboxylative allylation of 1a: A crimp-cap reaction vessel was charged with nickel(II) chloride (13.0 mg, 0.10 mmol), BINAP (76.2 mg, 0.12 mmol) and zinc powder (65.4 mg, 1.00 mmol). Under an inert atmosphere, degassed NMP (2 mL) and **1a** (252 mg, 1.00 mmol, 183 µL) were added via syringe. The reaction mixture was stirred at 100 °C for 16 h and then cooled to room temperature. The slight pressure build-up caused by the partially dissolved CO_2 was carefully released by piercing the septum with a syringe needle before uncapping. Pentane (20 mL) was added, and the mixture was washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated (40 °C). The crude product was further purified by flash chromatography (SiO_2, pentane), yielding the allyl benzene **2a** as colorless liquid (171 mg, 0.82 mmol, 82%). The analytical data matched those described for allyl 2,3,4,5,6-pentafluorobenzene [CAS: 1736-60-3].

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4.1.7. Nickel–katalysierte decarboxylierende Biarylsynthese

Zur genaueren Untersuchung der Nickel–katalysierten Decarboxylierung aromatischer Benzoesäuren und zur Evaluierung geeigneter Substrate für die decarboxylierende Kreuzkupplung erfolgten nun zunächst Protodecarboxylierungsstudien freier Carbonsäuren mit Nickel(II)–Katalysatoren. Da Nickel(0)–Katalysatoren in C(Allyl)–O und auch C(Aryl)–O Bindungen insertieren können (siehe 2.2.4, S. 21) und nun auch erstmals die Nickel–katalysierte Decarboxylierung aromatischer Benzoesäuren beobachtet wurde, sollte anschließend die Entwicklung eines monometallischen Nickel–Katalysators erfolgen, der die decarboxylierende Biarylsynthese ausgehend von einfachen Benzoesäurearylestern ermöglicht.

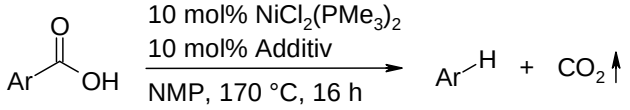
4.1.7.1. Protodecarboxylierung aromatischer Carbonsäuren

In ersten Reaktionen konnte Frau Dr. Florence Collet bereits zeigen, dass die bis–*ortho*–substituierte 2,6–Dimethoxybenzoesäure mit $NiCl_2(PMe_3)_2$ protodecarboxyliert werden kann. In eigenen Untersuchungen wurde diese mit 10 mol% $NiCl_2(PMe_3)_2$ in NMP bei 170 °C quantitativ zum 1,3–Dimethoxybenzol umgesetzt (Tabelle 7, Eintrag 1).

Die bereits bei der Nickel–katalysierten decarboxylierenden Allylierung umgesetzte 2,6–Difluorbenzoesäure (siehe 4.1.6, S. 55) konnte unter diesen Reaktionsbedingungen ebenfalls fast vollständig umgesetzt werden (Eintrag 2). Die 2–Fluor–6–Methoxybenzoesäure lieferte hingegen lediglich eine Ausbeute von 21% (Eintrag 3) und die monosubstituierte 2–Methoxybenzoesäure zeigte keinerlei Reaktion (Eintrag 4). Unter den monosubstituierten Benzoesäuren decarboxylierte nur die 2–(Dimethylamino)benzoesäure und lieferte das *N*,*N*–Dimethylanilin in 45% Ausbeute (Eintrag 5). Nitrobenzoesäuren und auch die getesteten Nicotin– und Isonicotinsäuren zeigten unter den gegebenen Bedingungen keinerlei Reaktivität (Einträge 6–9).

Mit dem Zusatz organischer Säuren konnte die Protodecarboxylierungsrate signifikant gesteigert und die Ausbeute des *N*,*N*–Dimethylanilins in Anwesenheit von 10 mol% Trifluoressigsäure auf 83% gesteigert werden (Eintrag 11). Dies deutet darauf hin, dass möglicherweise nicht die Decarboxylierung selbst, sondern die Protonolyse des Aryl–Nickel–Intermediates entscheidend für die Bildung der Protodecarboxylierungsprodukte ist.

Tabelle 7: Nickel–katalysierte Protodecarboxylierung aromatischer Carbonsäuren.



4.1.7-1 **4.1.7-2**

Eintrag	Carbonsäure	Additiv	4.1.7–2 [%]
1	2,6–Dimethoxybenzoesäure	–	quantitativ
2	2,6–Difluorbenzoesäure	–	88
3	2–Fluor–6–Methoxybenzoesäure	–	21
4	2–Methoxybenzoesäure	–	–
5	2–(Dimethylamino)benzoesäure	–	45
6	2–Nitrobenzoesäure	–	–
7	4–Nitrobenzoesäure	–	–
8	Pyridin–3–carbonsäure	–	–
9	Pyridin–4–carbonsäure	–	–
10	2–(Dimethylamino)benzoesäure	HOAc	62
11	2–(Dimethylamino)benzoesäure	TFA	83

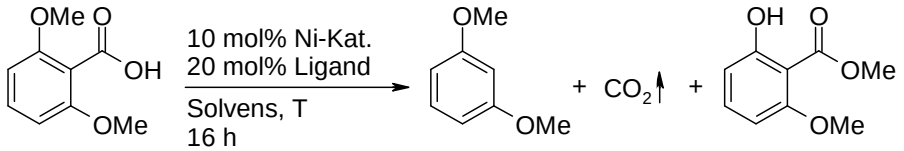
Reaktionsbedingungen: 0.50 mmol der Carbonsäure, 0.05 mmol $NiCl_2(PMe_3)_2$, 0.05 mmol Additiv, 1 mL NMP, 170 °C, 16 h. Ausbeuten wurden gaschromatographisch mit *n*–Tetradecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

Da die 2,6–Dimethoxybenzoesäure im ersten Screening die höchste Reaktivität zeigte, wurde der Einfluss des Lösungsmittels und des Ligandensystems an dieser Modellverbindung näher untersucht (Tabelle 8). Während die Protodecarboxylierung in DMF ebenfalls quantitativ verläuft (Eintrag 2), gibt sie im unpolaren Mesitylen, welches gewöhnlich für Nickel–katalysierte C–O Aktivierungen genutzt wird, eine deutlich schlechtere Ausbeute von nur 49% (Eintrag 3). Zudem kommt es zur unerwünschten C–O Aktivierung des Methoxysubstituenten, wodurch das Startmaterial in den inaktiven Methylester überführt wird. Vollständig verläuft die Protodecarboxylierung in Lösungsmittelgemischen aus NMP und Mesitylen (Einträge 4 & 5), wobei die Ausbeute der Protodecarboxylierung bei niedrigeren Temperaturen abnimmt und bei 150 °C gar keine Reaktion mehr zu beobachten ist (Einträge 6 & 7).

Im Gegensatz zur decarboxylierenden Allylierung zeigte ein umfangreiches Ligandenscreening, dass die Protodecarboxylierung nur in Gegenwart kleiner, elektronenreicher Phosphanliganden verläuft (Tabelle 4, Einträge 8 & 9). Entgegen des

Trends führte allerdings auch das sterisch gehinderte P^{t}Bu$_3$ zu geringen Produktausbeuten (Eintrag 12), während die Liganden PCy$_3$ und dcype, die gewöhnlich in Nickel–katalysierten Kreuzkupplungsreaktionen verwendet werden (vgl. 2.2.4, S. 21), und auch *N*–Donorliganden fast ausschließlich die Bildung des Methylesters begünstigen und in der Protodecarboxylierung zumeist inaktiv sind (Einträge 11, 14–16). Mono– und bidentate Arylphosphane wurden ebenfalls getestet, zeigten allerdings keine Reaktivität und wurden deshalb auch nicht in der Tabelle erwähnt.

Tabelle 8: Nickel–katalysierte Protodecarboxylierung der 2,6–Dimethoxybenzoesäure.



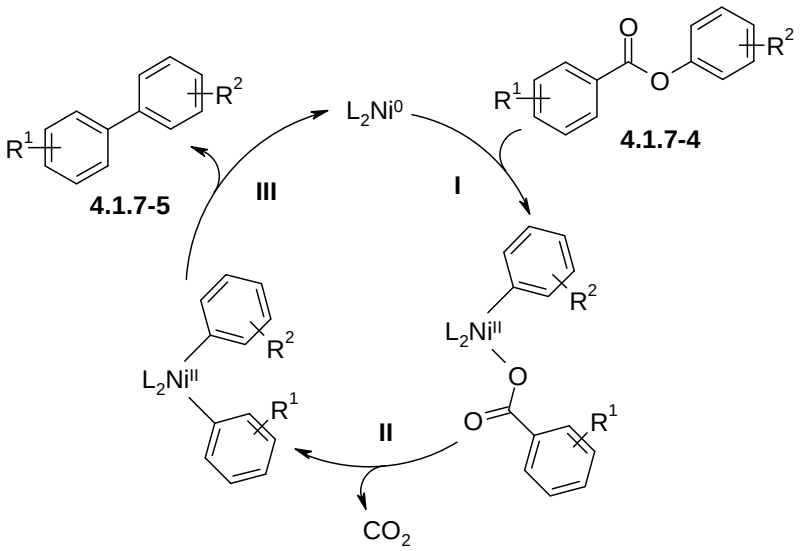
4.1.7-1a **4.1.7-2a** **4.1.7-3**

Eintrag	Ni–Quelle	Ligand	Solvens	T [°C]	4.1.7–2a [%]	4.1.7–3 [%]
1	$NiCl_2(PMe_3)_2$	–	NMP	170	quant.	–
2	"	–	DMF	"	quant.	–
3	"	–	Mes	"	49	10
4	"	–	NMP/Mes 1:1	"	quant.	–
5	"	–	NMP/Mes 1:3	"	quant.	–
6	"	–	"	160	47	–
7	"	–	"	150	–	–
8	$NiCl_2$	P^{n}Bu$_3$	"	170	47	12
9	"	PEt$_2$Ph	"	"	39	17
10	"	P^{i}Pr$_3$	"	"	–	32
11	"	PCy$_3$	"	"	–	28
12	"	P^{t}Bu$_3$	"	"	8	–
13	"	dmpe	"	"	8	24
14	"	dcype	"	"	–	–
15	"	TMEDA	"	"	–	24
16	"	bipy	"	"	–	16
17	"	–	"	"	–	–

Reaktionsbedingungen: 0.50 mmol 2,6–Dimethoxybenzoesäure, 10 mol% der Ni–Quelle, 20 mol% eines monodentaten Liganden bzw. 10 mol% eines bidentaten Liganden, 1 mL Lösungsmittel, 16 h. Ausbeuten wurden gaschromatographisch mit *n*–Tetradecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

4.1.7.2. Transformationen von Naphthylbenzoaten

Eine besonders nachhaltige Alternative zur traditionellen Kreuzkupplung organometallischer Verbindungen ist die Transformation von Carbonsäureestern, bei der lediglich CO_2 als leichtflüchtiges Nebenprodukt freigesetzt wird. Dieses Reaktionskonzept wurde bereits in den vorherigen Kapiteln am Beispiel decarboxylierender Allylierungen und Benzylierungen demonstriert. Mit den gewonnenen Erkenntnissen der Nickel–katalysierten Allylierung und Protodecarboxylierung erfolgten nun Untersuchungen zur Biarylsynthese ausgehend von Benzoesäurearylestern. Mechanistisch sollte der Nickel(0)–Katalysators dabei zunächst in die C(Aryl)–O Bindung der Esterfunktionalität insertieren (Schema 37, **I**). Die anschließende Nickel–katalysierte Extrusion von CO_2 führt zur Diaryl–Nickel(II)–Spezies (**II**), die das gewünschte Biaryl reduktiv eliminiert und den Nickel(0)–Katalysator regeneriert (**III**).



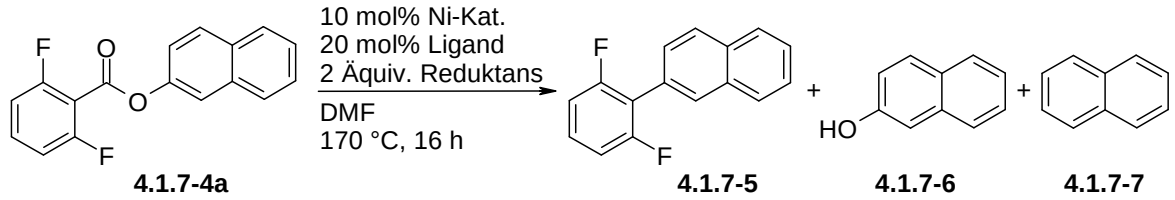
Schema 37: Mechanistische Überlegungen zur Nickel–katalysierten Biarylsynthese.

Da die 2,6–Difluorbenzoesäure in Gegenwart von Nickel(II)–Verbindungen bei 170 °C fast vollständig decarboxyliert und Naphth–2–ylester besonders gute Substrate zur Nickel–katalysierten C(Aryl)–O Aktivierung darstellen (vgl. 2.2.4, S. 21),[147] wurde der 2,6–Difluorbenzoesäurenaphth–2–ylester als Modellsubstrat anschließender Studien gewählt. Diese Verbindung besitzt neben der Esterfunktionalität zudem keine weiteren aktivierbaren C–O Bindungen, wie es etwa beim 2,6–Dimethoxybenzoat der Fall ist.

Erhitzt man diesen präformierten Ester in Gegenwart des Protodecaroxylierungskatalysators $NiCl_2(PMe_3)_2$ für 16 h auf 170 °C, beobachtet man lediglich die energetisch begünstigte, aber unerwünschte C(Acyl)–O Aktivierung (siehe 2.2.4)

und die damit verbundene Bildung von 2–Naphthol in 17% Ausbeute (Tabelle 9, Eintrag 1). Zur effektiven Reduktion der Nickel(II) Verbindung wurde Zink zugesetzt. Dies führte neben der Bildung von Naphthol auch in 2% Ausbeute zum gewünschten Produkt (Eintrag 2).

Tabelle 9: Nickel–katalysierte Aktivierung präformierter Naphthylester.



4.1.7-4a **4.1.7-5** **4.1.7-6** **4.1.7-7**

Eintr.	**Ni–Quelle**	**Ligand**	**Reduktans**	**4.1.7–5 [%]**	**4.1.7–6 [%]**	**4.1.7–7 [%]**
1	$NiCl_2(PMe_3)_2$	–	–	–	17	–
2	"	–	Zink	2	31	–
3	"	P^nBu_3	"	5	28	4
4	"	PCy_3	"	8	39	–
5	"	PCy_2Ph	"	9	34	3
6	"	dcype	"	6	35	10
7	$NiCl_2$	PCy_2Ph	"	–	11	–
8	"	$PCy_2Ph + PMe_3$	"	5	27	–
9	$Ni(cod)_2$	PCy_2Ph	–	4	7	–
10	"	PMe_3	–	2	9	–
11	"	$PCy_2Ph + PMe_3$	–	5	14	–

Reaktionsbedingungen: 0.50 mmol des Naphthylesters, 10 mol% der Nickel–Quelle, 20 mol% eines monodentaten oder 10 mol% eines bidentaten Liganden, 1.00 mmol des Reduktionsmittels, 1 mL DMF, 170 °C, 16 h. Ausbeuten wurden gaschromatographisch mit *n*–Tetradecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

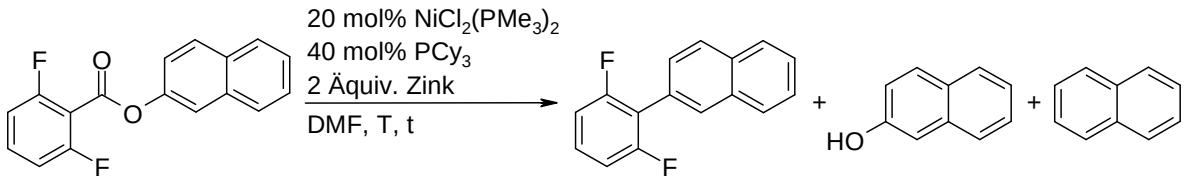
Die Anwesenheit zusätzlicher elektronenreicher mono– oder bidentater Alkylphosphane ermöglicht eine leichte Ausbeutensteigerung auf 9% (Einträge 3–6), wobei nun auch geringe Mengen Naphthalin als weiteres Nebenprodukt der C(Aryl)–O Spaltung detektiert wurden. Die Kontrollreaktion mit einem *in situ* generierten Katalysatorsystem aus $NiCl_2$ und PCy_2Ph zeigte keinerlei Produktbildung (Eintrag 7), während der Zusatz von PMe_3 erneut zu 5% Ausbeute führt und auf eine besondere Rolle beider Ligandensysteme hindeutet (Eintrag 8). Umgeht man den Reduktionsschritt der Nickel(II)–Vorstufe durch den direkten Einsatz von

$Ni(cod)_2$, erhält man vergleichbare Produktausbeuten um 5% und ebenfalls die Bildung von 2–Naphthol (Einträge 9–11).

Da das Lösungsmittel DMF zu deutlich homogeneren, klaren Reaktionsgemischen führte, wurden die Reaktionen der Naphthylbenzoate nicht in NMP durchgeführt. Dennoch erfolgten stets auch Kontrollreaktionen in NMP bzw. Lösungsmittelgemischen von NMP und Mesitylen. Diese führten mit reinem NMP meist zu geringfügig schlechteren Ausbeuten und mit den Lösungsmittelgemischen nur zur Nebenproduktbildung.

Erhöht man die Menge des Nickel–Katalysators, so steigt die Produktausbeute und die Menge des detektierten 2–Naphthols ebenfalls proportional an (Tabelle 10, Eintrag 1). Bei der Absenkung der Reaktionstemperatur kommt es nicht, wie vermutet, zum Erliegen der Reaktion, sondern zur Steigerung der Produktausbeute. Selbst bei 70 °C können mit einer Katalysatormenge von 20 mol% Ausbeuten von 25% erzielt werden (Eintrag 4).

Tabelle 10: Temperaturabhängigkeit der Nickel–katalysierten Esteraktivierung.



4.1.7-4a **4.1.7-5** **4.1.7-6** **4.1.7-7**

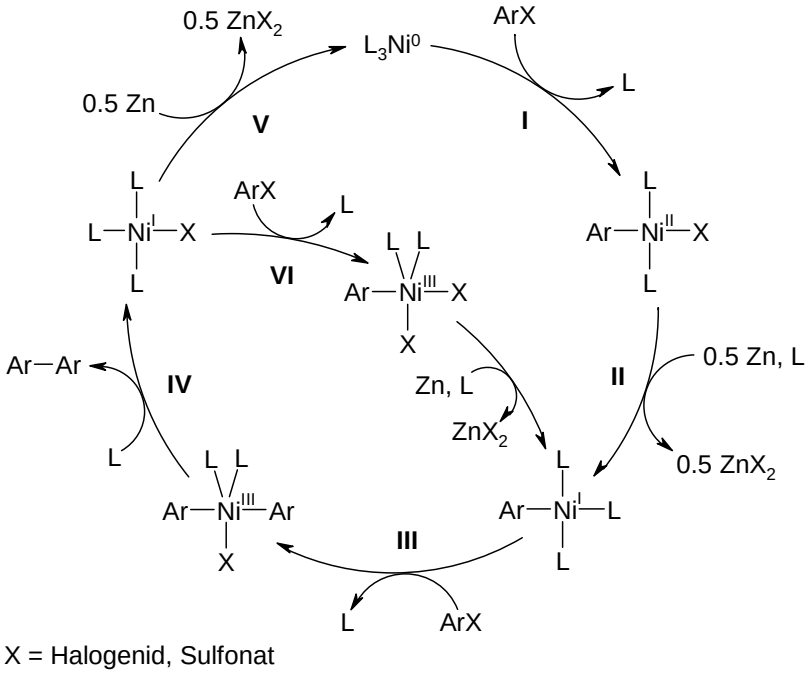
Eintrag	T [°C]	Zeit	4.1.7–5 [%]	4.1.7–6 [%]	4.1.7–7 [%]
1	170	16h	18	46	5
2	100	"	20	32	2
3	80	"	27	27	–
4	70	"	25	27	–
5	60	"	10	16	–
6	50	48h	17	20	–
7[a]	70	16h	38	47	–

Reaktionsbedingungen: 0.50 mmol des Esters, 20 mol% $NiCl_2(PMe_3)_2$, 40 mol% PCy_3, 1 mL DMF, 16 h. a) 50 mol% $NiCl_2(PMe_3)_2$, 0.50 mmol PCy_3, 1.00 mmol Zink, 2 mL DMF. Ausbeuten wurden gaschromatographisch mit *n*–Tetradecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

Die extrem niedrige Reaktionstemperatur deutet auf einen alternativen Reaktionsmechanismus hin, der keinen Decarboxylierungsschritt enthält. Da das Startmaterial komplett umgesetzt und 2–Naphthol stets in äquimolaren Mengen gebildet wird, könnte die

Produktbildung möglicherweise zwei Estermoleküle benötigen, die an jeweils unterschiedlichen C–O Bindungen der Esterfunktioalität aktiviert und dann gekuppelt werden. Das eine Substratmolekül könnte so an der C(Acyl)–O Bindung gespalten und decarbonylierend in eine Aryl–Nickel–Spezies überführt werden, während das zweite Molekül an der C(Aryl)–O Bindung aktiviert wird. Eine anschließende reduktive Kupplung könnte, analog zur reduktiven Kupplung zweier Arylhalogenide, zum Biaryl führen.[139]

Vergleicht man die Studien zur reduktiven, Nickel–katalysierten Homokupplung von Arylhalogeniden, stößt man auf eine Vielzahl postulierter Mechanismen mit unterschiedlichen Elektronentransferprozessen und Oxidationsstufen des Katalysators.[139] Die Arbeiten von Bontempelli *et al.* beschreiben einen Mechanismus, der sowohl die Oxidationsstufen Ni^0/Ni^{II} als auch Ni^I/Ni^{III} enthält (Schema 38) und in ähnlicher Form auch bei der Transformation der Arylester vorliegen könnte.[154] Eine Nickel(0)–Spezies soll dabei zunächst oxidativ in ein Arylhalogenid insertieren und ein Aryl–Nickel(II)halogenid bilden (**I**). Dieses wird durch Zink zur Aryl–Nickel(I)–Verbindung reduziert (**II**), welche ein weiteres Arylhalogenid aktiviert und zur Diaryl–Nickel(III)–Spezies reagiert (**III**). Die reduktive Produkteliminierung führt zum Biaryl und einer Nickel(I)–Verbindung (**IV**), die mit Zink zum Nickel(0)–Komplex reduziert wird (**V**) oder ein weiteres Substratmolekül aktiviert (**VI**). Weiterführende Arbeiten durch Amatore und Jutand untermauern diesen Mechanismus mit umfangreichen elektrochemischen Untersuchungen.[155]



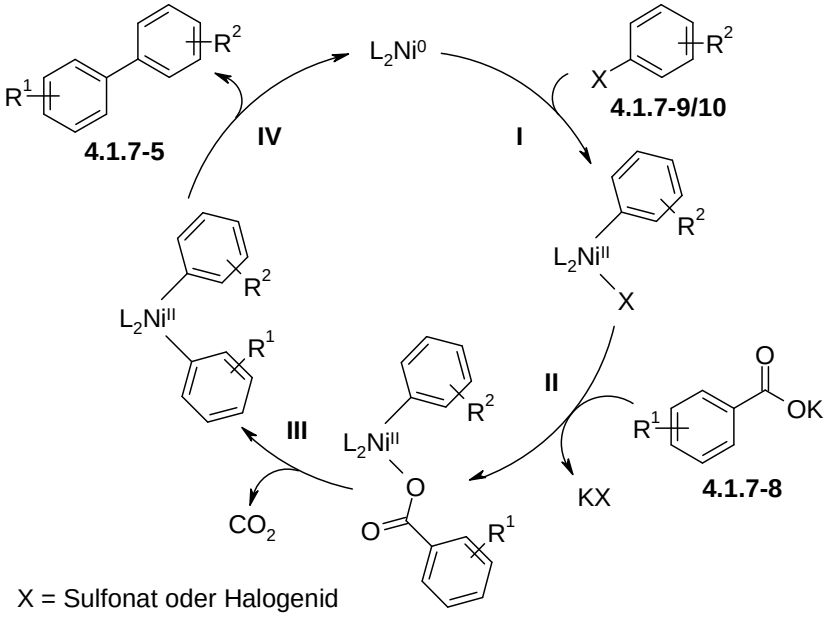
Schema 38: Mechanismus der reduktiven Kupplung von Arylhalogeniden.

Ob die Umsetzung der Arylbenzoate nun decarboxylierend oder über einen solchen alternativen Mechanismus mit den Oxidationsstufen Ni^0/Ni^{II} und Ni^I/Ni^{III} verläuft, müssen weiterführende Studien zeigen. Die eigenen Arbeiten zur Umsetzung der Benzoesäurearylester wurden an dieser Stelle aber eingestellt, um die decarboxylierende Kupplung von Kaliumbenzoaten mit Arylhalogeniden und –sulfonaten zu untersuchen, bei denen der Nickel–Katalysator keinen Carbonsäureester aktivieren muss.

4.1.7.3. Decarboxylierende Kupplung mit Sulfonaten

Am Beispiel der decarboxylierenden Allylierung von Allylbenzoaten konnte gezeigt werden, dass Nickel–Katalysatoren nicht nur gute Kupplungskatalysatoren sind, sondern auch die Decarboxylierung aromatischer Carbonsäuren ermöglichen. Diese duale Katalysatorfunktion sollte nun bei der decarboxylierenden Kreuzkupplung von Kaliumbenzoaten (**4.1.7–8**) mit Arylsulfonaten (**4.1.7–9**) und –halogeniden (**4.1.7.10**) eingehender untersucht werden und zur Entwicklung eines effizienten monometallischen Katalysatorsystems führen.

Mechanistisch würde diese Reaktion mit der Aktivierung des Arylhalogenides oder –sulfonats beginnen und eine Aryl–Nickel(II)–Verbindung bilden (Schema 39, **I**). Ein Anionenaustausch zum Aryl–Nickel(II)–carboxylat (**II**) mit anschließender Decarboxylierung würde dann zur Diaryl–Nickel(II)–Spezies führen (**III**), die das gewünschte Biaryl reduktiv eliminiert und den Nickel(0)–Katalysator regeneriert (**IV**).



Schema 39: Mechanismus der Nickel–katalysierten Kreuzkupplung von Kaliumbenzoaten.

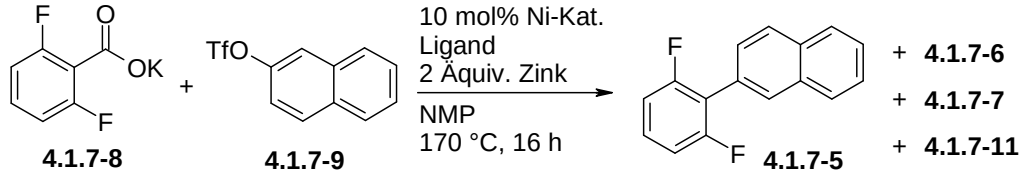
Die breits im vorherigen Kapitel angesprochene reduktive, Nickel–katalysierte Homokupplung von Arylhalogeniden oder –sulfonaten sollte die dabei am häufigsten zu beobachtende Konkurrenzreaktion darstellen (siehe Schema 38), welche durch die Wahl der Reationsbedingungen oder Ligandensysteme unterdrückt werden muss. Da die Rate solcher Homokupplungen enorm stark von der Natur der Abgangsgruppe abhängt (–I > –Br > –Cl >> $-OSO_2R$), wurde das 2–Naphthyltriflat zunächst als Modellsubstrat gewählt.

Erhitzt man dieses Triflat mit dem Kaliumsalz der 2,6–Difluorbenzoesäure in Gegenwart des besten Protodecarboxylierungskatalysators in NMP für 16 h auf 170 °C, erhält man das gewünschte Biaryl **4.1.7–5** in 4% Ausbeute, zusammen mit erheblichen Mengen der unerwünschten Spaltprodukte 2–Naphthol (**4.1.7–6**) und Naphthalin (**4.1.7–7**), sowie dem Homokupplungsprodukt 2,2‘–Binaphthalin (**4.1.7–11**) (Tabelle 11, Eintrag 1).

Der Zusatz mono– oder bidentater Phosphane führte zwar zur teilweise vollständigen Unterdrückung der Naphtholbildung, erhöht aber gleichzeitig auch die Ausbeuten an Naphthalin und Binaphthalin (Einträge 2–5). Der Wechsel vom $NiCl_2(PMe_3)_2$ hin zum simplen $NiCl_2$ führte direkt zur signifikanten Ausbeutesteigerung (Eintrag 6), sodass auch mit dieser Nickel–Quelle ein umfassendes Ligandenscreening erfolgte (Einträge 6–18). Während leicht elektronenreiche monodentate Phosphane zu schlechteren Produktausbeuten führen (Eintrag 9), ermöglichen elektronenärmere Phosphane gleiche Produktverteilungen wie PPh_3 (Eintrag 8). Liganden mit zusätzlichen π–Donoreigenschaften unterdrücken zwar die Naphthalin– und Binaphthalinbildung, führen aber dafür zur verstärkten Freisetzung von Naphthol (Eintrag 9). Ein erhöhter sterischer Anspruch resultiert ebenfalls in einer verstärkten Nebenproduktbildung, blockiert die Produktbildung aber nicht komplett (Einträge 10 & 11). Der Einsatz des bidentaten Liganden BINAP, der sich in der decarboxylierenden Allylierung als besonders aktiv zeigte, führt zu einer Produktverteilung, bei der das Biaryl und die Nebenprodukte jeweils in nahezu gleichen Mengen vorliegen (Eintrag 12). Dies ändert sich bei den anderen bidentaten Phosphanen, die die unerwünschte Naphtholbildung komplett unterdrücken, dafür aber das Binaphthalin verstärkt bilden (Einträge 13–16). Eine umgekehrte Reaktivität wird bei den *N*–Donorliganden Bipyridin und Terpyridin beobachtet, die neben dem gewünschten Biaryl nur die Naphtholbildung ermöglichen und die Naphthalin– und Binaphthalinbildung blockieren (Einträge 17 & 18). Kontrollreaktionen mit $NiCl_2$ alleine führten ebenfalls zur Bildung des gewünschten Biaryls in 7% Ausbeute, aber auch zu den drei

Nebenprodukte (Einträge 19 & 20). Die Nickelmenge hat dabei keinen Einfluss auf die Produktverteilung.

Tabelle 11: Nickel–katalysierte decarboxylierende Kupplung mit Aryltriflaten.



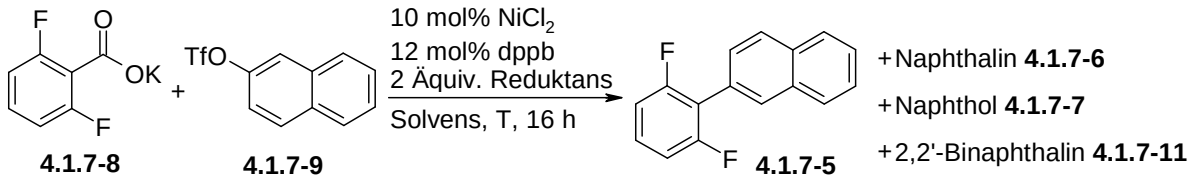
Eintr.	Ni–Quelle	Ligand	4.1.7–5 [%]	4.1.7–6 [%]	4.1.7–7 [%]	4.1.7–11 [%]
1	$NiCl_2(PMe_3)_2$	–	4	18	28	34
2	"	PCy_3	2	–	9	69
3	"	dcype	4	7	20	50
4	"	PPh_3	10	6	40	44
5	"	dppe	3	–	8	47
6	$NiCl_2$	PPh_3	20	13	38	16
7	"	P(*p*–Tol)$_3$	9	19	40	7
8	"	P(*p*–F–Ph)$_3$	19	13	34	16
9	"	P(*2*–Fur)$_3$	3	53	7	5
10	"	P(*o*–Tol)$_3$	10	28	32	33
11	"	JohnPhos	5	41	26	31
12	"	BINAP	21	11	32	23
13	"	dppp	6	–	29	59
14	"	dppb	15	–	19	64
15	"	dppf	9	–	32	57
16	"	XantPhos	12	–	22	55
17	"	bipy	3	61	–	–
18	"	terpy	15	41	7	–
19	"	–	7	21	36	25
20[a]	"	–	8	9	56	34

Reaktionsbedingungen: 0.50 mmol des Benzoats, 0.60 mmol des Triflats, 10 mol% der Nickel–Quelle, 0.10 mmol eines monodentaten oder 0.05 mmol eines bidentaten bzw. tridentaten Liganden, 1.00 mmol Zink, 1 mL NMP, 170 °C, 16 h. a) 30 mol% $NiCl_2$. Ausbeuten wurden gaschromatographisch mit *n*–Tetradecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

Nachfolgende Studien erfolgten mit dem bidentaten Liganden dppb (Tabelle 12), wobei zunächst das Substratverhältnis untersucht wurde. Dabei zeigte sich, dass ein Überschuss des

Aryltriflats keinen positiven Effekt auf die gewünschte Biarylbildung hat, sondern die Ausbeuten eher noch verschlechtert (Einträge 1–3). Wird das Benzoat hingegen im Überschuss eingesetzt, erhält man das Biaryl in 38% Ausbeute, zusammen mit Naphthalin und Binaphthalin in 12% bzw. 38% (Eintrag 4). Eine Verdünnung des Reaktionsgemisches führte insgesamt zu geringeren Ausbeuten (Einträge 5 & 6) und der Zusatz von Molsieben führte zu keinerlei Biarylbildung (Eintrag 7). Da Kontrollexperimente mit $NiCl_2$•$6H_2O$ oder Wasser als Additiv ebenfalls nur zu sehr geringen Produktausbeuten führten, ist der drastische Effekt der Molsiebe höchstwahrscheinlich nicht auf eine benötigte Wassermenge zurückzuführen.

Tabelle 12: Optimierung der Nickel–katalysierten Kupplung.



4.1.7-8 **4.1.7-9** **4.1.7-5**

Eintr.	**Substrat–verhältnis**	**Solvens**	**Reduktans**	**T [°C]**	**4.1.7–5 [%]**	**4.1.7–6 [%]**	**4.1.7–7 [%]**	**4.1.7–11 [%]**
1	1:2	NMP	Zink	170	15	8	57	72
2	1:1.5	"	"	"	18	–	40	65
3	1:1	"	"	"	19	–	10	54
4	1.5:1	"	"	"	**38**	–	12	38
5[a]	"	"	"	"	29	–	16	39
6[b]	"	"	"	"	7	26	20	13
7	"	NMP + MS4Å	"	"	–	28	31	5
8	"	DMF	"	"	**44**	–	–	48
9	"	DMSO	"	"	2	–	5	4
10	"	Diglyme	"	"	4	–	23	39
11	"	Mesitylen	"	"	–	–	14	23
14	"	NMP	Mangan	"	21	–	11	36
15	"	"	Magnesium	"	4	–	11	21
12	"	"	Zink	160	26	–	7	61
13	"	"	"	150	13	–	6	75

Reaktionsbedingungen: 0.50 mmol Ansatzgröße, 0.05 mmol $NiCl_2$, 0.12 mmol dppb, 1.00 mmol des Reduktionsmittels, 1 mL Lösungsmittel, 16 h. a) 2 mL NMP. b) 3 mL NMP. Ausbeuten wurden gaschromatographisch mit *n*–Tetradecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

Die Variation des Lösungsmittels zeigte, dass die Reaktion in DMF zu einer noch besseren Produktausbeute von 44% führt und neben dem Biaryl nur das Binaphthalin gebildet wird (Eintrag 8). In anderen Lösungsmitteln, darunter DMSO, Diglyme und Mesitylen, wurde nur eine geringe, oder überhaupt keine Produktbildung beobachtet (Einträge 9–11). Auch andere Reduktionsmittel wie Mangan und Magnesium führten zu schlechteren Ausbeuten (Einträge 12 & 13).

Während die Produktbildung bei einer Absenkung der Reaktionstemperatur rasch abnimmt, steigt die Ausbeute der reduktiven Homokupplung unterhalb von 150 °C stark an (Einträge 5 & 6). Diese stets konkurrierende Nebenreaktion stellt damit ein inhärentes Problem der gewünschten Kupplung dar, weshalb neben dem Aryltriflat nun auch weitere Kupplungspartner evaluiert wurden. Dabei zeigten Aryltosylate und –sulfamate eine etwa gleiche Produktverteilung wie die Aryltriflate und bei Reaktionen mit Arylmesylaten konnte keine Produktbildung, sondern lediglich die Spaltung des Naphthols beobachtet werden.

Die Verwendung von $Ni(cod)_2$ als Nickel(0)–Quelle führte ohne das Reduktionsmittel Zink nur zu geringen Umsätzen mit ebenfalls vergleichbaren Produktverteilungen. Auch das schnelle Aufheizen im Mikrowellenreaktor oder der Zusatz von Hilfbasen, darunter Chinolin, DBU, DABCO oder DMAP, führten zu keiner Ausbeutensteigerung. Da die Liganden immer nur eine der Nebenreaktionen unterdrücken konnten, wurden die Studien zur decarboxylierenden Kupplung mit Phenolderivaten an dieser Stelle beendet.

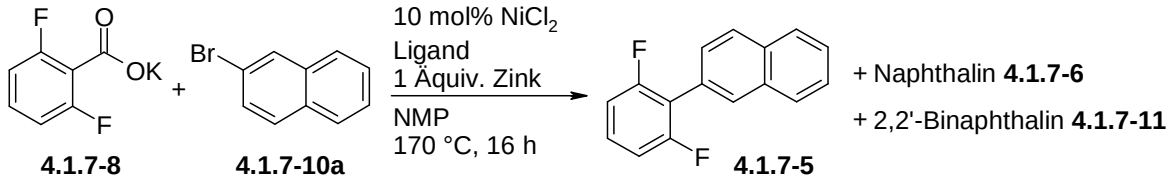
4.1.7.4. Decarboxylierende Kupplung mit Arylbromiden

Da die reduktive Homokupplung bei denen zur effektiven Decarboxylierung benötigten Temperaturen stets als Hintergrundreaktion abläuft, wurden nun direkt Arylhalogenide eingesetzt, bei denen kein Alkohol als Nebenprodukt einer unselektiven Substrataktivierung gebildet werden kann. Da die Homokupplung der Aryltriflate bereits effektiv durch den Einsatz von Bipyridin und Terpyridin unterdrückt werden konnte, erfolgten nun Reihenversuche mit Arylbromiden als Kupplungspartner.

Erhitzt man das Kaliumsalz der 2,6–Difluorbenzoesäure mit 2–Bromnaphthalin in Gegenwart von 10 mol% $NiCl_2$ und Bipyridin in NMP für 16 h auf 170 °C, erhält man das gewünschte Produkt nur in geringen Mengen und das dehalogenierte Naphthalin in etwa 80% Ausbeute (Tabelle 13, Einträge 2–4). Eine ganz andere Produktverteilung ergibt sich, wenn man Terpyridin als Ligandensystem wählt: Mit 10 mol% $NiCl_2$ und 5 mol% Terpyridin wird das gewünschte Biaryl in 53% Ausbeute gebildet (52% isolierte Ausbeute), aber zusammen

mit Naphthalin und Binaphthalin in jeweils etwa 25% (Eintrag 5). Erhöht man die Menge des Terpyridins auf 10 mol%, sinkt die Ausbeute des Biaryls auf 29% (Eintrag 6). Während das Naphthalin sogar in 66% gebildet wird, findet nun aber keine reduktive Homokupplung zum Binaphthalin statt. Eine weitere Erhöhung der Ligandenmenge auf 15 mol% setzt diesen Trend fort und führt nur noch zu einer Produktausbeute von 14% und 83% des dehalogenierten Naphthalins (Eintrag 7). Die Verwendung des Hexahydrats $NiCl_2$•6 H_2O oder auch der Zusatz von 20 mol% Wasser führte zum kompletten Erliegen der Kupplungsreaktion und zur quantitativen Dehalogenierung des 2–Bromtoluols.

Tabelle 13: Nickel–katalysierte decarboxylierende Kupplung mit 2–Bromnaphthalin.



4.1.7-8 **4.1.7-10a** **4.1.7-5**

Eintrag	Ligand	4.1.7–5 [%]	4.1.7–6 [%]	4.1.7–11 [%]
1	–	–	20	–
2	10% bipy	3	79	12
3	20% bipy	4	82	13
4	30% bipy	7	73	16
5	5% terpy	53	28	25
6	10% terpy	29	66	–
7	15% terpy	14	83	–

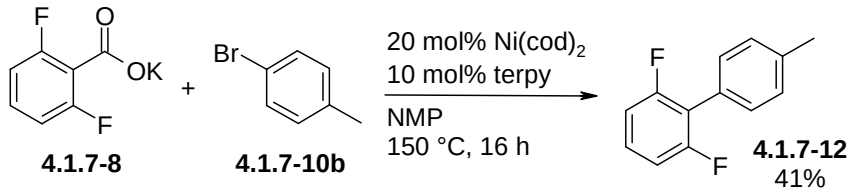
Reaktionsbedingungen: 0.75 mmol Benzoat, 0.50 mmol 2–Bromnaphthalin, 0.05 mmol $NiCl_2$, 0.50 mmol Zink, 2 mL NMP, 16 h. Ausbeuten wurden gaschromatographisch mit *n*–Tetradecan als interner Standard bestimmt und mit Responsefaktoren der Reinsubstanzen korrigiert.

Dieses Ergebnis wirft die Frage auf, wieso ein Unterschuss des Liganden zu höheren Produktausbeuten führt. Dies könnte einerseits damit zusammenhängen, dass unterschiedliche Nickel–Spezies zur effektiven Produktbildung benötigt werden, etwa ein Nickel(II)–System zur Decarboxylierung und eine von Terpyridin koordinierte Nickel(0)–Spezies zur Aktivierung und selektiven Kupplung des Arylbromids. Weiterhin besteht die Möglichkeit, dass mehrere Nickelatome von einem mehrzähnigen Ligandensystem koordiniert werden und es nur so zur direkten Interaktion der aktiven Zentren kommen kann. Fest steht, dass ein von drei *N*–Donoratomen koordinieres Nickelzentrum keine räumliche Möglichkeit zur

reduktiven Homokupplung der Arylbromide bietet und die Dehalogenierung als Nebenreaktion damit enorm an Bedeutung gewinnt.

In weiteren Ligandenscreenings wurden daher viele verschiedene Bipyridin– und Phenanthrolinderivate, sowie Terpyridin–ähnliche Substanzen auf ihre Reaktivität in der decarboxylierenden Kreuzkupplung hin untersucht. Dabei zeigte sich Terpyridin aber stets am aktivsten und auch am selektivsten.

Die Kupplung anderer Arylbromide führte selbst mit dem Liganden Terpyridin nur zu geringen oder gar keinen Produktausbeuten. Weitere Optimierungsarbeiten zeigten aber, dass auch 4–Bromtoluol (**4.1.7–10b**) mit 20 mol% $Ni(cod)_2$ und 10 mol% Terpyridin in 41% Ausbeute in das entsprechende Biaryl **4.1.7–12** überführt und isoliert werden kann (Schema 40).



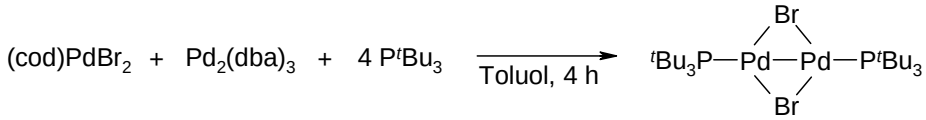
Schema 40: Nickel–katalysierte decarboxylierende Kreuzkupplung mit 4–Bromtoluol.

Zukünftige Arbeiten müssen zeigen, ob die Nickel–katalsierte decarboxylierende Kreuzkupplung zur synthetischen Reife gebracht werden kann. Dabei wird die Entwicklung neuer *N*–Donorliganden eine zentrale Rolle spielen. Nur die effektive Unterdrückung aller Nebenreaktionen kann zur selektiven Produktbildung und damit zur Entwicklung einer ressourcenschonenden Alternative klassischer Kreuzkupplungsreaktionen führen.

4.1.8. Palladium–katalysierte Isomerisierung von Allylestern

4.1.8.1. Hintergründe

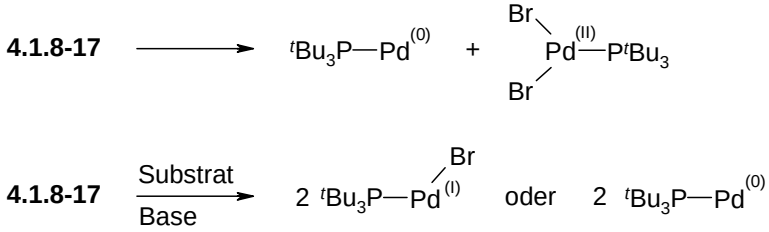
Erstmals beschrieben Mingos *et al.* 1996 die Synthese des Brom–verbrückten Palladium(I)–Dimers [Pd(μ–Br)(P^tBu_3)]$_2$ (Schema 41, **4.1.8–17**).[156–158] Die Kristallstrukturanalyse deutet, aufgrund des geringen Abstands, auf eine Pd–Pd Bindung hin, die durch zwei verbrückende Bromatome stabilisiert wird. Die Verbindung ist ein charakteristisch grüner, kristalliner Feststoff, der in deuteriertem Benzol ein einziges Signal im ^{31}P–NMR–Spektrum bei 87.0 ppm aufweist und im ^{1}H–NMR–Spektrum lediglich ein Singulett bei 1.33 ppm zeigt.[156] In chlorierten Lösungsmitteln zersetzt sich der Komplex rasch und bildet eine gelbe Lösung.



4.1.8-17, 60%

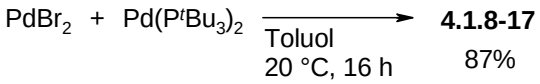
Schema 41: Synthese des Palladium(I)–Dimers [Pd(μ–Br)(P^tBu_3)]$_2$.

In Kreuzkupplungsreaktionen erwieß sich das Palladium(I)–Dimer als sehr aktiv und anderen Katalysatorsystemen oft überlegen.[158] Mit 0.5 mol% Katalysatorbeladung konnten Hartwig *et al.* so beispielsweise sterisch gehinderte Arylbromide mit Boronsäuren bereits bei Raumtemperatur kuppeln.[159] Neben C–N[159,160] und C–S Bindungsknüpfungen[161] ermöglicht der Komplex weiterhin auch die α–Vinylierung von Ketonen und Estern,[162] die α–Arylierung von Estern und Amiden,[163–165] sowie die Cyanierung von Arylhalogeniden[166] in sehr guten Ausbeuten. Die besonders hohe Aktivität der Komplexverbindung wird oft in der raschen Ausbildung der hochreaktiven, einfach koordinierten 12–Elektronenspezies [Pd(P^tBu_3)] erklärt, die *in situ* entweder durch Disproportionierung oder direkte Reduktion des Dipalladium–Komplexes in Gegenwart des Substrats und einer Base erfolgt (Schema 42).[158]



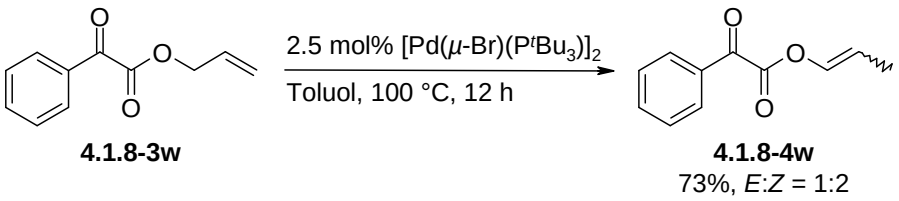
Schema 42: Aktivierung des Pd(I)–Dimers.

Aufgrund der geringen Ausbeuten bisheriger Syntheserouten erfolgte im Rahmen der Diplomarbeit eine Kooperation mit Umicore zur einfachen, schnellen und abfallminimierten Synthese des Palladium(I)−Dimers. In Zusammenarbeit mit Herrn Dr. Matthias Arndt wurde eine Komproportionierungsreaktion gefunden, bei der eine Lösung des homoleptischen $Pd(P^tBu_3)_2$ in Toluol zu einer Suspension äquimolarer Mengen $PdBr_2$ in Toluol zugetropft wird und spontan zur Bildung des grünen Dimers führt (Schema 43).[167]



Schema 43: Abfallminimierte Synthese des Palladium(I)−Dimers.

Aktivitätstests in der decarboxylierenden Allylierung von Arylglyoxylsäureallylestern führten aber überraschend nicht zum erwarteten Decarboxylierungsprodukt, sondern zu zwei neuen Produkten mit der Masse des Startmaterials. NMR−spektoskopische Analysen zeigten, dass es sich bei diesen Verbindungen um die beiden isomeren Vinylester handelt, die nur aus der Doppelbindungsisomerisierung der terminalen Doppelbindung hervorgehen konnten (Schema 44). Weitere Reaktionen mit elektronenreichen bis−*ortho*−substituierten Benzoesäureestern und dem Furan−2−carbonsäureester führten bei 100 °C in Toluol ebenfalls zu den entsprechenden Vinylestern mit einem *E*/*Z* Verhältnis von 1:2. Erste Optimierungsarbeiten zeigten, dass die Isomerisierung, aufgrund der thermischen Labilität des Katalysatorsystems, bei 50 °C noch höhere Ausbeuten liefert und selbst bei 30 °C verläuft.



4.1.8-3w

4.1.8-4w
73%, *E*:*Z* = 1:2

Schema 44: Isomerisierung von Allylglyoxylaten.

Während die Isomerisierung von Alkenen, Allylalkoholen, Allylaminen und Allylethern mit einer Vielzahl unterschiedlicher Übergangsmetalle, darunter Molybdän,[168] Eisen,[169–171] Rhodium,[172,173] Ruthenium,[174] Iridium,[175] Palladium[176,177] und Platin,[178,179] erfolgen kann, ist die Isomerisierung von Allylestern bisher auf wenige Eisen− und Rutheniumhydridkomplexe beschränkt.[170,171,180] Dies ist darin zu erklären, dass die meisten

Übergangsmetalle in die C(Allyl)–O Bindung des Esters insertieren und stabile Koordinationsverbindungen bilden.[181]

Die gefundene Reaktion ermöglicht erstmals die Palladium–katalysierte Synthese von Vinylestern aus leicht verfügbaren Allylestern. Gewöhnlich erfolgt die Synthese solcher Vinylestern durch die Umesterung mit Vinylacetat,[38] die *O*–Acylierung von Enolen[182] oder die Ruthenium–katalysierte Addition von Carbonsäuren an Alkine.[183] Sie spielen eine wichtige Rolle bei Polymerisierungsprozessen[184] und als Acylierungsreagenzien in der Synthese verschiedener Ester und Amide,[185] sodass ein nachhaltiger und selektiver Zugang solcher Enolester besonders wertvoll ist.

Aufgrund meines Industriepraktikums bei Novartis Pharma in Basel wurde die Projektleitung an dieser frühen Stelle an Frau Dr. Patrizia Mamone übertragen, die das Palladium(I)–Dimer zunächst mit den besten bekannten Isomerisierungskatalysatoren von Skrydstrup[177] und Krompiec[180] verglich und eine überragende Aktivität der Brom–verbrückten Koordinationsverbindung feststellte. In nachfolgenden Kontrollexperimente konnte sie darüber hinaus auch zeigen, dass *in situ* gebildete Koordinationsverbindungen monometallischer Palladiumvorstufen mit P^tBu_3 nur geringe Ausbeuten unter 10% ermöglichen und dass das Phosphan alleine keinerlei Aktivität besitzt. Studien zur Optimierung der Reaktionsbedingungen ergaben, dass bei 50 °C in Toluol auch 0.25 mol% $[Pd(\mu\text{–}Br)(P^tBu_3)]_2$ zur effizienten Doppelbindungsisomerisierung des Benzoesäureallylesters ausreichen. Zudem konnte gezeigt werden, dass die Reaktion auch in den Lösungsmitteln *n*–Hexan, THF, Diethylether und Dichlormethan mit nahezu gleicher Selektivität und Ausbeute erfolgt.

4.1.8.2. $[Pd(\mu\text{–}Br)(P^tBu_3)]_2$ als hochaktiver Isomerisierungskatalysator

Alle Untersuchungen zur Anwendungsbreite, zum Reaktionsmechanismus und zur asymmetrischen Hydrierung der Enolester sind in der nachfolgenden Publikation aufgeführt. Ein Großteil der praktischen Arbeiten wurde dabei von Frau Dr. Mamone durchgeführt. Mein Beitrag lag in der Entdeckung der Doppelbindungsisomerisierung durch $[Pd(\mu\text{–}Br)(P^tBu_3)]_2$ und den ersten Isomerisierungsreaktionen verschiedener Aryl– und Heteroarylcarbonsäureester in Toluol bei 30–100 °C. Weiterhin synthetisierte ich drei Ausgangsverbindungen, isomerisierte diese und isolierte die entsprechenden Enolester. Außerdem übernahm ich die Auswertung aller NMR–Spektren der Supporting Information.

Herr Dr. Bilal A. Khan synthetisierte zwei chirale Ester durch die asymmetrische Hydrierung der entsprechenden Enolester. Herr Andreas Fromm fertigte die DFT−Rechnungen zur Aufklärung der katalytisch aktiven Spezies an.

Die hier gezeigten Resultate wurden 2012 in Organic Letters, Vol. 14, 3716–3719 veröffentlicht. Die Publikation wurde für dieses Manuskript angepasst und mit Erlaubnis der American Chemical Society beigefügt.

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[Pd(μ-Br)(P^tBu_3)]$_2$ as a Highly Active Isomerization Catalyst: Synthesis of Enol Esters from Allylic Esters

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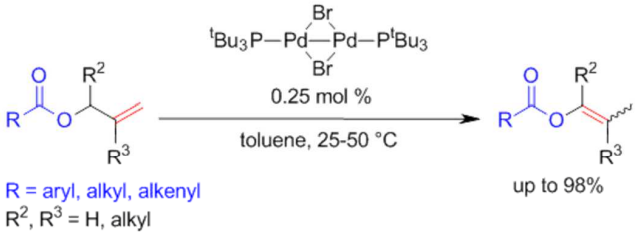
ABSTRACT



The dimeric Pd(I)-complex [Pd(μ-Br)(P^tBu_3)]$_2$ was found to be highly active for catalyzing double-bond migration in various substrates such as unsaturated ethers, alcohols, amides, and arenes, under mild conditions. It efficiently mediates the conversion of allylic esters into enol esters, rather than inserting into the allylic C–O bond. The broad applicability of this reaction was demonstrated with the synthesis of 22 functionalized enol esters.

Enol esters are important precursors in a variety of organic transformations such as aldol- and Mannich type reactions,[1] asymmetric hydrogenations,[2] cycloadditions,[3] or other cyclization reactions to afford, e.g., heterocycles or chromones.[4] They are employed as auxiliary reagents in the desymmetrization of alcohols,[5] as well as in the synthesis of vinylic amino alcohols and diols.[6]

Classical approaches to their synthesis involve transesterification between alkyl esters and enol acetates, or *O*-acylation of enolates.[7] However, these require stoichiometric amounts of bases, acids, or toxic mercury salts. Modern, catalytic syntheses of enol esters include the Zr-catalyzed methylalumination of alkynes,[8] the Cu-catalyzed oxidative esterification of aldehydes with β-dicarbonyl compounds,[9] the Au-catalyzed intramolecular rearrangements of propargylic esters and alcohols,[10] the Fe-catalyzed asymmetric coupling of ketenes with aldehydes,[11] and the addition of carboxylic acids to alkynes catalyzed by Ru,[12] Ru–Re,[13] or Rh complexes.[14]

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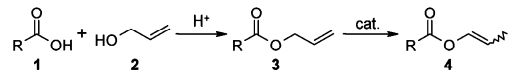
Scheme 1. Synthesis of Enol Esters via Catalytic Isomerization



The catalytic isomerization of allylic esters to enol esters would be an attractive alternative to the above approaches, because the starting materials are easily accessible by esterification of carboxylic acids (Scheme 1). However, because of the weak thermodynamic driving force for the double-bond migration and the tendency of many metal catalysts to insert into the C(allyl)−O bond with formation of stable carboxylate complexes,[15] this reaction is beyond the performance limit of most isomerization catalysts. Even for unsubstituted allyl esters, only two reports of double-bond migrations exist. Iranpoor et al. found that stoichiometric amounts of $Fe_3(CO)_{12}$ promote this reaction when irradiated with UV light.[16] Krompiec et al. achieved up to eight catalytic turnovers for the double-bond migration, along with C(allyl)−O bond cleavage, using the ruthenium hydride complex $RuClH(CO)(PPh_3)_3$.[17] Mechanistic studies by Tokunaga et al. confirmed the low catalytic activity of Ru complexes for this type of substrate.[18]

In the context of our research on isomerizing functionalizations of fatty acids,[19] we had thoroughly investigated the activity of various isomerization methods involving acid[20] or base mediators,[21] as well as metal catalysts reported for the isomerization of alkenes,[22] allylic benzenes,[23] allylic ethers,[15,24] allylic silyl ethers,[25] alkenyl alcohols,[26] allylic amines and amides.[27] However, none of these systems permitted to convert our test substrate, oleic acid, into an equilibrium mixture of isomers within a few hours at catalyst loadings below 1%.[19]

In our search for new lead structures for highly active isomerization catalysts, reports by Mingos/Vilar and Hartwig on the dimeric palladium complex $[Pd(\mu\text{-Br})(P^tBu_3)]_2$ caught our attention.[28] They discovered that this unusual, dimeric Pd^I species, which has found applications in catalytic cross-coupling reactions,[29] can be converted into hydridopalladium(II) complexes under remarkably mild conditions. We reasoned that a metal complex with such strong tendency to form Pd−H species, which are known to add across C−C double-bonds,[22,30] should also be an excellent catalyst for alkene isomerization. Indeed, oleic acid was converted to an equilibrium mixture of double-bond isomers with only 0.5 mol % of $[Pd(\mu\text{-Br})(P^tBu_3)]_2$ within less than an hour.[31]

The high activity of this one-component system led us to evaluate the catalytic activity of the Pd^I dimer as the catalyst for double-bond migrations in a range of standard test substrates. As a reference system, we used a mixture of $Pd(dba)_2$, isobutyryl chloride, and tri(*tert*-butyl)-phosphine. This catalyst has been shown by Lindhardt and Skrydstrup to set new standards with regard to catalytic activity and functional group tolerance for single-carbon migrations of various double bonds.[32] The examples in Scheme 2 demonstrate that the Pd^I dimer is an effective catalyst for double-bond migrations in allylic arenes (**5**), amides (**7**), ethers (**9**), and alcohols (**11** and **13**). In each case, the catalyst loading was reduced to the minimum effective level, in order to differentiate between the systems. For all substrate classes, the Pd^I dimer compared favorably even to the state-of-the-art Pd-catalyst for single-carbon migration of the double-bond. It is also able to move the bond over longer alkyl chains. Thus, hexanal (**14**) was obtained from 5-hexen-1-ol (**13**) in high yield and selectivity.

The most striking result obtained in this series of test reactions was that allyl benzoate (**3a**) was cleanly converted to the corresponding enol ester **4a**. Using only 0.25 mol % of Pd^I in toluene, near-quantitative conversion to 1-propenyl benzoate (**4a**) was achieved within 2 h at 50 °C, with a product (*E*/*Z*)-ratio of 1:2. The only other component detected in the reaction mixture was 2% of the

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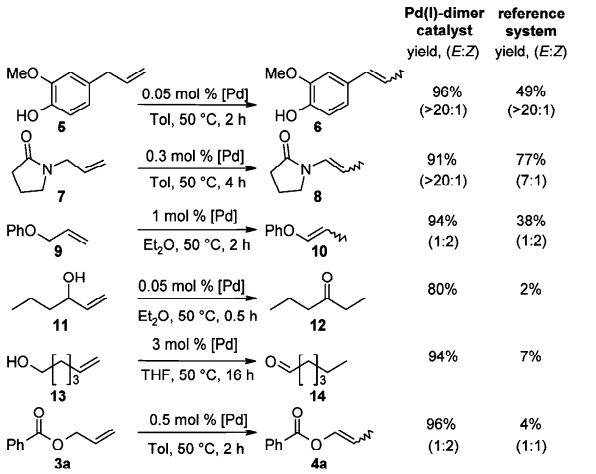
Scheme 2. Double-Bond Migration with the Pd^{I} Catalyst[33]



starting material **3a**, which did not disappear even after a prolonged reaction time, indicating that the equilibrium had been reached. In view of the rich chemistry of allylic acetate activation by palladium catalysts, it was surprising that no trace of benzoic acid arising from C(allyl)–O bond cleavage was observed.[34,15]

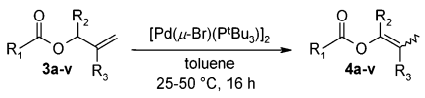
Encouraged by the observation that equilibration occurs so rapidly and that its position lies so far on the side of the enol esters, we optimized the catalyst loading and reaction conditions[33] and then explored the scope of the reaction protocol. As can be seen from the examples in Table 1, the reaction is broadly applicable with regard both to the carboxylate and allyl alcohol side of the esters.[35]

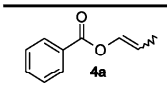
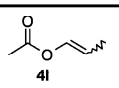
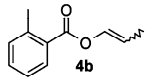
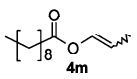
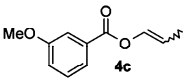
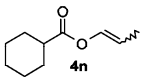
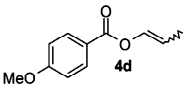
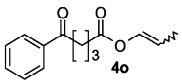
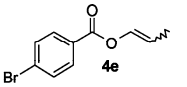
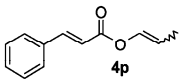
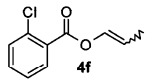
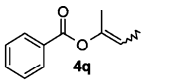
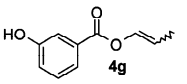
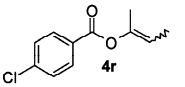
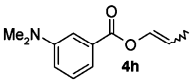
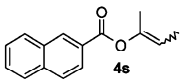
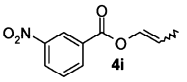
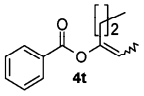
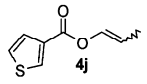
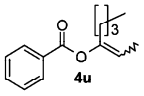
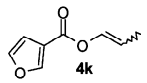
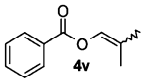
Allylic esters of electron-rich and electron-deficient aromatic (**4a**–**i**), heteroaromatic (**4j**,**k**), aliphatic (**4l**–**o**), and cinnamic (**4p**) carboxylates were successfully converted.

A variety of functionalities including alkoxy (**4c**,**d**), hydroxy (**4g**), amino (**4h**), nitro (**4i**), and keto groups (**4o**) were tolerated. Even halogen-containing substrates reacted smoothly without any indication of competing Heck-type reactions (**4e**,**f**). In all cases, (*E*:*Z*)-ratios between 1:2 and 1:5 were obtained.

The allyl residue can be linear or branched in the 1- and/or 2-positions (**4q**–**v**). Enol esters branched in the 1-position are of considerable interest as substrates for

Table 1. Isomerization of Allylic Esters to Enol Esters[f]



product	yield [%]/ (*E*:*Z*)	product	yield [%]/ (*E*:*Z*)
 **4a**	90 (1:2)	 **4l**	97[a,c] (1:2)
 **4b**	98 (1:2)	 **4m**	89 (1:2)
 **4c**	90 (1:2)	 **4n**	80 (1:2)
 **4d**	91 (1:2)	 **4o**	88 (1:2)
 **4e**	73 (1:2)	 **4p**	96 (1:2)
 **4f**	91[a] (1:2)	 **4q**	83[a] (1:3)
 **4g**	98[b] (1:2)	 **4r**	93[a] (1:3)
 **4h**	91[b] (1:2)	 **4s**	95[a] (1:3)
 **4i**	87[b] (1:1)	 **4t**	87[a,d] (1:5)
 **4j**	56[b] (1:2)	 **4u**	88[a,d] (1:5)
 **4k**	76 (1:2)	 **4v**	77[e]

[a] $[Pd(\mu\text{-Br})(P^tBu_3)]_2$ (0.50 mol %). [b] $[Pd(\mu\text{-Br})(P^tBu_3)]_2$ (2.50 mol %). [c] Yield and (*E*/*Z*)-selectivity was determined by NMR with anisole as internal standard. [d] 25 °C, 10% of other isomers. [e] $[Pd(\mu\text{-Br})(P^tBu_3)]_2$ (1.00 mol %). [f] Reaction conditions: Allylic esters **1a**–**v** (1.00 mmol), $[Pd(\mu\text{-Br})(P^tBu_3)]_2$ (0.25 mol %), 2 mL of toluene, 50 °C, 16 h, isolated yields. (*E*/*Z*)-selectivity was determined by GC.

enantioselective hydrogenations, but because of their limited availability, there are only few reports on such reactions.[2,36] We were thus pleased to find that compounds **4q**–**u** can be hydrogenated in high yields and enantiomeric excess (Scheme 3).[37] This demonstrates the viability of

(33) For details, see the Supporting Information.

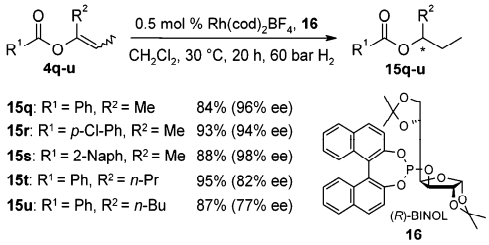
(34) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846.

(35) Synthesis of 1-propenyl benzoate (**4a**): Under a nitrogen atmosphere, a 50 mL vessel was charged with di-μ-bromobis(tri-*tert*-butylphosphine)dipalladium(I) (27.2 mg, 35.0 μmol), allyl benzoate (**3a**) (1.76 g, 10.0 mmol), and toluene (20 mL). The mixture was stirred at 50 °C for 16 h, diluted with diethyl ether (40 mL), and filtered through a pad of celite (5 g), and the solvent was removed in vacuo (50 mbar, 40 °C). The crude product was purified by column chromatography (SiO_2, diethyl ether/*n*-pentane gradient) to give prop-1-enyl benzoate (**4a**) (1.65 g, 94% yield, *E*:*Z* 1:2) as colorless liquid.

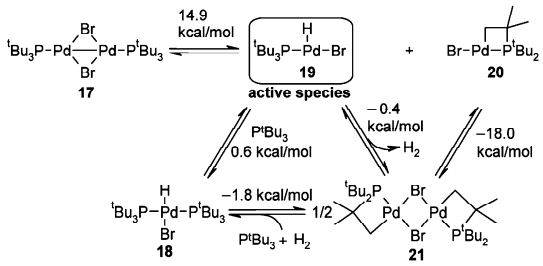
(36) (a) Jiang, Q.; Xiao, D.; Zhang, Z.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 516. *Angew. Chem.* **1999**, *111*, 578. (b) Jung, H. M.; Koh, J. H.; Kim, M.-J.; Park, J. *Org. Lett.* **2000**, *2*, 2487. (c) Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X. *Org. Lett.* **2002**, *4*, 4495.

(37) Reetz, M. T.; Goossen, L. J.; Meiswinkel, A.; Paetzold, J.; Jensen, J. F. *Org. Lett.* **2003**, *5*, 3099.

Scheme 3. Rh-Catalyzed Asymmetric Hydrogenation of Enol Esters



Scheme 4. Proposed Activation of the Pd^{I} Dimer



enantioselective syntheses via a double-bond isomerization/asymmetric hydrogenation sequence.

In order to evaluate how the catalytically active species may form from the Pd^{I} dimer, we calculated the standard Gibbs free energy ($\Delta_R G^{\ominus}$) for the formation of various Pd-hydride species using the B3LYP density functional.[33] The lowest energy expenditure was calculated for the formation of Pd hydride **19** along with the monomeric palladacycle **20** ($\Delta_R G^{\ominus}$ = 14.9 kcal/mol) (see Table S3 (Supporting Information) and Scheme 4). Since this reaction proceeds via an endergonic pathway, the driving force for the formation of **19** is the concomitant dimerization of **20** to the stable palladacycle **21** ($\Delta_R G^{\ominus}$ = −18 kcal/mol).

The Pd−H complex **19** likely acts as the catalytically active species, but because of its high reactivity, we were not surprised to detect the oxidized dimeric palladacycle **21** as major signal when monitoring the catalytic reaction by ^{1}H and ^{31}P NMR (^{31}P NMR: −8.6 ppm). A minor signal at −9.0 ppm also appeared, which might originate from an isomer of **21**. It is known that **21** can also form from Pd−H species **18**, with concomitant release of a phosphine and hydrogen gas.[38] Moreover, **21** may result from the decomposition of **19** after it has achieved the double bond migration. Another experimental result that supports **19** as the catalytically active species is that upon trapping with tri-*tert*-butylphosphine, the more stable bis(*tert*-butylphosphino)palladium hydride complex **18** was detected (^{1}H NMR: triplet at −15.6 ppm).[28a]

(38) Clark, H. C.; Goel, A. B.; Goel, S *J. Organomet. Chem.* **1979**, *166*, C29.

Starting from **19**, a possible mechanism for the isomerization reaction would involve an insertion of the alkene into the Pd−hydride **19** followed by β-hydride elimination with formation of the isomerized olefin and regeneration of the initial Pd−hydride **19**. Further mechanistic investigations to elucidate the origin of the high isomerization activity of $[Pd(\mu\text{-Br})(P^{t}Bu_3)]_2$ are underway.

In conclusion, the Pd^{I} dimer $[Pd(\mu\text{-Br})(P^{t}Bu_3)]_2$ possesses a new level of reactivity for catalyzing double bond migrations in a wide range of unsaturated substrate classes. It even catalyzes the isomerization of allylic esters to the corresponding enol esters, which are valuable starting materials, e.g., for asymmetric hydrogenation.

Acknowledgment. We thank D. Halter and Dr. W. Dzik (TU Kaiserslautern) for technical assistance, NanoKat, the DFG (SFB-TRR 88 "3MET"), the Landesgraduiertenstiftung Rheinland-Pfalz (fellowships to P.M., M.F.G., and A.F.) and the HEC Pakistan (fellowship to B.A.K.) for financial support, and Umicore for the donation of catalyst metals.

Supporting Information Available. Screening table, experimental procedures, characterization of all new compounds, and data of DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

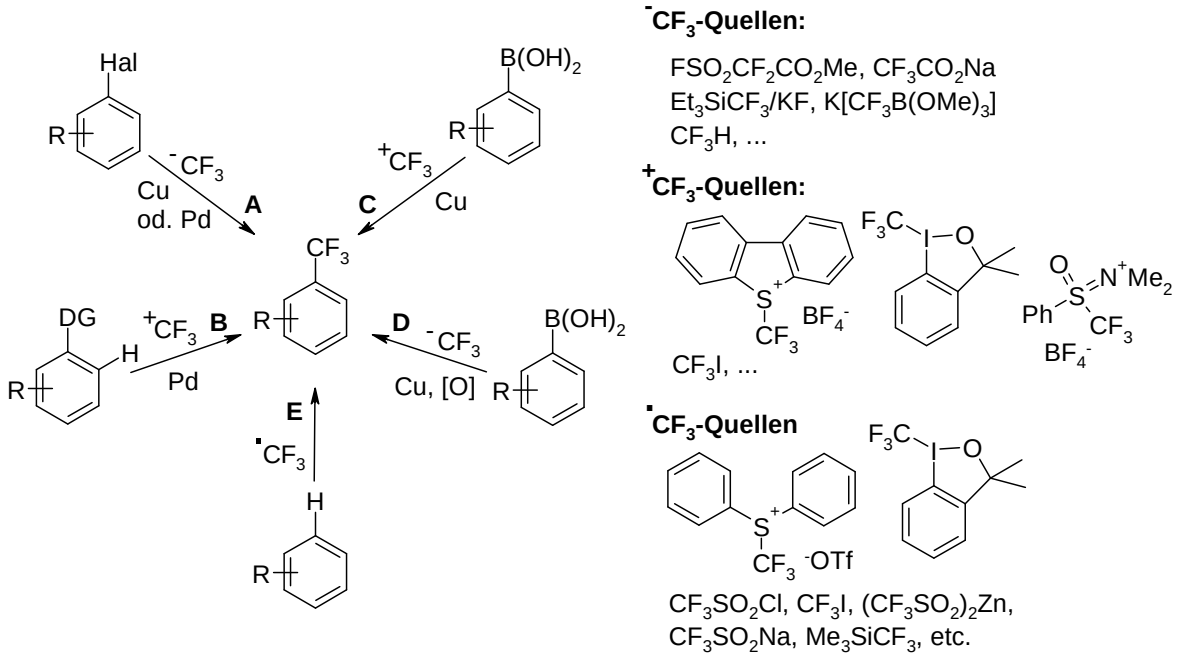
4.2. Sandmeyer–Trifluormethylierung und –Trifluormethylthiolierung

4.2.1. Hintergrund

Aufgrund ihrer hohen Elektronegativität führen Fluorsubstituenten zur starken Bindungspolarisierung in organischen Molekülen und damit auch zur Veränderung der chemischen und physikalischen Eigenschaften.[186] Solche C–F Bindungen sind in Naturstoffen extrem selten und einer enzymatischen Spaltung gegenüber meist inert.[187] Diese Eigenschaft wird in vielen Medikamenten[186,188–190] und Pflanzenschutzmitteln[191] genutzt, um metabolisch labile Positionen eines Wirkstoffs zu schützen und den frühzeitigen Abbau zu verhindern. Der Einbau von Fluorsubstituenten führt zur gesteigerten Lipophilie und erleichtert damit den Transport durch Lipidmembranen, was eine erhöhte Bioverfügbarkeit zur Folge hat.[186,192] Neben den Monofluorierungsreaktionen[193–199] hat vor allem auch die Einführung von Trifluormethyl– und Trifluormethylthiogruppen stark an Bedeutung gewonnen. Aufgrund der hohen Elektronegativität der drei Fluorsubstituenten sind diese Gruppen stark elektronenziehend und erhöhen die Lipophilie aufgrund ihrer geringen Polarisierbarkeit noch weiter (Hansch Konstanten: $\pi_F = 0.14$; $\pi_{CF3} = 0.88$; $\pi_{SCF3} = 1.44$).[200]

Klassisch erfolgt die Synthese solcher Verbindungen über die Swarts–Reaktion, bei der Alkylhalogenide mit Metallfluoriden unter rauen Reaktionsbedingungen in die entsprechenden Alkylfluoride überführt werden.[201] Aufbauend auf den frühen Arbeiten von McLoughlin, Yagupolskii, Burton, Chambers, Grushin und anderen zur Reaktivität von Kupfer– und Palladium–CF_3–Komplexen wurde eine Vielzahl selektiver Reaktionen entwickelt, mit denen Trifluormethylgruppen selbst in hochfunktionalisierte Moleküle eingeführt werden können (Schema 45).[202–207]

Diese Reaktionen lassen sich in fünf Kategorien einteilen:[208–214] Zur ersten Kategorie gehören Kupplungen von Arylhalogeniden mit nukleophilen Trifluormethylierungsreagenzien (Schema 45, **A**). Zu diesen zählen Kupfer–CF_3 Komplexe, die entweder in stöchiometrischen Mengen direkt eingesetzt[209,211,215,216] oder *in situ* aus Kupfersalzen und Rupperts Reagenz,[217–219] Fluoroform,[220] Kalium(trifluormethyl)trimethoxyborat,[221] Trifluoracetaten[212,222–224] oder Fluorsulfonyldifluoressigsäure[225] gebildet werden können. Grushin,[214] Sanford[226] und Buchwald[227,228] beschrieben zudem Trifluormethylierungsreaktionen mit Palladium–CF_3–Komplexen.



Schema 45: Strategien zur Einführung von Trifluormethylgruppen.

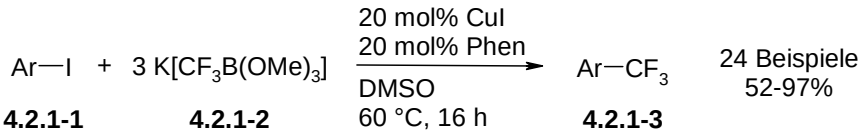
Palladium–Komplexe ermöglichen weiterhin auch C(Aryl)–H funktionalisierende Trifluormethylierungen mit Umemotos Reagenz oder Perfluoralkyliodiden (**B**).[229,230] Unter oxidativen Bedingungen können heteroaromatische Verbindungen auch mit nukleophilen Trifluormethylierungsreagenzien C–H–funktionalisiert werden.[231]

Zu den Kupplungen von Arylnukleophilen mit elektrophilen Trifluormethylierungsreagenzien gehören die von Shen und Liu beschriebenen Kupplungen von Arylboronsäuren mit Tognis und Umemotos Reagenzien (**C**).[232,233] Unter oxidativen Bedingungen können diese Kohlenstoffnukleophile auch mit nukleophilen Trifluormethylierungsreagenzien gekuppelt werden (**D**).[234,235]

Aufbauend auf den frühen Arbeiten von Langlois zur radikalischen Trifluormethylierung[236,237] entwickelten Baran[238,239] und MacMillan[240] zudem moderne Radikalreaktionen unter Verwendung von Peroxid– oder Rutheniuminitiatoren (**E**).

Von den genannten Reagenzien sind besonders die nukleophilen Trifluormethylierungsreagenzien CF_3SiMe_3 und $K^+[CF_3B(OMe)_3]^-$ in großen Mengen und günstig verfügbar. Vor kurzem wurde zudem gezeigt, dass sie auch aus Fluoroform, einem Nebenprodukt der Teflonproduktion, zugänglich sind.[241,242] Die Kupfer–katalysierte Trifluormethylierung von Aryl– und Heteroaryliodiden mit $K[CF_3B(OMe)_3]$ wurde 2011 von

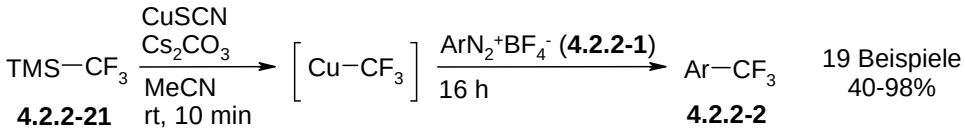
unserer Arbeitsgruppe beschrieben und ermöglicht die selektive Trifluormethylierung in Gegenwart zahlreicher funktioneller Gruppen (Schema 46).[221]



Schema 46: Kupfer–katalysierte Trifluormethylierung von Aryliodiden.

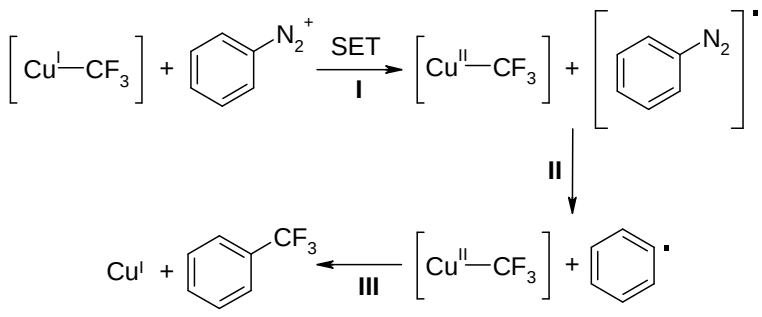
4.2.2. Sandmeyer Trifluormethylierung von Aryldiazoniumsalzen

In weiterführenden Studien entwickelte Herr Dr. Grégory Danoun die erste Sandmeyer–analoge Trifluormethylierung präformierter Diazoniumsalze mit Rupperts Reagenz und Kupfer(I)halogeniden. In Zusammenarbeit mit Herrn Dipl.–Chem. Bilguun Bayarmagnai war ich an der Optimierung der Reaktionsparameter beteiligt. Gemeinsam untersuchten wir schließlich die Anwendungsbreite der Reaktion.



Schema 47: Sandmeyer Trifluormethylierung von Aryldiazoniumsalzen.

Mechanistisch verläuft diese Reaktion analog zur klassischen Sandmeyer Reaktion, bei der Aryldiazoniumsalze in die entsprechenden Arylhalogenide überführt werden. In Gegenwart der Caesiumbase erfolgt aus dem Kupfer(I)–Salz und Rupperts Reagenz zunächst die Bildung einer Trifluormethyl–Kupfer(I)–Spezies, welche ein Elektron auf das Aryldiazoniumsalz überträgt (Schema 48, **I**). Dies führt zu einem Diazoradikal, welches Stickstoff freisetzt und ein Arylradikal bildet (**II**). Dieses reagiert mit der Trifluormethyl–Kupfer(II)–Spezies zum Benzotrifluorid und regeneriert die Kupfer(I)–Spezies (**III**).



Schema 48: Mechanismus der Sandmeyer Trifluormethylierung.

Alle Optimierungsarbeiten, sowie die Untersuchen zur Anwendungsbreite und zum Reaktionsmechanismus sind in der nachfolgenden Publikation aufgeführt. Die Katalysatoroptimierung erfolgte dabei durch Herrn Dr. Danoun und Herrn Bayarmagnai. Mein Beitrag bestand in der anteiligen Synthese der Benzotrifluoride. Das Schreiben des Manuskripts erfolgte durch Herrn Danoun, während sich Herr Bayarmagnai um die mechanistischen Studien kümmerte und ich eine Methode zur Isolierung der leichtflüchtigen Produkte entwickelte. Die anschließende Isolierung der Produkte erfolgte zu gleichen Teilen durch Herrn Bayarmagnai und mich. Weiterhin übernahm ich das Auswerten der analytischen Daten und das Schreiben der Supporting Information.

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Trifluoromethylation

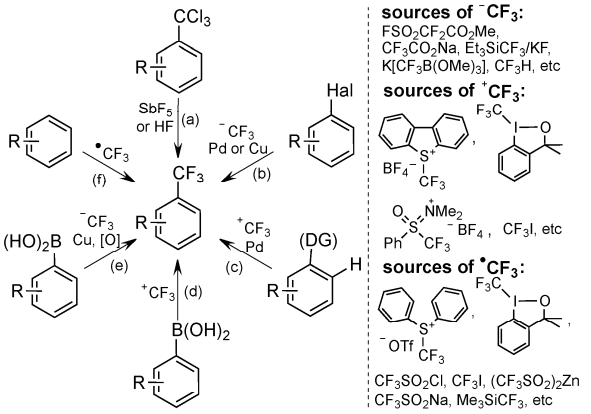
DOI: 10.1002/anie.201304276

Sandmeyer Trifluoromethylation of Arenediazonium Tetrafluoroborates**

*Grégory Danoun, Bilguun Bayarmagnai, Matthias F. Grünberg, and Lukas J. Gooßen**

The development of methods for the introduction of trifluoromethyl groups into functionalized molecules is of great importance due to their presence in many top-selling pharmaceuticals, agrochemicals, and functional materials. Trifluoromethyl groups are known to impart desirable properties, such as higher metabolic stability, increased lipophilicity, and stronger dipole moments to druglike molecules.[1] Celecoxib, dutasteride, fluoxetine, and sitagliptin are some examples of top-selling pharmaceuticals featuring trifluoromethyl groups, and beflubutamid, diflufenican, and norfluazon examples of agrochemicals.[2] However, traditional methods to access benzotrifluorides, for example, the Swarts reaction, typically require harsh conditions and have a low substrate scope, so that they are confined to the beginning of a synthetic sequence (Scheme 1 a).[3]

Building on pioneering work on Cu– and Pd–perfluoroalkyl complexes by McLoughlin, Yagupolskii, Burton, Chambers, Grushin, and others, substantial progress has recently been made in the development of trifluoromethylation reactions that allow the selective introduction of CF_3 groups into functionalized, late-stage synthetic intermediates.[4] A wealth of new reactions has been disclosed, which can be roughly divided into five categories (Scheme 1 b–f).[5] The first are couplings of aryl halides with nucleophilic CF_3 reagents (reaction type b), usually copper–CF_3 complexes in stoichiometric amounts.[5b,d,6] These complexes may also be generated in situ from copper salts and Ruppert's reagent (CF_3SiMe_3),[7] fluoroform,[8] potassium (trifluoromethyl)trimethoxyborate,[9] trifluoroacetate salts,[5e,10] methyl trifluoroacetate,[11] or fluorosulfonyldifluoroacetic acid.[12] Grushin,[5d] Sanford,[13] and Buchwald[14] also disclosed trifluoromethylations of aryl halides based on palladium complexes.



Scheme 1. Strategies for the introduction of trifluoromethyl groups.

Palladium complexes also promote C–H functionalizations of arenes with trifluoromethylating reagents (reaction type c). Examples are the *ortho*-trifluoromethylation of donor-substituted arenes with Umemoto's reagent described by Yu et al.[15] and the Pd-catalyzed coupling of arenes with perfluoroalkyl iodides reported by Sanford et al.[16] C–H trifluoromethylations of heteroarenes have recently been reported also with nucleophilic trifluoromethylation reagents under oxidative conditions.[17] Examples of couplings of aryl nucleophiles with electrophilic CF_3 sources (reaction type d) include the coupling of arylboronic acids with Togni's and Umemoto's reagent disclosed by Shen and Liu, respectively.[18] Sanford et al. employed a copper/ruthenium photocatalyst system to promote a radical trifluoromethylation of boronic acids.[19]

The copper-catalyzed syntheses of benzotrifluorides from boronic acids and CF_3SiMe_3 or $K^+[CF_3B(OMe)_3]^-$ developed by Qing et al.[20] and ourselves[21] exemplify oxidative couplings of aryl nucleophiles with nucleophilic CF_3 reagents (reaction type e). The radical trifluoromethylation of arenes (reaction type f) was pioneered by Langlois.[22] Baran[23] and MacMillan[24] recently reported modern variants of this reaction concept based on peroxide or ruthenium initiators.

From a practical standpoint, nucleophilic reagents are appealing for the introduction of trifluoromethyl groups for the following reasons. CF_3SiMe_3 and $K^+[CF_3B(OMe)_3]^-$ are available in large quantities for a reasonable price, and are easy to store and handle. They are accessible not only from halofluorocarbons, but also from fluoroform, a by-product in the production of Teflon.[25] One of the most widely used methods for the introduction of halides and related nucleophiles is the Sandmeyer reaction.[26] Aromatic amines, which are available in great structural diversity, are diazotized using, for example, $NaNO_2$ or organic nitrites. Upon treatment with the appropriate copper(I) halides, nitrogen gas is released, and a halide group is installed regiospecifically in the position

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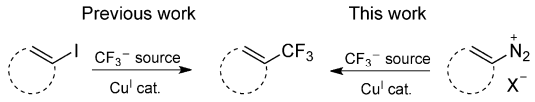
of the former amino group. Based on our experiences with copper-catalyzed trifluoromethylations of aryl iodides, we were convinced that a similar strategy should also allow the synthesis of benzotrifluorides from aromatic amines (Scheme 2).[27,28]

In order to probe the viability of this approach, we treated 4-methoxybenzenediazonium tetrafluoroborate (**1**) with K^+-

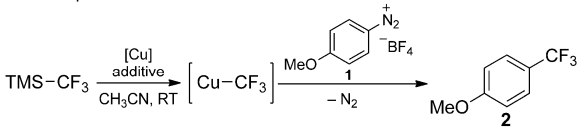


Scheme 2. Trifluoromethylations with nucleophilic reagents.

$[(CF_3)B(OMe)_3]^-$ in the presence of 20 mol% of CuI and phenanthroline in DMSO at 60°C, conditions previously optimized for the trifluoromethylation of aryl iodides.[9] The trifluoromethylated product was indeed observed in modest yield, along with the protodediazotization product, anisole. Encouraged by these results, we systematically optimized the reaction conditions for this model reaction (Table 1).

A decisive increase in the yields was obtained when the diazonium salt was added to a trifluoromethyl–copper species preformed from a copper salt and $K^+[(CF_3)B(OMe)_3]^-$ (Table 1, entry 1). A combination of Ruppert's reagent ($TMSCF_3$)[29] and cesium fluoride was found to provide higher yields than the milder borate reagent (Table 1, entry 2), which led us to continue our optimization work with the latter reagent. The desired product was obtained in 63% yield when a copper(I) iodide solution in acetonitrile was stirred with $TMSCF_3$ and cesium fluoride for 10 min at room temperature, followed by addition of the diazonium salt and continued stirring for 12 h (Table 1, entry 2).

Table 1: Optimization of the reaction conditions.[a]



Entry	[Cu]	Additive	Yield of **2** [%][b]
1[c]	CuI	CsF	30[d]
2	CuI	CsF	63
3	$[Cu(MeCN)_4]BF_4$	CsF	62
4	CuOAc	CsF	81
5	CuSCN	CsF	98
6	Cu	CsF	0
7	$Cu(OAc)_2$	CsF	21
8	CuSCN	KF	traces
9	CuSCN	NaF	0
10	CuSCN	Cs_2CO_3	98
11	CuSCN	–	0
12	–	Cs_2CO_3	0
13[e]	CuSCN	Cs_2CO_3	98
14[f]	CuSCN	Cs_2CO_3	72

[a] Reaction conditions: 0.75 mmol of $TMSCF_3$, 0.75 mmol of [Cu], 0.75 mmol of additive, 1 mL of MeCN, 10 min, RT, followed by dropwise addition of 0.50 mmol of **1** in 1 mL of solvent, 12 h, room temperature. [b] Yields were determined by ^{19}F NMR spectroscopy using trifluoroethanol as an internal standard. [c] Using $KCF_3B(OMe)_3$ instead of $TMSCF_3$ at 60°C. [d] Yield was determined by ^{19}F NMR spectroscopy using 1,3-difluorobenzene as an internal standard. [e] Using 0.3 mmol of CuNCS. [f] With in situ diazotization of *p*-anisidine using *tert*-butyl nitrite/*p*TSA. TMS = trimethylsilyl, *p*TSA = *p*-toluenesulfonic acid.

The main by-product observed was the iodinated arene. For this reason, we replaced copper iodide by copper salts with other counterions (Table 1, entries 3–5). Among them, copper thiocyanate was most effective. The desired benzotrifluoride **2** was obtained in almost quantitative yield (Table 1, entry 5). Using this copper source, neither the proto-dediazotization product anisole nor the aryl thiocyanate were observed. The only detectable side product was di(*p*-methoxy)azobenzene (2% yield).

Copper(0) and copper(II) salts were less effective which supports our theory that this is a Sandmeyer-type reaction (Table 1, entries 6 and 7). Similarly to related reactions of diazonium salts, acetonitrile was the most effective solvent (see the Supporting Information). Several additives besides CsF were investigated for promoting the transfer of the CF_3 group from silicon to the copper. Among the fluoride salts tested, only CsF was effective (Table 1, entries 5, 8, and 9). When the counterion on the cesium was varied, we found that carbonate and fluoride are similarly effective, while other counterions gave inferior results (Table 1, entries 5 and 10). Control experiments confirmed that the reaction does not proceed without either copper or basic additives (Table 1, entries 11 and 12). The amount of copper could be decreased to 60 mol% without negatively impacting the yield (Table 1, entry 13). With this prototype system, further reduced catalyst loadings resulted in incomplete conversions. However, the observation that full conversions can be reached with substoichiometric amounts of copper nurtures the hope that this reaction can be made truly catalytic in copper in the near future. When the *p*-methoxyaniline was diazotized with *tert*-butyl nitrite/*p*-toluenesulfonic acid (pTSA) and the resulting diazonium salt solution subjected to the reaction conditions without intermediary workup, the product was obtained in 72% based on the aniline (Table 1, entry 14).

Having thus found an effective protocol for the Sandmeyer trifluoromethylation, we next investigated its scope. Various arenediazonium tetrafluoroborates were smoothly converted into the corresponding benzotrifluorides in high yields (Scheme 3). Only for some simple, low-boiling substrates, the products could not be isolated in the high yields observed by in situ spectroscopic analysis due to their volatility. Both electron-rich and electron-deficient substrates gave similarly high yields. Many common functionalities were tolerated including ester, ether, amino, keto, carboxylate, cyano, and even iodo groups. This demonstrates the utility of the new reaction for the late-stage trifluoromethylation of complex, highly functionalized intermediates. Various heterocycles were also trifluoromethylated in good yields. Most products were obtained in sufficiently pure form to allow for straightforward isolation. Only for a few substrates was it necessary to subject the product to elaborate separation procedures to remove traces of the protodediazotization products.

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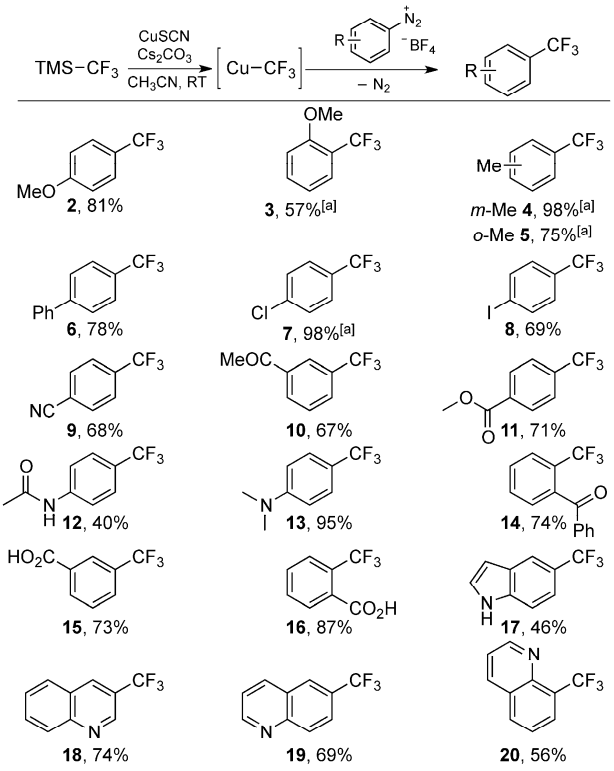
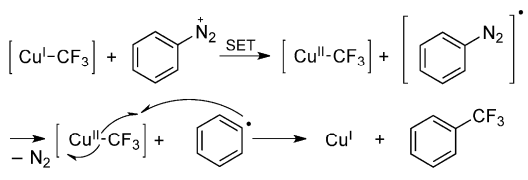


Scheme 3. Scope of the Sandmeyer trifluoromethylation. Reaction conditions: 1.5 mmol of $TMSCF_3$, 0.6 mmol of CuSCN, 1.5 mmol of Cs_2CO_3, 2 mL of MeCN, 10 min, RT, followed by dropwise addition of 1.0 mmol of arenediazonium tetrafluoroborate in 2 mL of MeCN, 12 h, room temperature; yield of isolated product. [a] Yield determined by ^{19}F NMR spectroscopy using trifluoroethanol as an internal standard.

We assume that the reaction proceeds analogously to Sandmeyer halogenations of diazonium salts, which are generally believed to proceed via radical intermediates (Scheme 4).[30] It is plausible that the trifluoromethyl copper(I) species, generated from the copper precursor and $TMSCF_3$ in the presence of the cesium base, transfers one electron to the diazonium salt. The resulting diazo radical releases nitrogen with formation of an aryl radical, which abstracts the trifluoromethyl group from the copper(II) intermediate to form the trifluoromethylated product along with a copper(I) species.

In conclusion, the newly discovered Sandmeyer trifluoromethylation allows the straightforward synthesis of trifluoromethylated compounds from the corresponding aromatic amines under mild conditions at room temperature. Ongoing research is directed towards combining the diazotization and the Sandmeyer reaction into a one-pot procedure, and towards reducing the amount of copper to truly catalytic quantites.



Scheme 4. Proposed mechanism.

Experimental Section

Standard procedure for the synthesis of benzotrifluorides from the corresponding arenediazonium salts**:** An oven-dried 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with copper thiocyanate (73.5 mg, 0.60 mmol) and cesium carbonate (489 mg, 1.50 mmol) under an atmosphere of dry nitrogen. Acetonitrile (2 mL) and trifluoromethyltrimethylsilane (240 μL, 1.50 mmol) were added by syringe. The resulting suspension was stirred at room temperature for 10 min and a solution of the arenediazonium tetrafluoroborate (1 mmol) in acetonitrile (2 mL) was added dropwise by syringe. The reaction mixture was stirred at ambient temperature for 16 h. The resulting mixture was filtered through a pad of celite (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (3×10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient), yielding the corresponding benzotrifluoride.

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Keywords: copper · diazonium salts · Sandmeyer reaction · trifluoromethylation

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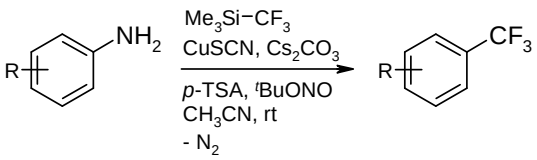
4.2.3. Sandmeyer Trifluormethylierung aromatischer Amine

Nachfolgende Arbeiten unserer Gruppe führten zur Entwicklung einer weiteren Reaktionsvariante, bei der die Aryldiazoniumsalze nicht präformiert werden müssen, sondern *in situ* aus den Anilinderivaten gebildet werden (Schema 49).[243] Diese Ergebnisse sind im nachfolgenden Manuskriptentwurf gemeinsam mit unserem ersten Protokoll, an dessen Entwicklung ich beteiligt war, zusammengefasst und werden als „Practical Synthetic Procedure"–Artikel in Synthesis veröffentlicht. Mein Beitrag bestand im anteiligen Verfassen des Manuskripts.



Schema 49: Sandmeyer Trifluormethylierung von Anilinderivaten.

Sandmeyer Trifluoromethylation

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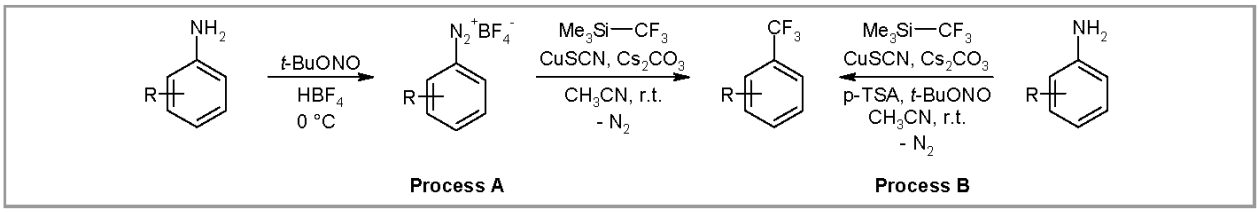
Abstract: Various benzotrifluorides are conveniently accessible in high yields from broadly available (hetero)aromatic amines and the inexpensive trifluoromethylating agent $TMSCF_3$ via a copper-mediated Sandmeyer trifluoromethylation reaction. Two practical procedures are presented. In the first one, the diazonium salts are preformed in an extra reaction step, in the second one, the diazotization and the trifluoromethylating are combined into a one-pot procedure.

Key words: anilines, copper, Sandmeyer reaction, trifluoromethylation, diazonium salts.



Scheme 1 Sandmeyer trifluoromethylation

Introduction

Trifluoromethyl groups impart unique chemical and physical properties to organic molecules, including improved metabolic stability, better receptor binding selectivity, higher lipophilicity, and stronger dipole moments compared to their non-fluorinated analogs.[1]

Traditional approaches for the synthesis of benzotrifluorides,[2] such as the Swarts reaction, require harsh conditions and display limited substrate scope. Based on pioneering studies by McLoughlin, Yagupolskii, Burton, Chambers, Grushin and others, various selective Cu- and Pd-mediated trifluoromethylation methods were developed within recent years.[3]

In this context, several Sandmeyer-type trifluoromethylations were almost simultaneously disclosed by the groups of Fu,[4] Wang[5] and us.[6] They are based on aromatic amines that are widely available in great structural diversity, which is a distinct advantage over other trifluoromethylation methods.[7] Moreover, most chemists are familiar with Sandmeyer reactions since their undergraduate laboratory training and will not hesitate to add such trifluoromethylations to their chemical toolbox. In the new processes, the aniline diazotization and trifluoromethylation steps can optionally be combined into one pot.

Wang and Fu's protocols are based on costly Umemoto reagent or preformed $AgCF_3$, whereas our method employs the inexpensive Ruppert-Prakash reagent TMS-CF_3. This reagent has been shown to be accessible directly from fluoroform, a byproduct in the Teflon production.[8]

Sequential Diazotization / Trifluoromethylation

In this procedure, arenediazonium tetrafluoroborates are synthesized from *tert*-butyl nitrite (2 equiv.) and the corresponding amine in aqueous HBF_4 (2 equiv.) at 0 °C. After stirring for one hour, diethyl ether is added to precipitate the diazonium salts, which are then isolated by simple filtration.

For their trifluoromethylation, the diazonium salts are dissolved in dry acetonitrile (2 mL) and added dropwise to a solution of 0.6 equiv. copper(I) thiocyanate, 1.5 equiv. cesium carbonate and 1.5 equiv. $TMSCF_3$ in acetonitrile (2 mL), and stirring is continued for 12 hours at room temperature. The corresponding benzotrifluorides are obtained in good to excellent yields following aqueous work-up and purification (Table 1, Process A). The slow addition is crucial for suppressing both unwanted proto-dediazotization and the formation of azoarenes and biaryls, common byproducts in Sandmeyer reactions. Mechanistic investigations suggest that the actual trifluoromethylation reagent formed in the reaction of copper thiocyanate with TMS-CF_3 and the mild base Cs_2CO_3 is a $Cu(CF_3)^{2-}$ species.[9] The reason for using copper thiocyanate is that the anion at the copper

competes with CF_3 as the nucleophile in the Sandmeyer reaction. For copper halides, considerable amounts of haloarenes are formed as byproducts, whereas at most trace amounts of arenethiocyanates were observed when starting from copper thiocyanates. Another advantage is the high solubility of this copper precursor in the reaction solvent. The addition of the mild base cesium carbonate facilitates the transfer of the CF_3 group from the silane to the copper without affecting the reactivity of the diazonium salts. Due to the hygroscopic character of this base, the reactions are best performed under a dry nitrogen atmosphere to minimize proto-dediazotization.

One-Pot Diazotization / Trifluoromethylation

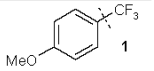
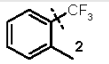
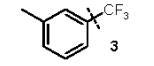
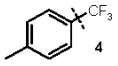
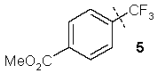
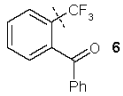
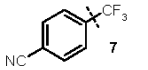
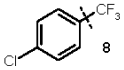
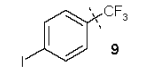
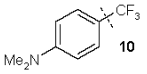
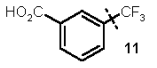
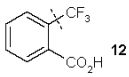
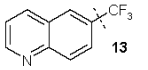
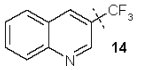
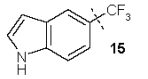
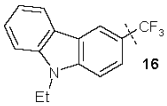
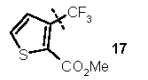
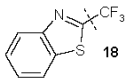
Especially for small-scale reactions and sensitive diazonium salts,[10,11] it may be convenient to diazotize the amine directly in the reaction mixture. This can be done by adding *tert*-butyl nitrite (1 equiv.) to a solution of the aniline and anhydrous *p*-toluenesulfonic acid (1.5 equiv.) in MeCN. The absence of water is decisive, the monohydrate of the acid already leading to reduced yields. After stirring for 0.5 hours at RT, a suspension of CuSCN (0.5 equiv.), $TMSCF_3$ (1.5 equiv.) and Cs_2CO_3 (1.5 equiv.) in MeCN is added to the reaction mixture, and stirring is continued for 12 hours.[12] This one-pot process gives comparable, sometimes even higher yields than the two-step protocol (Table 1, Process B).

Scope and Limitations

The Sandmeyer trifluoromethylation is widely applicable to various aromatic amines. Due to the mild reaction conditions, common functionalities such as ether, ester, ketone or cyano groups are tolerated (Table 1, entries 1–5). Even basic amino groups and free carboxylates are tolerated (entries 8–10). Various heterocycles, such as quinolines and indole, were also smoothly converted (entries 11–13). Remarkably, the trifluoromethylation can be performed in the presence of halo-, even iodo-substituents, so that it is orthogonal to many palladium-catalyzed cross-couplings (entries 6, 7). Most products are obtained in pure form after aqueous workup and column chromatography.

In most cases, the isolated yields of both protocols are comparable. For quinolines, the *in situ* diazotization led to the formation of an insoluble precipitate. Even when redissolving it by adding 0.5 mL acetone, the yield of protocol B remains lower than that of the two-step protocol A. For aminoindoles and -benzoic acids, which give reasonable yields with protocol A, almost no product was formed in the one-pot procedure B. In contrast, aminocarbazole, thiophene and benzothiazole are successfully converted only using method B, which may be caused by the instability of the diazonium salts when isolated. Substrates that lead to even less stable diazonium salts, such as 2-aminopyridines, could not be trifluoromethylated with either protocol.

Table 1 Sandmeyer trifluoromethylation

Product	Yield (%)[a]	Product	Yield (%)[a]
 1	A: 81 B: 85	 2	A: 75[b] B: 78[b]
 3	A: 98[b] B: 84[b]	 4	A: 98[b] B: 98[b]
 5	A: 71 B: 83	 6	A: 74 B: 79
 7	A: 68 B: 91	 8	A: 98[b] B: 98[b]
 9	A: 69 B: 61	 10	A: 95 B: 91
 11	A: 73 B: 0	 12	A: 87 B: 0
 13	A: 69 B: 53	 14	A: 74 B: 55
 15	A: 46 B: 0	 16	A: - B: 89
 17	A: - B: 69	 18	A: - B: 61

[a] Isolated yield; A: starting from the arenediazonium tetrafluoroborate; B: starting from the aniline. [b] Yield determined by ^{19}F NMR using trifluoroethanol as internal standard.

Conclusion

The Sandmeyer trifluoromethylation is a beneficial strategy to access benzotrifluorides from readily available starting materials and inexpensive reagents. The reaction is possible either with intermediate isolation of the diazonium salts, or as a one-pot procedure starting from the anilines.

Experimental Section

All reactions were performed under a nitrogen atmosphere in dry glassware containing a Teflon-coated stirrer bar. Acetonitrile was dried by refluxing over CaH_2 and fractional distillation. All reactions were monitored by GC, spectroscopic yields were determined by ^{19}F NMR using trifluoroethanol as internal standard. GC analyses were carried out using a HP-5 capillary column (Phenyl Methyl Siloxane 30 m x 320 x 0.25) and a time program beginning with 2 min at 60 °C followed by 30 °C/min ramp to 300 °C,

then 3 min at this temp. Column chromatography was performed using an Isco Combi Flash Companion Chromatography System and pre-packed flash columns (12 g). NMR spectra were obtained using chloroform-*d*, methanol-d_4 or DMSO-d_6 as deuterated solvents, with proton, carbon and fluorine resonances at 400 MHz, 101 MHz and 376 MHz, respectively.
The diazonium salts were prepared from the corresponding anilines following the procedure below and were directly used. All other starting materials were commercially available. All anilines and solvents were purified by distillation or sublimation prior to use. The other chemicals were used without further purification.

Synthesis of Arenediazonium Salts from Anilines; General Procedure: In a 50 mL round-bottom flask, the aniline (10 mmol) was dissolved in a mixture of ethanol (3 mL) and aqueous HBF_4 (50%, 2.5 mL, 20 mmol). *tert*-Butyl nitrite (2.7 mL, 20 mmol) was added dropwise to the solution at 0 °C. The reaction was stirred at room temperature for 1 h, then diethyl ether (20 mL) was added to precipitate the arenediazonium tetrafluoroborate, which was filtered off and washed with diethyl ether (3 × 10 mL). The arenediazonium tetrafluoroborate was dried *in vacuo* (10^{-3} mbar) for 10 minutes, then directly used without further purification. Some arenediazonium tetrafluoroborates were recrystallized by dissolution in acetone, followed by the re-precipitation by addition of diethyl ether.

Two-Pot Synthesis of Benzotrifluorides from Arenediazonium Salts: Procedure A: A 20 mL crimp-cap vessel with Teflon-coated stirrer bar was charged with copper thiocyanide (73.5 mg, 0.60 mmol) and cesium carbonate (489 mg, 1.50 mmol) under an atmosphere of dry nitrogen. Acetonitrile (2 mL) and trifluoromethyl trimethylsilane (240 µL, 1.50 mmol) were added via syringe. The resulting suspension was stirred at room temperature for 10 minutes and a solution of the arenediazonium tetrafluoroborate (1 mmol) in acetonitrile (2 mL) was added dropwise via syringe. The reaction mixture was stirred at ambient temperature for 16 h. The resulting mixture was filtered through a short pad of Celite (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (3 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient), yielding the corresponding benzotrifluorides.

One-Pot Synthesis of Benzotrifluorides from Anilines; Procedure B: A 20 mL crimp cap vessel with Teflon-coated stirrer bar was charged with the amine (1.00 mmol), *p*-toluenesulfonic acid (258 mg, 1.50 mmol) and acetonitrile (2 mL) under nitrogen. *tert*-Butyl nitrite (133 µL, 1.00 mmol) was added dropwise via syringe. The resulting solution was stirred at room temperature for 30 minutes and then added dropwise to a suspension of copper thiocyanate (61.0 mg, 0.50 mmol), cesium carbonate (489 mg, 1.50 mmol) and trifluoromethyl trimethylsilane (240 µL, 1.50 mmol) in acetonitrile (2 mL) that was pre-stirred at room temperature for 10 min. The resulting suspension was stirred at room temperature for another 12 h. The resulting mixture was filtered through a short pad of Celite (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient), yielding the corresponding benzotrifluorides.

Synthesis of 1-methoxy-4-(trifluoromethyl)benzene (1) [CAS: 402-52-8]. Prepared from 4-methoxybenzenediazonium tetrafluoroborate (444 mg, 2.00 mmol) by following Procedure A and isolated as a colorless liquid (286 mg, 1.62 mmol, 81%). The product was also prepared from 4-methoxyaniline (123 mg, 1.00 mmol) by following Procedure B (150 mg, 0.85 mmol, 85%). The spectroscopic data were reported previously.[6,12]

Synthesis of 1-methyl-2-(trifluoromethyl)benzene (2) [CAS: 5140-17-6]. Prepared from 2-methylbenzenediazonium tetrafluoroborate (103 mg, 0.50 mmol) by following Procedure A (75% yield determined by 19F NMR spectroscopic analysis). The product was also prepared from 2-methylaniline (54 mg, 0.50 mmol) by following Procedure B (78% yield by 19F NMR spectroscopic analysis).[6,12]

Synthesis of 1-methyl-3-(trifluoromethyl)benzene (3) [CAS: 401-79-6]. Prepared from 3-methylbenzenediazonium tetrafluoroborate (103 mg, 0.50 mmol) by following Procedure A (98% yield as determined by 19F NMR spectroscopic analysis). The product was also prepared from 3-methylaniline (54 mg, 0.50 mmol) by following Procedure B (84% yield by 19F NMR spectroscopic analysis).[6,12]

Synthesis of 1-methyl-4-(trifluoromethyl)benzene (4) [CAS: 6140-17-6]. Prepared from 4-methylbenzenediazonium tetrafluoroborate (103 mg, 0.50 mmol) by following Procedure A (98% yield as determined by 19F NMR spectroscopic analysis). The product was also prepared from 4-methylaniline (54 mg, 0.50 mmol) by following Procedure B (98% yield by 19F NMR spectroscopic analysis).[6,12]

Synthesis of methyl 4-(trifluoromethyl)benzoate (5) [CAS: 2967-66-0]. Prepared from 4-(methoxycarbonyl)benzenediazonium etrafluoroborate (250 mg, 1.00 mmol) by following Procedure A and isolated as a colorless liquid (144 mg, 0.71 mmol, 71%). The product was also prepared from methyl 4-aminobenzoate (154 mg, 1.00 mmol) by following Procedure B as a liquid (169 mg, 0.83 mmol, 83%). The spectroscopic data were reported previously.[6,12]

Synthesis of phenyl(2-(trifluoromethyl)phenyl)methanone (6) [CAS: 727-

99-1]. Prepared from 2-benzoylbenzenediazonium tetrafluoroborate (296 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (184 mg, 0.74 mmol, 74%). The product was also prepared from (2-aminophenyl)(phenyl)methanone (201 mg, 1.00 mmol) by following Procedure B (198 mg, 0.79 mmol, 79%). The spectroscopic data were reported previously.[6,12]

Synthesis of 4-(trifluoromethyl)benzonitrile (7) [CAS: 455-18-5]. Prepared from 4-cyanobenzenediazonium tetrafluoroborate (108 mg, 0.50 mmol) by following Procedure A and isolated as a colorless solid (58 mg, 0.34 mmol, 68%). The product was also prepared from 4-cyanoaniline (118 mg, 1.00 mmol) by following Procedure B (156 mg, 0.91 mmol, 91%). The spectroscopic data were reported previously.[6,12]

Synthesis of 1-chloro-4-(trifluoromethyl)benzene (8) [CAS: 98-56-6]. Prepared from 4-chlorobenzenediazonium tetrafluoroborate (113 mg, 0.50 mmol) by following Procedure A (98% yield as determined by 19F NMR spectroscopic analysis). The product was also prepared from 4-chloroaniline (65 mg, 0.50 mmol) by following Procedure B (98% yield by 19F NMR spectroscopic analysis).[6,12]

Synthesis of 1-iodo-4-(trifluoromethyl)benzene (9) [CAS: 455-13-0]. Prepared from 4-iodobenzenediazonium tetrafluoroborate (649 mg, 2.00 mmol) by following Procedure A and isolated as a light-yellow liquid (373 mg, 1.37 mmol, 69%). The product was also prepared from 4-iodoaniline (221 mg, 1.00 mmol) by following Procedure B (166 mg, 0.61 mmol, 61%). The spectroscopic data were reported previously.[6,12]

Synthesis of *N*,*N*-dimethyl-4-(trifluoromethyl)aniline (10) [CAS: 329-17-9]. Prepared from 4-(dimethylamino)benzenediazonium tetrafluoroborate (470 mg, 2.00 mmol) by following Procedure A and isolated as a colorless solid (358 mg, 1.89 mmol, 95%). The product was also prepared from *N*,*N*-dimethylbenzene-1,4-diamine (140 mg, 1.00 mmol) by following Procedure B (172 mg, 0.91 mmol, 91%). The spectroscopic data were reported previously.[6,12]

Synthesis of 3-(trifluoromethyl)benzoic acid (11) [CAS: 454-92-2]. Prepared from 3-carboxybenzenediazonium tetrafluoroborate (236 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (139 mg, 0.73 mmol, 73%). The spectroscopic data were reported previously.[6]

Synthesis of 2-(trifluoromethyl)benzoic acid (12) [CAS: 433-97-6]. Prepared from 2-carboxybenzenediazonium tetrafluoroborate (236 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (166 mg, 0.87 mmol, 87%). The spectroscopic data were reported previously.[6]

Synthesis of 6-(trifluoromethyl)quinoline (13) [CAS: 325-13-3]. Prepared from quinoline-6-diazonium tetrafluoroborate (243 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (136 mg, 0.69 mmol, 69%). The product was also prepared from quinoline-6-amine (147 mg, 1.00 mmol) by following Procedure B (105 mg, 0.53 mmol, 53%). The spectroscopic data were reported previously.[6,12]

Synthesis of 3-(trifluoromethyl)quinoline (14) [CAS: 25199-76-2]. Prepared from quinoline-3-diazonium tetrafluoroborate (243 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (145 mg, 0.74 mmol, 74%). The product was also prepared from quinolin-3-amine (146 mg, 1.00 mmol) by following procedure B (108 mg, 0.55 mmol, 55%). The spectroscopic data were reported previously.[6,12]

Synthesis of 5-(trifluoromethyl)-1H-indole (15) [CAS: 100846-24-0]. Prepared from 1H-indole-5-diazonium tetrafluoroborate (231 mg, 1.00 mmol) by following Procedure A and isolated as a colorless solid (85 mg, 0.46 mmol, 46%). The spectroscopic data were reported previously.[6]

Synthesis of 9-ethyl-3-(trifluoromethyl)-9H-carbazole (16). Prepared from 9-ethyl-9H-carbazol-3-amine (221 mg, 1.00 mmol) by following Procedure B and isolated as a colorless solid (234 mg, 0.89 mmol, 89%). The spectroscopic data were reported previously.[12]

Synthesis of methyl 3-(trifluoromethyl)thiophene-2-carboxylate (17). Prepared from methyl 3-aminothiophene-2-carboxylate (157 mg, 1.00 mmol) by following Procedure B and isolated as a colorless solid (145 mg, 0.69 mmol, 69%). The spectroscopic data were reported previously.[12]

Synthesis of 2-(trifluoromethyl)-1,3-benzothiazole (18) [CAS: 14468-40-7]. Prepared from 2-amino-benzothiazole (155 mg, 1.00 mmol) by following Procedure B and isolated as a colorless solid (124 mg, 0.61 mmol, 61%). The spectroscopic data were reported previously.[12]

Acknowledgment

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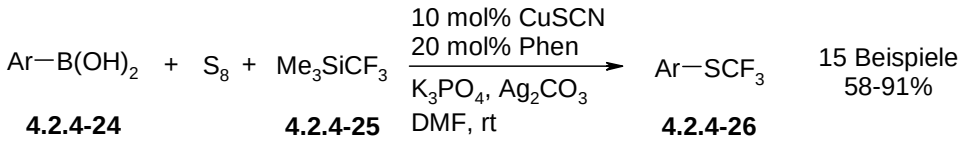
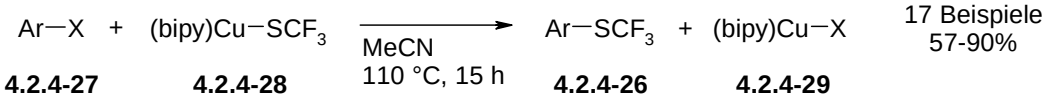
4.2.4. Sandmeyer Trifluormethylthiolierung

In den vergangenen Jahren wurden neben der Trifluormethylierung ebenso einige Verfahren zur Einführung von Trifluormethylthiolgruppen in organische Moleküle entwickelt.[244–247] Erst kürzlich beschrieben Qing *et al.* eine Kupfer–katalysierte, oxidative Trifluormethylthiolierung von Arylboronsäuren mit elementarem Schwefel und Rupperts Reagenz (Schema 50).[248] Das Kupfer(I)–Salz bildet dabei zunächst einen Kupfer(I)–Disulfidkomplex, der mit der Boronsäure zum Cu–SAr Verbindung reagiert und mit Rupperts Reagenz unter oxidativen Bedingungen den Aryltrifluormethylthioether bildet.



Schema 50: Oxidative Trifluormethylthiolierung von Arylboronsäuren.

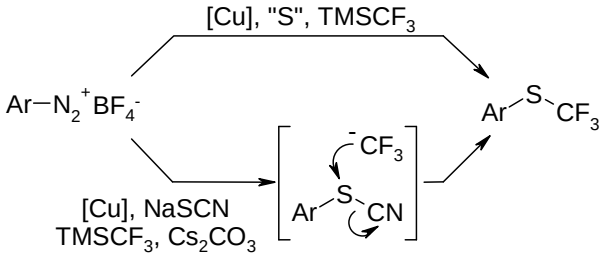
Zu den redox–neutralen, nukleophilen Trifluormethylthiolierungen gehören Buchwalds Palladium–katalysierte Trifluormethylthiolierung von Arylhalogeniden mit präformiertem $AgSCF_3$,[249] eine Nickel–katalysierte Variante mit dem vergleichbar empfindlichen Me_4NSCF_3 nach Zhang und Vicic[250] und die Umsetzung mit präformiertem $CuSCF_3$ nach Huang (Schema 51).[251] Bei diesen Reaktionen erfolgt zunächst die oxidative Addition des Metalls in die C–Halogenid Bindung des Substrats und, in den beiden ersten Fällen, die Transmetallierung der SCF_3–Gruppe auf das Metall. Das Produkt wird anschließend durch eine reduktive Eliminierung erhalten.



Schema 51: Trifluormethylthiolierung mit präformiertem $CuSCF_3$.

Der Sandmeyer–analoge Transfer einer SCF_3–Gruppe von präformiertem $CuSCF_3$ auf wenige, elektronenarme Diazoniumsalze beschrieben Clark *et al.* bereits 1990.[252] Ausgehend von unseren eigenen Arbeiten zur Sandmeyer Trifluormethylierung von Aryldiazoniumsalzen[253] erfolgten nun Studien zur analogen Trifluormethylthiolierung mit einer *in situ* gebildeten $CuSCF_3$ Spezies. Erste Experimente zeigten, dass eine Kombination aus Kupfer(I)salz, Schwefelquelle und Rupperts Reagenz die gewünschten

trifluormethylthiolierten Produkte höchstens in Spuren liefern (Schema 52). Erst eine Sandmeyer Thiocyanierung gefolgt von einer Trifluormethylierung mit Rupperts Reagenz führte schließlich zur regioselektiven Umwandlung der Aryldiazoniumsalze in die Zielverbindungen.

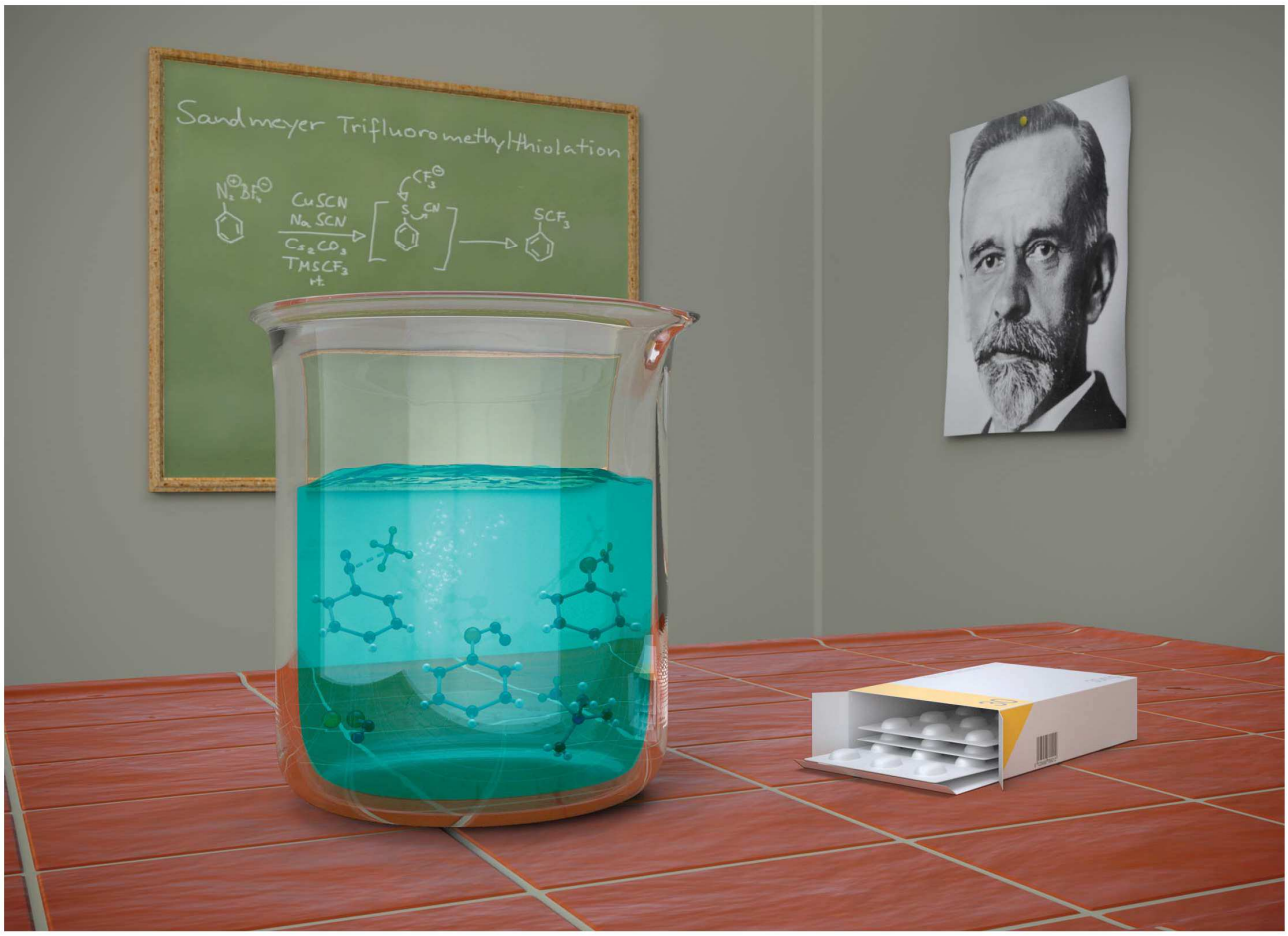


Schema 52: Strategien zur Sandmeyer Trifluormethylierung.

Auch dieses Projekt erfolgte in Zusammenarbeit mit Herrn Dr. Danoun und Herrn Bayarmagnai. Alle Optimierungsarbeiten, sowie die Untersuchungen zur Anwendungsbreite und zum Reaktionsmechanismus sind in der nachfolgenden Publikation aufgeführt. Die Katalysatoroptimierung erfolgte erneut durch Herrn Dr. Danoun und Herrn Bayarmagnai. Mein Beitrag bestand in der anteiligen Synthese der trifluormethylthiolierten Produkte. Das Schreiben des Manuskripts erfolgte durch Herrn Danoun, während sich Herr Bayarmagnai um die mechanistischen Studien kümmerte und ich die leichtflüchtigen Produkte isolierte. Weiterhin kümmerte ich mich um das Auswerten der analytischen Daten und das Schreiben der Supporting Information.

Die hier gezeigten Resultate wurden 2014 in Chemical Science, Vol. 5, 1312–1316 publiziert. Die Publikation wurde für dieses Manuskript angepasst und mit Erlaubnis der Royal Society of Chemistry beigefügt.

G. Danoun, B. Bayarmagnai, M. F. Gruenberg and L. J. Goossen, *Chem. Sci.* **2014**, *5*, 1312–1316, Sandmeyer trifluoromethylthiolation of arenediazonium salts with sodium thiocyanate and Ruppert–Prakash reagent – Published by The Royal Society of Chemistry (RSC) on behalf of the Centre National de la Recherche Scientifique (CNRS) and the RSC



Showcasing research from Prof. Lukas J. Gooßen's laboratory, Technische Universität Kaiserslautern, Kaiserslautern, Germany.

Sandmeyer trifluoromethylthiolation of arenediazonium salts with sodium thiocyanate and Ruppert-Prakash reagent

Trifluoromethyl thioethers are obtained directly from aryl and heteroaryl diazonium salts, sodium thiocyanate and the inexpensive, easy-to-use trifluoromethylating reagent $Me_3Si–CF_3$ in the presence of a copper thiocyanate catalyst. The preparative utility of this Sandmeyer-type trifluoromethylthiolation is demonstrated by the synthesis of 22 aryl and heteroaryl trifluoromethyl thioethers bearing various functionalities from the corresponding anilines.

As featured in:

See Lukas J. Gooßen, *et al.*, *Chem. Sci.*, 2014, **5**, 1312.

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Sandmeyer trifluoromethylthiolation of arenediazonium salts with sodium thiocyanate and Ruppert–Prakash reagent†

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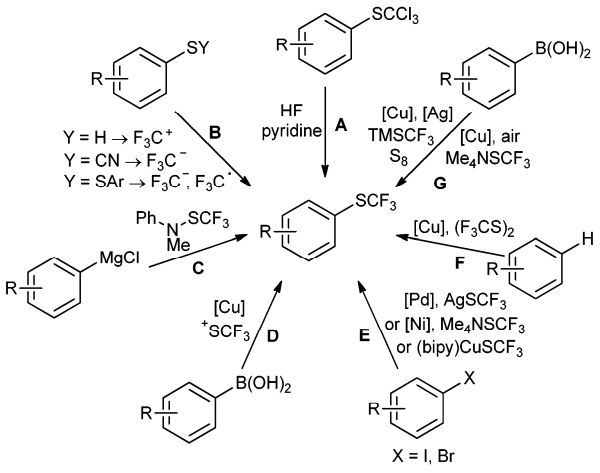
In the presence of copper thiocyanate, sodium thiocyanate and the inexpensive, easy-to-use trifluoromethylating reagent $Me_3Si–CF_3$, diazonium salts are smoothly converted into the corresponding aryl trifluoromethyl thioethers. Combined with diazotisation, this convenient and inexpensive method allows the straightforward synthesis of aryl or heteroaryl trifluoromethyl thioethers from the corresponding anilines.

Introduction

In recent years, methods for the introduction of fluorine-containing groups into organic molecules have attracted great attention within organic synthesis, as they can impart desirable properties to bioactive compounds.[1] Substantial progress has recently been achieved in the field of late-stage trifluoromethylations,[2] whereas the corresponding trifluoromethylthiolations are less developed.[3] In general, trifluoromethylthio groups induce even higher lipophilicity than trifluoromethyl substituents (Hansch constant $\pi = 1.44$ *versus* 0.88),[4] and are more bulky. This allows a more effective transport of drug molecules through lipid membranes, thereby increasing their bioavailability. Thus, SCF_3 groups are often seen as key functionalities of many pharmaceutical and agrochemical products, such as tiflorex, toltrazuril (Baycox®) or vaniliprole.[5]

Traditional strategies

As shown in Scheme 1, several access routes exist for the formation of trifluoromethyl thioethers. Traditional strategies for the introduction of SCF_3 groups include halogen–fluorine exchange reactions of trihalogenomethyl thioethers (A),[6] as well as trifluoromethylations of sulfur-containing compounds such as thiols,[7] thiocyanates[8] and disulfides,[9] all of which have to be synthesised in additional steps (B). More modern, one-step trifluoromethylthiolation methods can be divided into four main categories: electrophilic (C and D), nucleophilic (E) and radical (F), as well as oxidative cross-couplings (G). Examples of electrophilic processes are the reactions of trifluoromethanesulfonamides with aryl-magnesium or lithium reagents reported by Billard *et al.* (Scheme 1, C)[10] and the copper-mediated reaction of arylboronic acids with hypervalent iodine–SCF_3 reagents by Lu and Shen (D).[11] Nucleophilic trifluoromethylthiolations include, for example, the palladium-catalysed trifluoromethylthiolation of aryl halides with sensitive $AgSCF_3$ by Buchwald *et al.*,[12] and the nickel-catalysed coupling of aryl halides either with the similarly unstable Me_4NSCF_3 by Zhang and Vicic,[13] or with stable, but laborious-to-prepare copper–trifluoromethylthiolate complexes by Huang (E).[14] C–H functionalizations are exemplified by the copper-mediated *ortho*-trifluoromethylthiolation of benzamides with $CF_3S–SCF_3$ by Daugulis *et al.* (F).[15] Oxidative trifluoromethylthiolations have been reported by Qing *et al.*,[16,17] who treated boronic acids with the Ruppert–Prakash reagent ($TMSCF_3$) and sulfur in the



Scheme 1 Strategies for the introduction of trifluoromethylthio groups.

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† Electronic supplementary information (ESI) available: procedural and spectral data. See DOI: 10.1039/c3sc53076k

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presence of CuSCN and silver carbonate (G). Very recently, Zhang and Vicic developed a similar oxidative trifluoromethylthiolation using Me_4NSCF_3 as the source of SCF_3.[18]

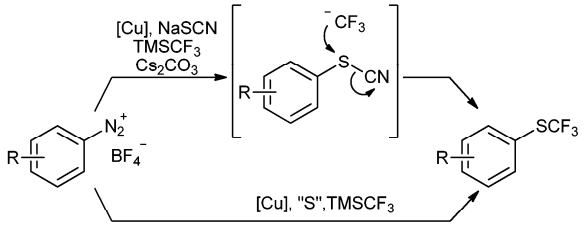
Although the above approaches provide viable routes for the formation of trifluoromethyl thioethers, they all entail shortcomings, such as the laborious multi-step preparation of starting materials or the use of expensive, air-sensitive or poorly available reagents. As an alternative, we present a cheap and straightforward synthesis of trifluoromethyl thioethers *via* a Sandmeyer-type reaction.

Sandmeyer trifluoromethylthiolation

In the context of our work on new trifluoromethylation reactions,[19,20] we have developed an effective synthesis of benzotrifluorides *via* a Sandmeyer reaction.[21] The key advantage of this reaction over related processes[22] is that the Cu–CF_3 reagents are generated *in situ* from simple trifluoromethyl silanes or borates. An analogous reaction concept, in which easily accessible diazonium salts are converted into the corresponding trifluoromethyl thioethers *via* a redox-neutral reaction involving a nucleophilic CF_3 reagent in combination with a sulfur source, appeared to be a plausible and attractive way of introducing trifluoromethylthio groups (Scheme 2, bottom). Clark *et al.* have shown the principal feasibility of Sandmeyer trifluoromethylthiolations starting from preformed $CuSCF_3$. However, they found that their laboriously prepared $CuSCF_3$ complex transfers its SCF_3 group only reluctantly to diazonium salts, so that only a few electron-poor aryl trifluoromethyl thioethers could be accessed in reasonable yields.[23]

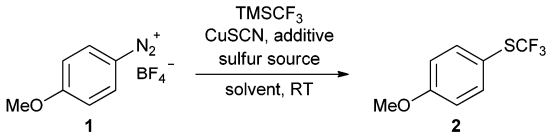
Simply combining Clark's process with the *in situ* formation of the Cu–SCF_3 reagents from a trifluoromethylating and a sulfurising agent thus did not appear to be a promising strategy towards a one-step trifluoromethylthiolation process. This assumption was supported by a series of test experiments (Table 1, entries 1–3).

While searching for another straightforward strategy to introduce trifluoromethylthio groups, we reasoned that it should be advantageous to first connect the aryl-C–S and then the S–CF_3 bonds. In search for a viable reaction pathway, we struck upon a report by Langlois *et al.* in which they demonstrated that aryl thiocyanates can be trifluoromethylated with Ruppert–Prakash's reagent.[8] We reasoned that if we performed a Sandmeyer thiocyanation[24] in the presence of a nucleophilic trifluoromethylation reagent, the arenediazonium salts might directly be converted into the corresponding aryl trifluoromethyl thioethers (Scheme 2, top). However, this appeared to be merely a theoretical possibility, since nucleophilic CF_3 sources are known to react smoothly with copper salts.[2e,19–21] Thus, one would expect that any trifluoromethylating reagent capable of substituting a cyano group in an aryl thiocyanate would also react with CuSCN intermediates to give unwanted Cu–CF_3 or Cu–SCF_3 species. Nevertheless, we were intrigued by the prospects offered by a one-pot trifluoromethylthiolation process and decided to evaluate its fcasibility.



Scheme 2 Approaches to Sandmeyer trifluoromethylthiolations.

Table 1 Optimisation of the reaction conditions[a]



Entry	Sulfur source	Additive	Solvent	Yield of 2[b] [%]
1[c]	S_8	CsF	MeCN	5
2[c]	Lawesson's reagent	CsF	MeCN	Traces
3[c]	Na_2S	CsF	MeCN	0
4	NaSCN	CsF	MeCN	30
5	KSCN	CsF	MeCN	Traces
6	NH_4SCN	CsF	MeCN	Traces
7	NaSCN	Cs_2CO_3	MeCN	98
8	NaSCN	Cs_2CO_3	DMF	81
9	NaSCN	Cs_2CO_3	Acetone	18
10	NaSCN	—	MeCN	0
11	—	Cs_2CO_3	MeCN	0
12[d]	NaSCN	Cs_2CO_3	MeCN	0
13[e]	NaSCN	Cs_2CO_3	MeCN	34
14[f]	NaSCN	Cs_2CO_3	MeCN	98
15[g]	NaSCN	Cs_2CO_3	MeCN	67

[a] *Reaction conditions*: 0.5 mmol CuSCN, 2 equiv. additive, 1.5 equiv. sulfur source, 2 mL solvent, RT, dropwise addition of 0.5 mmol **1** in 2 mL of solvent, then 2 equiv. $TMSCF_3$, 12 h. [b] Yields were determined by ^{19}F NMR using 1,3-difluorobenzene as an internal standard. [c] $TMSCF_3$ added before **1**. [d] Without CuSCN. [e] 1 equiv. Cs_2CO_3. [f] 0.5 equiv. CuSCN. [g] 0.1 equiv. CuSCN. Lawesson's reagent = 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-dithione.

Results and discussion

Development of a Sandmeyer trifluoromethylthiolation

We systematically investigated the reaction of 4-methoxybenzenediazonium tetrafluoroborate with sodium thiocyanate and TMS–CF_3 as a model system in the presence of various copper catalysts (see ESI†). As expected, anisole and 4-methoxybenzotrifluoride were formed in most cases, while the desired trifluoromethyl thioether **2** was only a minor product. However, when slowly adding the diazonium salt **1** and $TMSCF_3$ to a mixture of sodium thiocyanate, CuSCN and CsF in acetonitrile, the desired trifluoromethyl thioether **2** was obtained in an encouraging 30% yield, along with a residual aryl thiocyanate intermediate (Table 1, entry 4). Under these conditions, the formation of 4-(trifluoromethyl)anisole was no longer observed.

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Further experiments revealed that sodium thiocyanate is the most effective reagent, whereas many other thiocyanate salts suppressed the subsequent trifluoromethylation step (entries 5 and 6). A decisive step-up in the yields was achieved when replacing CsF, which is commonly used to activate $TMSCF_3$, with Cs_2CO_3 (entry 7). Acetonitrile was confirmed to be the most effective solvent, which corresponds well with the findings for other Sandmeyer reactions (entries 8 and 9).[25]

Control experiments revealed that the reaction does not proceed if the copper mediator, the basic additive or sodium thiocyanate are omitted (entries 10–12). Reducing the amount of base to one equivalent led to decreased yields (entry 13). Even when the amount of copper was reduced to 50 mol%, the aryl trifluoromethyl thioether **2** was formed in a near-quantitative yield, with traces of the aryl thiocyanate as the only detectable by-product (entry 14). Reasonable yields were obtained even with only 10 mol% of copper (entry 15), which suggests that future catalyst generations will allow the metal loading to be lowered to truly catalytic amounts.

Scope of the new transformation

Having thus found an effective protocol for the trifluoromethylthiolation of arenediazonium salts, we next investigated its scope. As can be seen from the examples in Table 2, various arenediazonium tetrafluoroborates were smoothly converted into the corresponding aryl trifluoromethyl thioethers in moderate to excellent yields. In contrast to the reaction of diazonium salts with preformed $CuSCF_3$, the new process is in no way limited to strongly electron-deficient derivatives.

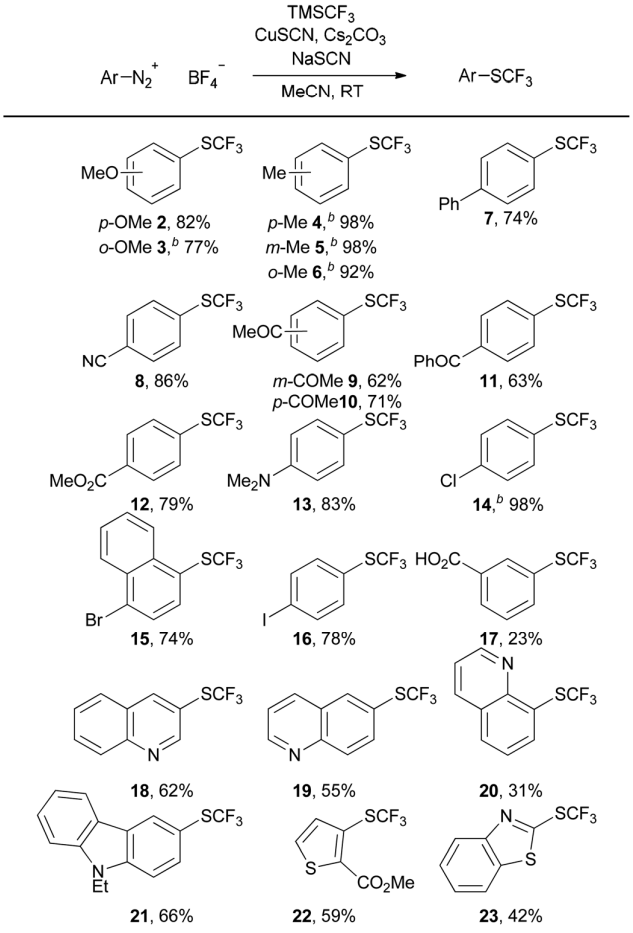
Common functionalities including ester, ether, amino, keto, carboxylate and cyano groups were tolerated. Substrates containing chloro, bromo or even iodo substituents were trifluoromethylthiolated selectively at the position of the diazonium group. Various heterocycles such as quinoline, thiophene, benzothiazole and carbazole were also smoothly converted. Most products were directly obtained in a sufficiently pure form to allow their straightforward isolation. Only in a few cases did traces of the protodediazotisation products complicate the purification of the crude products. These results demonstrate the utility of the new reaction for the late-stage trifluoromethylthiolation of highly functionalised intermediates.

Mechanistic investigations

In order to gain a deeper mechanistic understanding, the reaction was investigated by ^{19}F NMR. Mixtures of CuSCN, TMS–CF_3 and Cs_2CO_3 in MeCN were found to contain $CuCF_3$ (−28.1 ppm) and $[Cu(CF_3)_2]^-$ (−31.2 ppm), but no $CuSCF_3$ species.[26] This indicates that the SCN^- anion does not react with TMS–CF_3 under the reaction conditions. When NaSCN was added to the above mixture, the formation of CF_3–copper species was no longer observed. This explains why no trifluoromethylation products are obtained under the optimised conditions. Further experiments confirmed that 4-methoxybenzenediazonium tetrafluoroborate (**1**) is smoothly converted into the aryl thiocyanate by treatment with CuSCN, NaSCN and Cs_2CO_3 in MeCN in the absence of a nucleophilic CF_3 source. Moreover, preformed aryl thiocyanate quickly reacted to the corresponding aryl trifluoromethyl thioether **2** in the presence of a mixture of $TMSCF_3$ and Cs_2CO_3, a process that does not require copper. Thus, a Sandmeyer trifluoromethylthiolation pathway involving $CuSCF_3$ species was ruled out. Based on these results, we propose a mechanistic cycle, as depicted in Scheme 3.

The diazonium salt is initially converted into the thiocyanate *via* a Sandmeyer process, in which the $Cu^{I}SCN$ species first transfers a single electron to the diazonium salt (I). The resulting diazo radical II releases nitrogen gas with the formation of an aryl radical III, which takes up the thiocyano group from the copper(II) intermediate to form the aryl thiocyanate IV. The presence of intermediate radicals was confirmed by the finding that the addition of TEMPO resulted in strongly

Table 2 Scope of the trifluoromethylthiolation of arenediazonium salts[ab]



[a] *Reaction conditions*: 1 mmol of arenediazonium tetrafluoroborate in 4 mL MeCN and 2 equiv. of $TMSCF_3$ were slowly added to 0.5 equiv. CuSCN and 2 equiv. Cs_2CO_3 in 4 mL MeCN and stirred for 12 h at RT. Isolated yields are noted. [b] Yields determined by ^{19}F NMR using 1,3-difluorobenzene as an internal standard.

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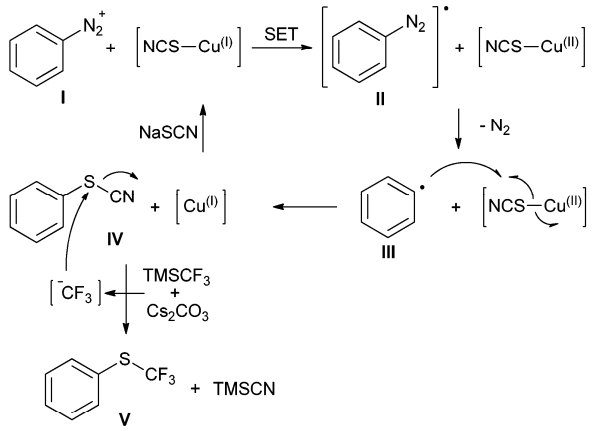

Scheme 3 Proposed mechanism.

decreased yields (20%). In the presence of Cs_2CO_3, the nucleophilic trifluoromethylation reagent $TMSCF_3$ does not interfere with the above reaction steps, but efficiently converts the newly formed aryl thiocyanate to the trifluoromethyl thioether. This nucleophilic displacement of a cyanide leaving group by CF_3 is promoted by Cs_2CO_3, probably by coordinating to the silicon atom in $TMSCF_3$.

Conclusion

In conclusion, we have developed a straightforward, inexpensive and expedient method for the regiospecific conversion of arenediazonium salts into the corresponding aryl trifluoromethyl thioethers. The reaction is broadly applicable to electron-rich and electron-poor arene- and heteroarenediazonium salts and tolerates various functional groups. The availability of the substrates from the large pool of aromatic amines, the use of inexpensive reagents and the mild reaction conditions make this reaction particularly attractive for various applications from drug discovery to industrial-scale syntheses.[5]

Experimental section

The standard procedure for the synthesis of trifluoromethyl thioethers from the corresponding arenediazonium salts is as follows. Under a nitrogen atmosphere, an oven-dried 20 mL crimp cap vessel with a Teflon-coated stirrer bar was charged with copper thiocyanate (61.4 mg, 0.50 mmol), caesium carbonate (652 mg, 2.00 mmol) and sodium thiocyanate (122 mg, 1.50 mmol). Acetonitrile (4 mL) was added *via* syringe and the resulting suspension was stirred at room temperature for 10 minutes. A solution of the arenediazonium tetrafluoroborate (1.00 mmol) in acetonitrile (4 mL) was added dropwise *via* syringe and the reaction mixture was stirred for another 10 minutes. Trifluoromethyl-trimethylsilane (321 μL, 2.00 mmol) was then added *via* syringe and the mixture was stirred at ambient temperature for 16 h. The resulting mixture was filtered through a short pad of Celite (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further purified by flash chromatography (SiO_2, diethyl ether–hexane gradient), yielding the corresponding trifluoromethyl thioethers.

Acknowledgements

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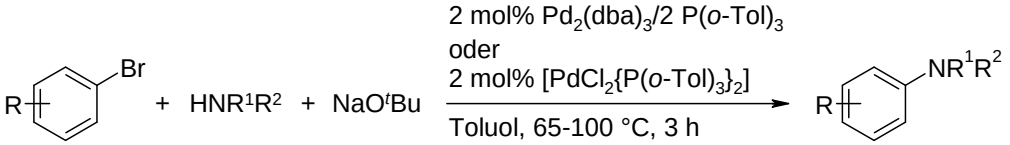
4.3. Selektive Monoarylierung primärer Amine

4.3.1. Hintergrund

Klassisch erfolgen C–N Bindungsknüpfungen über die Kupfer–vermittelte Ullmann–Goldberg–Reaktion von Arylhalogeniden mit aromatischen Aminen,[254,255] die nukleophile Substitution elektronenarmer aromatischer oder heteroaromatischer Halogenide,[38] die Additionen an Arinintermediate[256–258] oder die reduktive Alkylierungen primärer Amine.[39] Diese Methoden besitzen alle inhärente Limitierungen, etwa eine begrenzte Substratbreite oder eine geringe Toleranz gegenüber funktionellen Gruppen. In den letzten zwanzig Jahren wurden zahlreiche Verfahren zur Palladium–katalysierten C–N Bindungsknüpfung entwickelt, die allgemein unter dem Begriff der Buchwald–Hartwig–Kupplungen bekannt sind.[259–262] Diese Reaktionen erlauben den Einsatz eines breiten Substratspektrums und gehören mittlerweile zum Standardrepertoir eines jeden Laborchemikers.

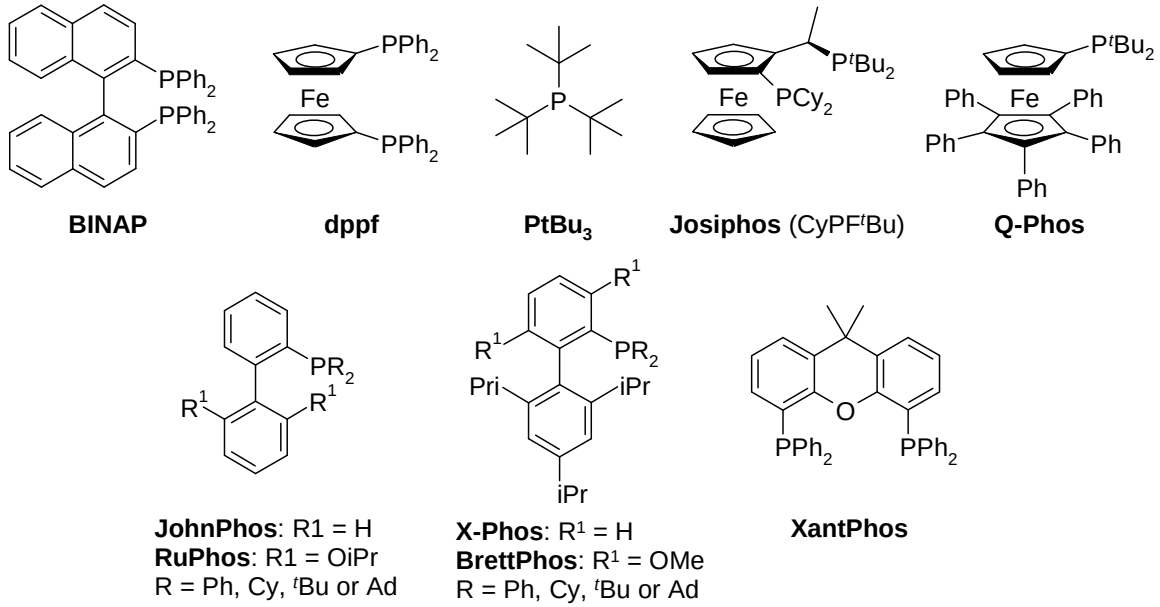


4.3.1-1 **4.3.1-2** **4.3.1-3** **4.3.1-4**

Schema 53: Buchwald–Hartwig–Aminierung sekundärer Amine.

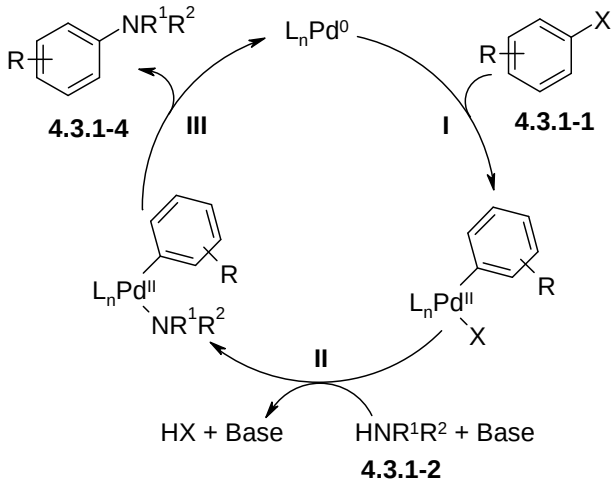
Aufbauend auf den Pionierarbeiten von Kosugi, Kameyama und Migita zur Kupplung von Zinnamiden mit Arylhalogeniden[263] erschienen 1995 zeitgleich Arbeiten von Buchwald[264] und Hartwig[265] zur Palladium–katalysierten Kupplung sekundärer, aromatischer Amine mit Arylbromiden und –iodiden in Gegenwart einer Base (Schema 53). Der Einsatz der bidentaten Phosphinliganden BINAP[266,267] und dppf[268] ermöglichte kurz darauf auch die Kupplung primärer Amine. Elektronenreiche, sterisch gehinderte Phosphanliganden zeigten sich in nachfolgenden Studien als besonders aktiv in der Transformation günstiger Arylchloride (Schema 54).[269] Während sich Hartwigs Arbeiten dabei hauptsächlich mit P^{t}Bu$_3$[159,270] und den Ferrocenylliganden Josiphos[271] und Q–Phos[272] beschäftigten, entwickelte die Gruppe um Buchwald unter anderem die Biarylphosphine JohnPhos,[273] RuPhos,[274] XPhos[275] und BrettPhos.[276] Diese Liganden liefern maßgeschneiderte Katalysatorsysteme zur Kupplung einer Vielzahl von Substraten bereits bei Raumtemperatur und Katalysatorbeladungen weit

unter 1 mol%. In den Folgejahren wurden noch zahlreiche weitere potente Ligandensysteme entwickelt, darunter Xantphos durch van Leeuwen,[277] Triaminophosphine durch Verkade,[278–281] Adamantyl–[282] und Imidazolylphosphine[283] durch Beller und zahlreiche NHC–Liganden,[284,285] die die Anwendungsbreite der Palladium–katalysierten C–N Bindungsknüpfung noch erweitern.



Schema 54: Liganden zur Palladium–katalysierten Buchwald–Hartwig–Aminierung.

Mechanistisch verläuft die Aminierungsreaktion zunächst über die oxidative Addition des Arylhalogenids an den Palladium(0)–Katalysator (Schema 55, **I**).[260] Es folgt die Koordination und Deprotonierung des primären oder sekundären Amins (**II**), gefolgt von der reduktiven Eliminierung des Produkts (**III**), bei der die aktive Palladium(0)–Spezies gleichzeitig regeneriert wird.

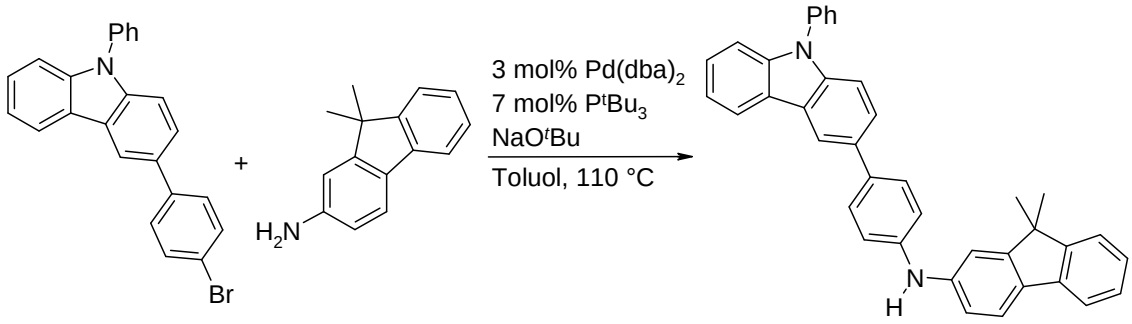


Schema 55: Mechanismus der Buchwald–Hartwig–Aminierung.

Neben der Synthese wichtiger Pharmaka und Pflanzenschutzmittel ist die Buchwald–Hartwig–Aminierung von großer Bedeutung für die Synthese neuer Funktionsmaterialien, etwa den Lochleiterschichten moderner OLED– und Photovoltaik–Anwendungen.[286–289] Diese Lochleitermaterialien bestehen in der Regel aus komplexen Triarylaminen, die sequentiell aus einem Anilinderivat und zwei Arylhalogeniden aufgebaut werden. Obwohl die modernsten Katalysatorsysteme eine C–N Bindungsknüpfung bereits bei Raumtemperatur ermöglichen,[159] ist die hochselektive Monoarylierung primärer Aniline noch immer problematisch. Selbst die selektivsten Katalysatorsysteme benötigen einen Überschuss von 1.2–1.4 Äquivalenten des Amins[267,276,290] und damit verbunden auch zusätzliche Trennungsschritte bei der Produktisolierung.

4.3.2. Pd(dippf)maleimid als hochselektives Katalysatorsystem

In Zusammenarbeit mit der Umicore AG & Co. KG erfolgte die Entwicklung eines neuen Katalysatorsystems zur selektiven Monoarylierung äquimolarer Substratmengen in konzentrierter Reaktionslösung. Auf Kundenwunsch wurde die Kupplung eines Carbazolderivates mit 2–Fluorenamin als Modellreaktion gewählt (Schema 56).



4.3.2-1a **4.3.2-2a** **4.3.2-3a**

Schema 56: Modellreaktion zur Optimierung der C–N Bindungsknüpfung.

In zahlreichen Kontrollexperimenten wurden zunächst Katalysatoren unterschiedlichster Struktur miteinander verglichen. In fast allen Fällen wurden deutliche Mengen des diarylierten Nebenprodukts gebildet. Die hohe UV Absorption des Produkts und des Nebenprodukts erlaubten deren einfache dünnschichtchromatographische Detektion und Auswertung unter UV Licht, sodass selbst kleinste Spuren des diarylierten Nebenprodukts unmittelbar sichtbar waren.

Es erfolgte ein umfangreiches Ligandenscreening, bei dem die geringsten Nebenproduktmengen mit Ferrocenylphosphin–Liganden mit dialkylsubstituierten

Phosphinen beobachtet wurden. Die weitaus höchste Selektivität wurde mit 1,1'−Bis(diisopropylphosphino)ferrocen (dippf) erhalten. Andere Liganden, auch solche, die bekanntermaßen bei Arylierungen mit Arylbromiden besonders hohe Ausbeuten liefern, erwiesen sich als deutlich weniger selektiv. Gewöhnlich wird dippf nur selten für Arylierungen von Aminen eingesetzt und hat sich bisher nie als ausgesprochen vorteilhaft erwiesen. Umso erstaunlicher war es, dass mit diesem System gerade für die Kombination aus Arylaminen und Arylbromiden so gute Ergebnisse erzeugt wurden. Mit einem *in situ* aus $Pd(dba)_2$ und dippf erzeugten Katalysatorsystem und in Gegenwart von 1.2 Äquivalenten KO^tBu als Base konnte gezeigt werden, dass in Toluol bei 70 °C selbst in konzentrierter Reaktionslösung ausschließlich das monoarylierte Produkt gebildet wird. Unter diesen Bedingungen konnte die Katalysatorbeladung zudem von 3 mol% auf 0.2 mol% gesenkt werden.

Neben diesem *in situ* gebildeten Katalysator wurde die kristalline Koordinationsverbindung Pd(dippf)maleimid als präformierte Spezies dargestellt und Pd(dippf)(vs)tol als lagerstabile Katalysatorlösung in Toluol als alternative Katalysatordarreichungsform entwickelt. Alle Ergebnisse des Ligandenscreenings und der Optimierungsarbeiten, die Untersuchungen der Anwendungsbreite, die Synthesen im präparativen Maßstab und der Einsatz des Katalysators in Eintopfreaktionen sind im nachfolgenden Manuskriptentwurf enthalten. Die selektive Monoarylierung wurde weiterhin zum Patent angemeldet, weshalb die Veröffentlichung des Manuskripts derzeit noch zurückgehalten wird. Die Katalysatorlösung Pd(dippf)(vs)tol ist bei Umicore mittlerweile kommerziell verfügbar.

COMMUNICATION

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Pd(dippf)maleimide as highly selective catalyst for the monoarylation of primary amines

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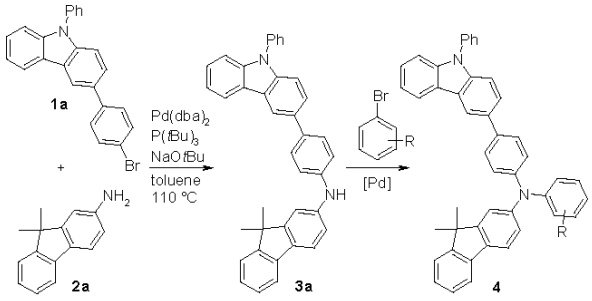
Abstract. Pd(dippf)maleimide was found to selectively promote the Pd-catalyzed monoarylation of primary amines using a catalyst loading of 0.2 mol% in concentrated solution. The advantage of the catalyst system was demonstrated on the selective formation of several secondary amines, preparative scale syntheses and the one-pot synthesis of tertiary amines. Furthermore, Pd(dippf)vs was introduced as ready-made catalyst solution.

Keywords: amination; heterocycles; homogeneous catalysis; palladium; phosphane ligands

Since the first report in 1987 by Tang and Van Slyke,[1] organic light emitting diodes (OLED) have undergone a tremendous development.[2] An intensive research effort has vastly improved the performance and lifetime of electroluminescent materials and has led to their application in digital displays and solid-state lighting.[3] Beside polymer-based devices,[4] especially small molecule OLEDs proved to exhibit an excellent efficiency and a high durability.[2c] Furthermore, they allow a high flexibility in molecular design and the exact deposition of thin layers by vacuum sublimation.[5]

Modern OLEDs have multilayered structures, consisting of an emitter layer that is usually situated between electron and hole transporting layers and the positive and negative electrodes. Among the hole transport materials, triphenylamine-based compounds with carbazole[6] and fluorene[7] moieties possess a remarkably high thermal stability ($\Delta T_{5\%}$) and glass transition temperature (T_g), important parameters for the development of organic semiconductors. However, the quality of the precursors is crucial for the desired longevity and performance of electronical devices and advanced solutions for their high-purity fabrication are constantly sought.

Nowadays, arylamines are commonly synthesized via Buchwald-Hartwig amination, the transition-metal catalysed coupling of primary or secondary amines with aryl bromides or chlorides in the presence of a base (Scheme 1).[8,9] However, known procedures for the synthesis of diarylamines often employ an excess of the primary amine or catalyst loadings higher than 1 mol% of palladium.



Scheme 1. Sequential synthesis of tertiary amines.

Therefore, we headed out for the development of a convenient, scalable and highly selective monoarylation procedure that works in high concentration, requires only equimolar amounts of the coupling partners and small amounts of palladium.

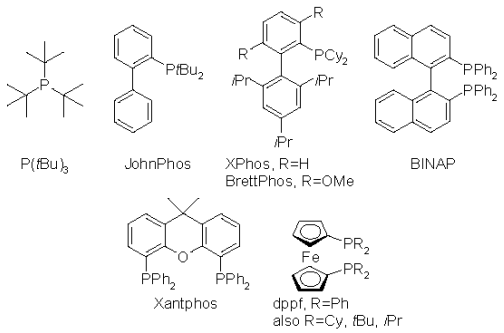


Figure 1. State-of-the-art ligand systems.

Several state-of-the-art catalyst systems (Figure 1)[8] were benchmarked in the model reaction of 4-bromotoluene (**1b**) with aniline (**2b**) in the presence of 1.2 equivalents of NaO*t*Bu as base and toluene as solvent (Table 1). After 20 h at 70 °C, most of the catalysts led to a full conversion of the starting materials (entries 1–11), only the Pd-NHC systems

were far less effective and furnished the desired product **3b** in only 7-9% yield (entries 12, 13).

Table 1. Benchmark of several state-of-the-art catalysts.[a)]

Entry	Pd source	Ligand	Yield [%]	
			3b	**5b**
1	$Pd(PtBu_3)_2$	-	91	4
2	$[Pd(\mu Br)(PtBu_3)]_2$	-	90	4
3	$Pd(dba)_2$	JohnPhos	90	2
4	"	XPhos	94	1
5	"	CyBrettPhos	87	1
6	"	BINAP	71	1
7	"	XantPhos	88	2
8	"	dppf	72	1
9	"	dcypf	76	trace
10	"	dtbupf	92	4
11	"	dippf	94	n.d.
12	(IPr)Pd(allyl)Cl	-	9	n.d.
13	(IPr)Pd(cinnamyl)Cl	-	7	n.d.
14	Pd(dippf)vs	-	92	n.d.
15	Pd(dippf)maleimmide	dippf	93	n.d.

[a)] *Conditions:* 1.00 mmol of **1b**, 1.00 mmol of **2b**, 1.20 mmol NaO*t*Bu, 0.2 mol% Pd source, 0.3 mol% of a monodentate ligand or 0.2 mol% of a bidentate ligand, 1 mL toluene, 70 °C, 20 h. GC yields with *n*-tetradecane as internal standard. dippf = 1,1'-Bis(diisopropylphosphino)ferrocene.

However, the formation of the desired amine was always accompanied by the formation of the byproduct **5b** in 1-4%. Only the ferrocenyl ligand dippf led to the selective formation of the secondary amine and did not even show traces of **5b** (entry 11).

To confirm these findings, the screening experiments were repeated with the large π-conjugated starting materials depicted in Scheme 1.[10] The catalysts with the electron-rich $P(tBu)_3$ as well as the Buchwald type biaryl phosphines led to the precipitation of the white product already after 30 minutes. In contrast, the catalysts employing bidentate phosphine ligands required significantly longer to form substantial amounts of the desired product, probably due to the steric bulk of the ligands. The conversion was followed by TLC and showed comparable selectivities as before. While GC yields of 1-4% for the side product seemed negligible, the huge π-conjugated skeleton of the amine led to significant spots under UV light. This underlines the necessity of an absolutely selective amination catalyst, especially for applications where material or manufacturing faults cannot only alternate the conductivity of the electrical material, but can lead to its premature deterioration and, in case of OLEDs, the formation of black spots.[11]

We continued to explore the reactivity of Pd(0)dippf complexes and found that a ready-made catalyst solution of Pd(dippf)vs (vs = 1,3-divinyltetramethyldisiloxane) in toluene serves equally well in the mentioned couplings (Table 1, entry 14) and allows the convenient liquid addition to the starting materials.

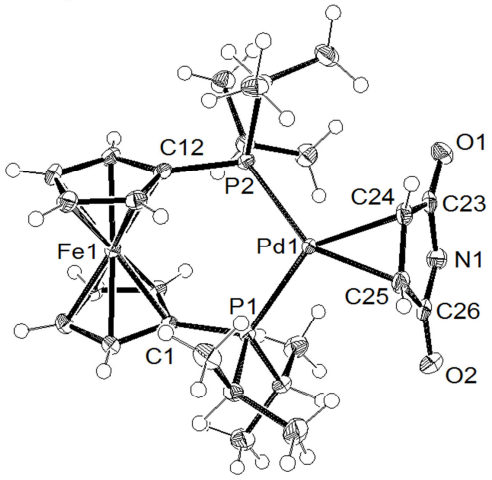


Figure 2. ORTEP illustration of Pd(d*i*ppf)maleimide **6** (50% probability ellipsoids).

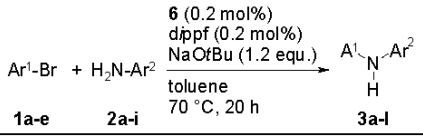
Upon the addition of maleimide to a Pd(dippf)vs solution in diethyl ether, Pd(dippf)maleimide (**6**) precipitates as air-stable yellow solid. Albeit this preformed complex showed a slightly lower reactivity than the in situ generated complex from $Pd(dba)_2$, additional dippf not only compensated this effect,[10] but also rendered the catalyst more robust in terms of thermal stability and selectivity at reaction temperatures higher than 80 °C. Using the combination of **6** and dippf in the synthesis of **3b** led to an isolated yield of 94%. Figure 2 illustrates the structure of complex **6** with a dippf bite angle of 105.9° and the η^2-coordinated maleimide ligand.

Having the optimal catalyst system in hand, we next examined the scope of the monoarylation reaction (Table 2). Several mono- and polycyclic aromatic compounds, dibenzofurane and –thiophene as well as carbazole and fluorene derivatives were selectively transformed into the corresponding secondary amines in excellent yields and selectivities. Furthermore, ketones and also secondary amines were tolerated under the reaction conditions, without undesired nucleophilic additions or arylations.

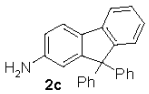
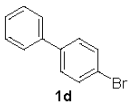
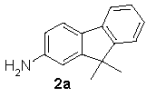
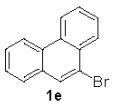
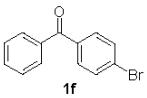
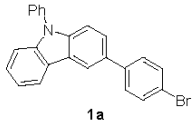
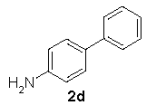
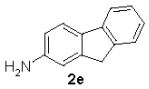
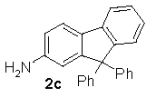
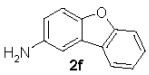
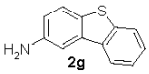
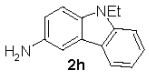
To further investigate the utility of the protocol in preparative scale syntheses, we employed 0.2 mol% **6** with 0.1 mol% dippf or 0.2 mol% Pd(dippf)vs in 20 mmol scale reactions and isolated **3a** in 97% respectively 92% yield.

We next tried to use the selective formation of the secondary amines in the one-pot synthesis of tertiary amines and added *p*-anisyl chloride to the model reaction depicted in Table 1. While the aryl chloride stayed unchanged after 20 h at 70 °C, the remaining

Table 2. Reaction scope of the monoarylation reaction.[a)]



1a-e 2a-i 3a-l

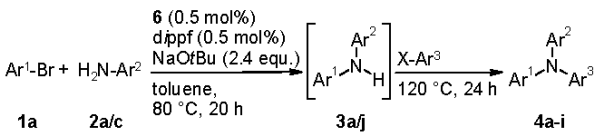
Entry	Ar^1-Br	H_2N-Ar^2	Yield [%]
1	 1c	 2c	95
2	 1d	 2a	89
3	 1e	"	87
4	 1f	"	76
5	 1a	"	94
6	"	 2d	95
7	"	 2e	92
8	"	 2c	93
9	"	 2f	88
10	"	 2g	96
11	"	 2h	95
12	"	 2i	84

[a)] *Conditions:* 1.00 mmol aryl bromide, 1.00 mmol amine, 1.20 mmol NaO*t*Bu, 0.2 mol% **6** and 0.2 mol% dippf, 2 mL toluene, 70 °C, 20 h.

reaction proceeded as desired. Increasing the reaction temperature from 70 °C to 120 °C for another 24 h led to the formation of the tertiary amine along with some unreacted secondary amine. Further optimizations showed that 0.5 mol% of the catalyst, a small excess of the second aryl halide and an initial reaction temperature of 80 °C were beneficial to entirely convert the intermediate secondary amine into the final product and to increase the solubility of the additional base. However, the best selectivity was achieved when the second halide was not directly added to the reaction mixture, but after 20 h, when the secondary amine was already formed.

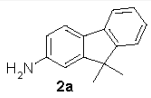
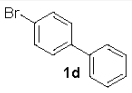
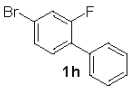
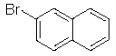
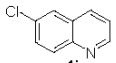
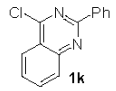
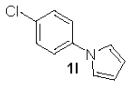
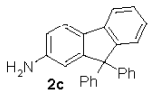
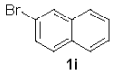
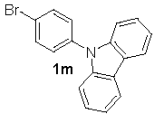
The scope of the one-pot procedure is illustrated in Table 3. Aryl chlorides and bromides served equally well as coupling partners. Beside the unfunctionalized biaryl and naphthyl substituents, also quinolinyl, quinazolinyl and *N*-arylpyrrole derivatives were tolerated and furnished the corresponding products in excellent yields.

Table 3. Highly selective synthesis of tertiary amines.[a)]



1a 2a/c 3a/j 4a-i

Ar^1 = 4-(9-phenyl-9H-carbazol-3-yl)phenyl; X = Br, Cl

Entry	H_2N-Ar^2	X-Ar^3	Yield [%]
1	 2a	 1d	92
2	"	 1h	94
3	"	 1i	96
4	"	 1j	91
5	"	 1k	75
6	"	 1l	95
7	 2c	 1i	96
8	"	 1m	95

[a)] *Conditions:* 1.00 mmol Ar^1-Br, 1.00 mmol amine, 2.40 mmol NaO*t*Bu, 0.5 mol% **6** and 0.5 mol% d*i*ppf, 2 mL toluene, 80 °C, 20 h. Then 1.10 mmol Ar^3-X in 0.5 mL toluene, 120 °C, 24 h.

In conclusion, a catalyst system consisting of Pd(dippf)maleimide and dippf efficiently promotes the selective monoarylation of primary amines without traces of the diarylated side product. The reaction scope was demonstrated on the preparation of various secondary amines of particular importance for the synthesis of functional materials. The utility of the new protocol was shown in preparative scale

syntheses and the one-pot synthesis of several tertiary amines. The overall process complements the known amination procedures and offers a new synthetic tool for the highly selective formation of amines without undesired byproducts. This report may stimulate the development of new generations of functional materials with new light emitting properties and electrical behaviors.

Experimental Section

Standard procedure for the selective monoarylation of primary amines: A dry 20 mL crimp cap vessel was charged with the aryl bromide (1.00 mmol), the primary amine (1.00 mmol), sodium *tert*-butoxide (118 mg, 1.20 mmol) and a magnetic stir bar and was kept in vacuum for 10 min. After three nitrogen-vacuum cycles, a stock solution of Pd(dippf)maleimide (1.24 mg, 0.002 mmol) and dippf (0.85 mg, 0.002 mmol) in dry, distilled toluene (2 mL) was added via syringe. The reaction mixture was stirred at 70 °C for 20 h, cooled to room temperature and diluted with dichloromethane (30 mL) and water (30 mL). The aqueous layer was separated and extracted with fresh dichloromethane (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo (40 °C, 500 mbar). The crude product was further purified by flash chromatography (basic Al_2O_3, hexane/ethyl acetate or hexane/diethyl ether), yielding the corresponding amine (76-96%).

One-pot procedure for the synthesis of tertiary amines: A dry 20 mL crimp cap vessel was charged with the aryl bromide (1.00 mmol), the primary amine (1.00 mmol), sodium *tert*-butoxide (235 mg, 2.40 mmol) and a magnetic stir bar and was kept in vacuum for 10 min. After three nitrogen-vacuum cycles, a stock solution of Pd(dippf)maleimide (3.11 mg, 0.005 mmol) and dippf (2.13 mg, 0.005 mmol) in dry, distilled toluene (2 mL) was added via syringe. The reaction mixture was stirred at 80 °C for 20 h, whereupon a solution of the second aryl halide (1.10 mmol) in toluene (0.5 mL) was added via syringe. The temperature was increased to 120 °C and the mixture was stirred for another 24 h, then allowed to cool to room temperature and diluted with dichloromethane (30 mL) and water (30 mL). The aqueous layer was separated and extracted with fresh dichloromethane (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo (40 °C, 500 mbar). The crude product was further purified by flash chromatography (basic Al_2O_3, hexane/ethyl acetate), yielding the corresponding tertiary amine (75-96%).

Acknowledgements

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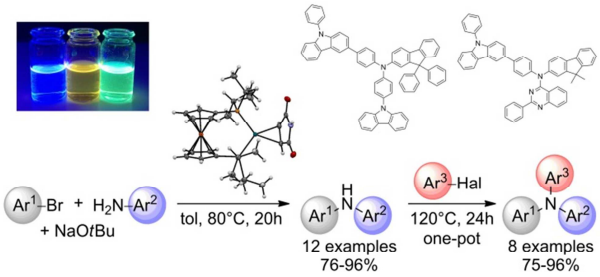
COMMUNICATION

Highly selective monoarylation of primary amines with Pd(d*i*ppf)maleimide

Adv. Synth. Catal. **2015**, *Volume*, Page – Page

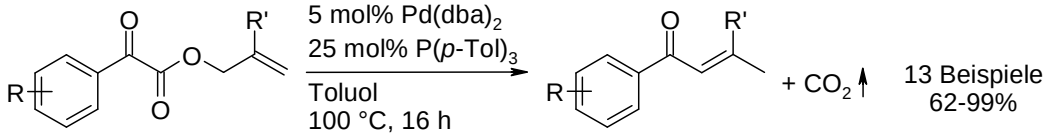
M. F. Grünberg, L. J. Gooßen*



5. Zusammenfassung der Arbeit

Im Rahmen dieser Arbeit konnten neue Konzepte zur nachhaltigen und regioselektiven C–C, C–S und C–N Bindungsknüpfung entwickelt werden. Das Spektrum der bearbeiteten Themengebiete umfasste dabei hauptsächlich decarboxylierende Kupplungen, aber auch Sandmeyer–analoge Reaktionen und Buchwald–Hartwig–Kupplungen.

Ausgehend von der decarboxylierenden Allylierung besonders aktivierter β–Ketocarbonsäureallylester konnte zunächst ein effizientes Katalysatorsystem zur Aktivierung und decarboxylierenden Kupplung präformierter α–Ketocarbonsäureallylester entwickelt werden, mit dem zahlreiche Phenylglyoxylsäureester in hohen Ausbeuten zum α,β–ungesättigten Keton umsetzt werden können (Schema 57). Der entscheidende Decarboxylierungsschritt erfolgt dabei organokatalytisch durch ein freies Phosphan und führt zu Acylanionen, die in der Koordinationssphäre des Palladiums gekuppelt werden. Diese Decarboxylierung entspricht formal der Umpolung eines Aldehyds, bei der aber keine zusätzlichen Schutzgruppen benötigt werden.



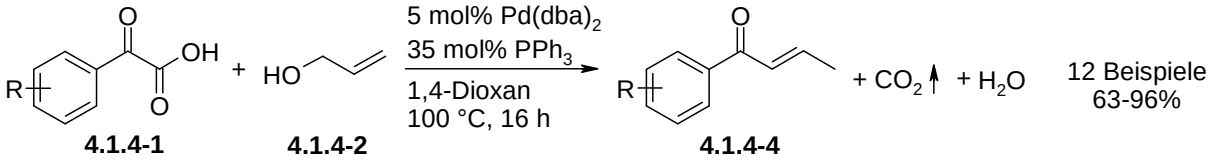
4.1.2-1 **4.1.2-3**

Schema 57: Decarboxylierende Allylierung präformierter Phenylglyoxylsäureester.

Aufbauend auf diesen Arbeiten erfolgte die Entwicklung intermolekularer Reaktionsvarianten, bei denen die freien Arylglyoxylsäuren direkt umgesetzt werden können und eine vorangehende Estersynthese entfällt. Unter den getesteten Allylquellen zeigte sich Diallylcarbonat als besonder aktiv, da der Palladium(0)–Katalysator zunächst in eine C(Allyl)–O Bindung insertiert und das Carbonat anschließend in einem Metatheseschritt gegen das Carboxylat austauscht. Die Produktbildung erfolgt daraufhin analog zur intramolekularen Reaktionsvariante.

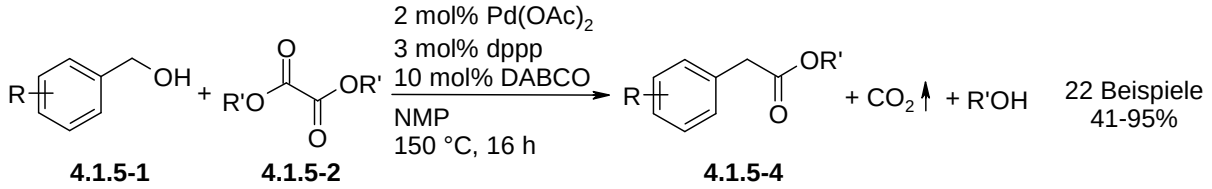
In nachfolgenden Studien wurde die Kombination aus *in situ* Veresterung und decarboxylierender Kupplung einer Arylglyoxylsäure mit Allylalkohol näher untersucht. Dabei konnte ein effizientes Katalysatorsystem bestehend aus $Pd(dba)_2$ und PPh_3 entwickelt werden, das in 1,4–Dioxan zunächst den Veresterungsschritt begünstigt, den gebildeten

Allylester aktiviert und bei 100 °C decarboxylierend zum Produkt überführt (Schema 58). Als Nebenprodukte dieser salzfreien Kupplung werden lediglich Wasser und CO_2 gebildet.



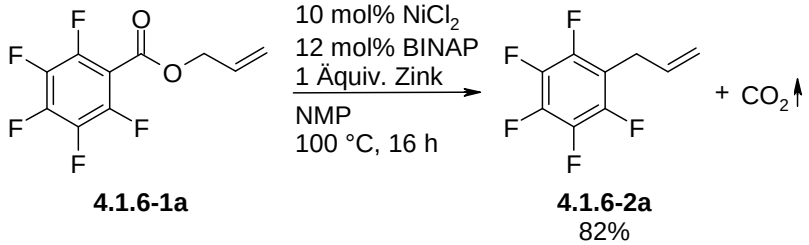
Schema 58: Decarboxylierende Allylierung mit Allylalkohol.

Das Reaktionskonzept der vorgelagerten Veresterung mit anschließender C–O Aktivierung und irreversibler Decarboxylierung konnte weiterhin auch erfolgreich auf die decarboxylierende Benzylierung von Oxalsäureestern erweitert werden (Schema 59). Dabei werden die Benzyloxalate zunächst Phosphan–katalysiert aus den Benzylalkoholen und Dialkyl– oder Diaryloxalaten gebildet, vom Palladium(0)–Katalysator aktiviert und in Gegenwart des Organokatalysators DABCO decarboxylierend gekuppelt. Auch hier konnte die Anwendungsbreite anhand zahlreicher Substrate demonstriert werden.



Schema 59: Decarboxylierende Benzylierung von Oxalaten.

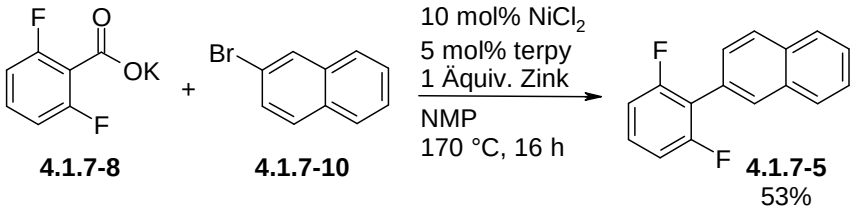
Nachfolgend wurde die Reaktivität von Benzoesäureallylestern untersucht. Dabei erfolgten zunächst Machbarkeitsstudien mit einem Palladium(0)–Katalysator und danach die Entwicklung einer Nickel–katalysierten decarboxylierenden Allylierung (Schema 60). Bei dieser Reaktion zeigte sich die Kombination aus $NiCl_2$, BINAP und Zinkpulver als besonders aktiv und konnte die Modellverbindung in 82% Ausbeute zum gewünschten Produkt überführen.



Schema 60: Nickel–katalysierte decarboxylierende Allylierung von Benzoaten.

Die Nickel–katalysierte Decarboxylierung wurde zunächst in der Protodecarboxylierungsreaktion näher untersucht und dann mit der C–O Bindungsaktivierung

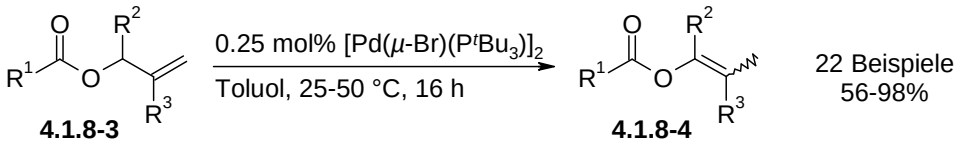
kombiniert. Da dies aber zu zahlreichen unselektiven Nebenreaktionen und maximalen Produktausbeuten von 25% führte, wurde die Biarylsynthese ausgehend von Arylestern nicht weiter verfolgt. Stattdessen wurde die Reaktivität zahlreicher Kohlenstoffelektrophile, darunter Arylbromide, –triflate, –tosylate, –mesylate und –sulfamate, in Nickel–katalysierten decarboxylierenden Kreuzkupplungen untersucht. Neben der überwiegenden reduktiven Homokupplung konnte das gewünschte Biaryl allerdings nur in maximal 53% Ausbeute dargestellt werden (Schema 61). Die Entwicklung neuer *N*–Donorliganden wird in zukünftigen Arbeiten eine zentrale Rolle spielen, denn nur die effektive Unterdrückung aller Nebenreaktionen kann zur selektiven Produktbildung führen.



4.1.7-8 **4.1.7-10** **4.1.7-5** 53%

Schema 61: Nickel–katalysierte decarboxylierende Kreuzkupplung von Arylbromiden.

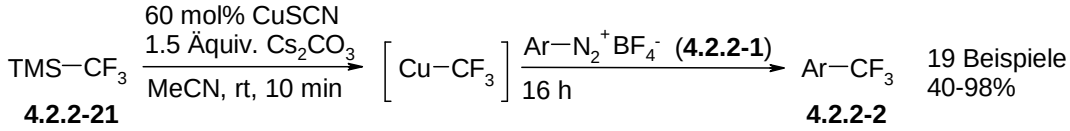
Im Rahmen der decarboxylierenden Allylierung wurde die Aktivität zahlreicher Katalysatorsysteme getestet, darunter auch die des Palladium(I)–Dimers $[Pd(\mu\text{–}Br)(P^tBu_3)]_2$. Überraschend führte dieses aber nicht zur C–O Bindungsaktivierung und Decarboxylierung, sondern zur Doppelbindungsisomerisierung und der damit verbundenen Synthese wertvoller Enolester (Schema 62). Die Optimierung der Reaktionsbedingungen führte zu einem hochaktiven Katalysatorsystem, das selbst den besten literaturbekannten Isomerisierungskatalysatoren weit überlegen ist.



4.1.8-3 **4.1.8-4**

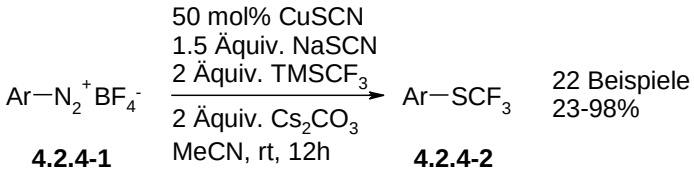
Schema 62: $[Pd(\mu\text{–}Br)(P^tBu_3)]_2$ katalysierte Doppelbindungsisomerisierung.

In einem weiteren Teilprojekt erfolgte die Entwicklung einer Sandmeyer–analogen Trifluormethylierungsreaktion. Dabei können leicht zugängliche Aryldiazoniumsalze mit *in situ* generierten Cu–CF_3 Verbindungen bereits bei Raumtemperatur in die entsprechenden Benzotrifluoride überführt werden (Schema 63). Die Anwendungsbreite dieser milden Reaktion konnte an zahlreichen aromatischen und heteroaromatischen Diazoniumsalzen demonstriert werden.



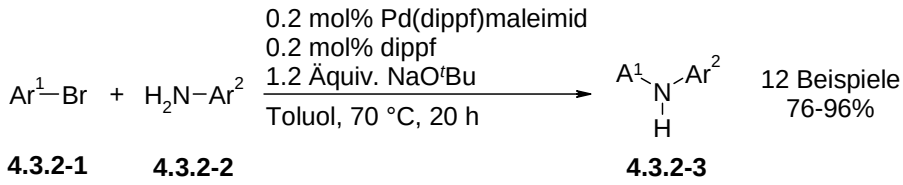
Schema 63: Sandmeyer–analoge Trifluormethylierung von Aryldiazoniumsalzen.

Nachfolgende Arbeiten führten zur Erweiterung dieses Reaktionskonzepts auf die Sandmeyer–Trifluormethylthiolierung. Dabei erfolgt zunächst eine Sandmeyer–Thiocyanierung zum Arylthiocyanat, welches in Gegenwart von Rupperts Reagenz direkt in das trifluormethylthiolierte Produkt überführt wird. Auch dieses Verfahren ermöglicht die Umsetzung (hetero)aromatischer Diazoniumsalze unter sehr milden Reaktionsbedingungen und ermöglicht die Funktionalisierung selbst hochkomplexer Verbindungen.



Schema 64: Sandmeyer–analoge Trifluormethylthiolierung von Aryldiazoniumsalzen.

Im letzten Teilprojekt dieser Doktorarbeit ergab sich aus einer Kooperation mit Umicore die anwendungsbezogene Optimierung eines Kreuzkupplungsverfahrens zur selektiven Monoarylierung primärer Amine mit äquimolaren Arylbromidmengen in konzentrierter Lösung. In einem umfangreichen Ligandenscreening zeigte sich der bidentate Ligand dippf allen anderen System überlegen und ermöglichte nicht nur die hochselektive Synthese der Zielverbindung, sondern auch eine Verringerung der Katalysatorbeladung von 3 mol% auf 0.2 mol%.



Schema 65: Hochselektive Monoarylierung aromatischer Amine.

Neben den Synthesen im präparativen Maßstab konnte die Anwendungsbreite an zahlreichen Substraten mit ausgedehnten konjugierten π–Systemen demonstriert werden. Weiterhin wurden auch andere Darreichungsformen des Katalysators untersucht und sowohl das präformierte Pd(dippf)maleimid als auch die Katalysatorlösung Pd(dippf)(vs)tol entwickelt, von denen letztere mittlerweile kommerziell von Umicore vertrieben wird.

6. Experimenteller Teil

6.1. Allgemeine Anmerkungen

6.1.1. Chemikalien und Lösungsmittel

Kommerziell verfügbare Chemikalien wurden bei einem Reinheitsgrad von ≥95% direkt eingesetzt oder andernfalls nach Standardverfahren aufgereinigt.[291] Luft– und feuchtigkeitsempfindliche Substanzen wurden mit Standard–Schlenktechniken stets unter einer Stickstoff– oder Argonatmosphäre gelagert und gehandhabt. Flüssige Einsatzstoffe wurden unmittelbar vor der Reaktion mit dem Durchleiten von Argon (20 min) von Sauerstoff befreit. Toluol, 1,4–Dioxan und Mesitylen wurden über Natrium/Benzophenon getrocknet. NMP und DMF wurden durch die azeotrope Destillation mit Toluol von Feuchtigkeitsspuren befreit. Acetonitril, Diglyme und DMSO wurden zunächst über CaH_2 refluxiert und anschließend fraktionierend destilliert. Alle Lösungsmittel wurden über Molsieben (3 Å) gelagert, die zuvor im Mikrowellenofen (2 × 2 min, 600 W) erhitzt und im Vakuum (10^{-3} mbar) abgekühlt wurden. Die Benzoate wurden vor der Verwendung 1 h im Vakuum (10^{-3} mbar) bei Raumtemperatur getrocknet. Alle anderen organischen Salze wurden über Nacht bei 60 °C im Vakuum (10^{-3} mbar) getrocknet. Die anorganischen Salze wurden über Nacht im Vakuum (10^{-3} mbar) auf 160 °C erhitzt.

6.1.2. Durchführung von Parallelreaktionen

Die Reihenversuche wurden in 20 mL Headspace–Vials für die Gaschromatographie durchgeführt und mit Aluminium–Bördelkappen mit Teflon–beschichteten Butylgummisepten verschlossen. Das Aufheizen der Gefäße erfolgte in 8 cm hohen Aluminiumblöcken mit 7 cm tiefen, zylindrischen Bohrungen vom Durchmesser der Reaktionsgefäße und einer Bohrung für den Temperaturfühler. Der Durchmesser der Heizblöcke entsprach genau dem der Heizplatten gängiger Labor–Magnetrührer.

Zum parallelen Evakuieren und Rückbefüllen mehrerer Reaktionsgefäße wurden Vakuumverteiler verwendet, die an die Schlenk–Linie angeschlossen werden konnten. Diese Verteiler verfügten über jeweils zehn vakuumfeste 3 mm Teflonschläuche mit Adaptern zur Befestigung von Luer–Lock–Spritzennadeln.

Die festen Einsatzstoffe der Reihenversuche wurden an der Luft in die Reaktionsgefäße eingewogen, 20 mm Magnet–Rührkerne zugegeben und mit einer Septumkappe luftdicht verschlossen. Das Einwiegen besonders luft– oder feuchtigkeitsempfindlicher Substanzen erfolgte in einer Glovebox mit Stickstoff als Inertgas. Die Gefäße wurden in die Bohrungen eines Aluminiumblocks gesteckt und über die Hohlnadeln mit dem Vakuumverteiler verbunden. Die Reaktionsgefäße wurden anschließend dreimal hintereinander evakuiert und mit Stickstoff rückbefüllt. Mit Hilfe von Spritzen wurden die reinen Lösungsmittel, Stammlösungen oder flüssigen Einsatzstoffe durch die Septen hindurch injiziert. Anschließend wurde der Aluminiumblock auf Reaktionstemperatur gebracht und die Hohlnadeln des Vakuumverteilers entfernt.

Nach Ablauf der Reaktionszeit und dem Abkühlen auf Raumtemperatur wurden die Gefäße vorsichtig geöffnet und mit einem geeigneten organischen Lösungsmittel und Wasser verdünnt. Die Phasen wurde mit einer 1 mL Einwegpipette zunächst gut durchmischt und 1.5 mL der organischen Phasen anschließend durch 0.3 mL trockenes Magnesiumsulfat in 2 mL GC–Probengläschen filtriert. Dabei wurden Glaspipetten als Filter verwendet, die mit einem Wattepfropfen versehen waren. Die so vorbereiteten Proben wurden schließlich gaschromatographisch untersucht.

6.1.3. Analytische Methoden

Dünnschichtchromatographische Untersuchungen wurden mit Kieselgel DC–Folien Polygram SIL G/UV254 der Firma Macherey–Nagel durchgeführt. Zur Detektion der Substanzen wurden Fluoreszenzlöschungen bei 254 nm und Fluoreszenzen bei 366 nm genutzt.

Säulenchromatographische Trennungen erfolgten mit einem Combi Flash Companion–Chromatographie–System der Firma Isco–Systems. Als stationäre Phase wurden fertig gepackte RediSep und Grace Reveleris Flashkieselgel–Kartuschen oder Telos Kartuschen mit basischem Aluminiumoxid (0.063–0.200 mm, Aktivitätsstufe I) verwendet.

Gaschromatographische Untersuchungen erfolgten mit einem Hewlett Packard 6890 und HP−5−Säulen mit 5% Phenyl−Methyl−Siloxan (30 m × 320 µm × 1.0 µm) der Firmen Agilent, Macherey−Nagel und Perkin Elmer. Dabei betrug die Temperatur des Injektors 220 °C und die des Detektors 330 °C. Das Standardtemperaturprogramm startete mit 2 min bei 60 °C, gefolgt von einem linearen Temperturanstieg auf 300 °C mit einer Rate von 30 °C/min. Anschließend wurden die 300 °C für weitere 3 min gehalten.

Massenspektren wurden mit einem Varian GC−MS Saturn 2100 T oder einem Agilent GC−MS 5973N System gemessen. Die Ionisierung erfolgte dabei per Elektronenstoß (EI). Hochauflösende Massenspektren wurde mit einem Waters GTC Premier erhalten.

Infrarotspektroskopische Messungen erfolgten mit einem Perkin Elmer Fourier Transform Spektrometer oder einem Perkin Elmer Spectrum BX, FT−IR System (He, Ne 633 nm < 0.4 mW). Die Signalintensitäten sind mit vs (very strong), s (strong), m (medium) und w (weak) angegeben.

Der Großteil der NMR Spektren wurde mit einem Bruker AMX 400 System gemessen. Dabei wurden Benzol−d_6, Chloroform−*d*, Deuteriumoxid, Dioxan−d_8, Methanol−d_4 und Toluol−d_8 als Lösungsmittel und Wasserstoff−, Kohlenstoff−, Fluor− und Phosphorresonanzen von 400 MHz, 101 MHz, 376 MHz bzw. 162 MHz verwendet. Einzelne Messungen erfolgten weiterhin an Bruker FT−NMR DPX 200 und Avance 600 Geräten und sind jeweils als solche gekennzeichnet. Die Auswertung der Spektren erfolgte mit ACD−Labs 12. Die Multiplizität der Signale wird durch die Abkürzungen s = Singulett, d = Dublett, dd = Dublett eines Dubletts, dt = Dublett eines Tripletts, t = Triplett, usw. angegeben. Alle Kopplungskonstanten sind in Hertz angegeben.

Die Elementaranalysen wurden mit einem Hanau Elemental Analyzer vario Micro cube durchgeführt. Alle Schmelzpunkte wurden mit einem Mettler FP61 bestimmt.

6.2. Synthesis of α,β–Unsaturated Ketones by Pd–Catalyzed Decarboxylative Allylation of α–Oxocarboxylates

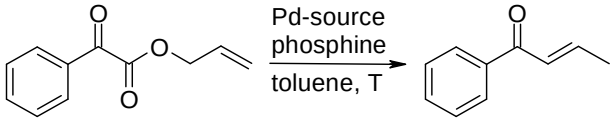
6.2.1. General Methods

Pyridine was dried using KOH followed by fractioned distillation prior to use. Toluene and mesitylene were dried by fractioned distillation from sodium prior to use. All other compounds are commercially available and were used without further purification.

Compounds **4.1.2–4a**, **4.1.2–4k** and **4.1.2–4l** are commercially available. The other derivatives, **4.1.2–4b** [CAS: 7163–50–0],[28] **4.1.2–4c** [CAS: 26153–26–4],[28] **4.1.2–4d** [CAS: 79477–86–4],[28] **4.1.2–4e** [CAS: 76590–50–6],[292] **4.1.2–4f** [CAS: 577744–48–0],[292] **4.1.2–4g** [CAS: 5449–21–8],[28] **4.1.2–4h** [CAS: 577744–34–4],[292] **4.1.2–4i** [CAS: 79477–86–4],[292] **4.1.2–4j** [CAS: 467435–08–1][292] and **4.1.2–4m** [CAS: 7099–91–4][292] were synthesised following known synthetic procedures in 61–98% yields.

6.2.2. Catalyst development

Reaction conditions: 0.50 mmol allyl–2–oxophenylacetate (**4.1.2–1aa)**, 5 mol% palladium, 15 mol% phosphine (7.5 mol% for bidentate phosphines), 4.0 mL toluene, 4 h. Yields were determined by GC analysis using *n*–dodecane as internal standard; a) 20 mol% P(*p*–Tol)$_3$; b) 25 mol% P(*p*–Tol)$_3$



4.1.2-1aa **4.1.2-3aa**

Entry	Pd–source	phosphine	T (°C)	Yield/%
1	$Pd(PPh_3)_4$	–	25	0
2	“	–	60	0
3	“	–	80	5
4	“	–	100	15
5	$Pd_2(dba)_3$	–	100	0
6	”	”	100	29
7	”	P(*p*–$ClC_6H_4)_3$	”	21
8	”	P(*p*–Tol)$_3$	”	37
9	”	P(*p*–$MeOC_6H_4)_3$	”	24
10	”	P(^{i}Pr)(Ph)$_2$	”	18
11	”	PCy_3	”	0
12	”	CyJohnPhos	”	9
13	”	BINAP	”	0
14[a]	”	P(*p*–Tol)$_3$	”	59
15[b]	”	”	”	79

6.2.3. Mechanistic Studies

Decarboxylative allylation cross–over experiment

A 20 mL vessel was charged with tris(dibenzylideneacetone)dipalladium(0) (22.9 mg, 0.025 mmol) and tri–*p*–tolylphosphine (77.6 mg, 0.25 mmol). After the vessel was flushed with alternating vacuum and nitrogen purge cycles, a solution of **4.1.2–1ab** (205 mg, 1 mmol) and **4.1.2–1ba** (204 mg, 1 mmol) in mesitylene (4 mL) was added via syringe. The reaction mixture was stirred at 150 °C for 12 h and cooled to room temperature, *n*–dodecane (50 mL) was then added via syringe and the sample was analyzed via GC and GC–MS. The GC chromatogram showed 4 signals that based on their mass patterns were assigned as **4.1.2–3aa** (20%), **4.1.2–3ab** (14%), **4.1.2–3ba** (18%), **4.1.2–3bb** (9%).

Transesterification experiment

A 20 mL vessel was charged with **4.1.2–1ab** (205 mg, 1 mmol), **4.1.2–1ba** (204 mg, 1 mmol) and mesitylene (4 mL). The reaction mixture was stirred at 150 °C for 12 h and was then allowed to cool to room temperature, *n*–dodecane (50 µl) was added via syringe and the sample was analyzed via GC and GC–MS. The GC chromatogram showed 2 signals that based on their mass patterns were assigned as **4.1.2–1ab** and **4.1.2–1ba**.

Time dependent study

A 20 mL crimp cap vessel was charged with tris(dibenzylideneacetone)dipalladium(0) (11.4 mg, 0.012 mmol) and tri–*p*–tolylphosphine (38.8 mg, 0.125 mmol). The vessel was flushed with alternating vacuum and nitrogen purge cycles, a solution of **4.1.2–1** (1mmol) in toluene (4 mL) was added via syringe. The reaction mixture was stirred at 100 °C, stopped after 30min and then cooled to room temperature. To the reaction mixture *n*–dodecane (50 µl) was added via syringe. The sample was analyzed via GC, the chromatogram showed the formation of **4.1.2–1aa** (88%) and **4.1.2–3aa** (4%).

Decarboxylative allylation in the presence of a carbonate base

A 20 mL crimp cap vessel was charged with with tris(dibenzylideneacetone)dipalladium(0) (11.4 mg, 0.012 mmol), tri–*p*–tolylphosphine (38.8 mg, 0.125 mmol) and potassium carbonate (69.1 mg, 0.5 mmol). After the vessel was flushed with alternating vacuum and nitrogen purge

cycles, a solution of **4.1.2–1** (0.5 mmol) in toluene (4 mL) was added via syringe. The reaction mixture was stirred at 100 °C for 12 h, cooled to room temperature and *n*–dodecane (50 µl) was added via syringe. The sample was analyzed via GC and the chromatogram showed the formation of **4.1.2–3aa** (17%).

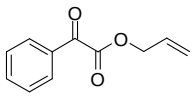
6.2.4. Synthesis of the allyl α–oxocarboxylates

Standard procedure for the synthesis of the allyl α–oxocarboxylates.

A 50 mL vessel was charged with a solution of the α–oxocarboxylic acid **4.1.2–4** (10 mmol) in CH_2Cl_2 (5 mL). To this, a solution of DMAP (122 mg, 1.00 mmol) in CH_2Cl_2 (2 mL) and the allylic alcohol (1.17 g, 20 mmol) were added via *syringe*. The reaction mixture was then cooled to 0 °C and stirred for 15 min before adding a solution of DCC (3.09 g, 15 mmol) in CH_2Cl_2dropwise. After 6 h, the reaction mixture was filtered, diluted with 20 mL of saturated aqueous $NaHCO_3$ and extracted with Et_2O (3x30 mL). The organic layers were combined and washed with saturated NaCl aqueous solution (2x20 mL). After drying ($MgSO_4$), the solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, ethyl acetate/hexane (1:10)) yielding the corresponding allyl α–oxocarboxylates **4.1.2–1aa–4.1.2–1la** (62–99%).

Synthesis of ally–2–oxo–2–phenylacetate (4.1.2–1aa).

[CAS: 62936–34–9]



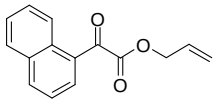
Compound **4.1.2–1aa** was prepared following the standard procedure, starting from phenylglyoxylic acid (**4.1.2–4a**) (1.50 g, 10.00 mmol). After purification **4.1.2–1aa** was isolated as colourless liquid (3.14 g, 80%).

^{1}H–NMR (600 MHz, $CDCl_3$) δ= 8.02 (dd, *J*=8.2, 1.2 Hz, 2H) 7.67 (t, *J*=7.5 Hz, 1H) 7.52 (t, *J*=7.8 Hz, 2H) 6.03 (m, 1H) 5.46 (dd, *J*=17.2, 1.3 Hz, 1H) 5.36 (dd, *J*=10.3, 0.9 Hz, 1H) 4.88 ppm (d, *J*=6.2 Hz, 2H); **^{13}C–NMR** (151 MHz, $CDCl_3$) δ: 186.0, 163.4, 134.9, 132.4, 130.7,

130.0, 128.9, 120.0, 66.5 ppm; **CHN** Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30 found: C, 69.51; H, 5.25.

Synthesis of allyl 2–(1–naphthyl)–2–oxoacetate (4.1.2–1ca).

[CAS: 1360924–08–8]

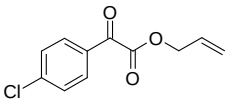


Compound **4.1.2–1ca** was prepared following the standard procedure, starting from 1–naphthylglyoxylic acid (**4.1.2–4c**) (2.00 g, 10.00 mmol). After purification **4.1.2–1ca** was isolated as brown oil (2.36 g, 98%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 9.05 (s, 1H), 8.09 (s, 1H), 7.97 (s, 1H), 7.89 (s, 1H), 7.67 (s, 1H), 7.55 (s, 2H), 6.04 (s, 1H), 5.46 (s, 1H), 5.35 (s, 1H), 4.91 ppm (s, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 188.4, 164.2, 135.9, 134.0, 133.8, 130.9, 130.8, 129.2, 128.7, 128.0, 127.0, 125.5, 124.2, 119.9, 66.6 ppm; **MS** (Ion trap, EI): m/z (%) = 240 [M^+] (60), 155 (100), 127 (64), 101 (40), 77 (5); **CHN** Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.0; H, 5.0; found: C, 75.1; H, 5.2.

Synthesis of allyl 2–(4–chlorphenyl)–2–oxoacetate (4.1.2–1da).

[CAS: 1360924–09–9]

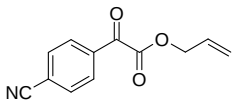


Compound **4.1.2–1da** was prepared following the standard procedure, starting from 4–chlorphenylglyoxylic acid (**4.1.2– 4.1.2–4d**) (1.85 g, 10.00 mmol). After purification **4.1.2–1da** was isolated as brown oil (1.80 g, 80%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.96 (m, *J*=8.5 Hz, 2H), 7.47 (m, *J*=8.5 Hz, 2H), 6.00 (ddt, *J*=16.9, 10.7, 5.9, 5.9 Hz, 1H), 5.44 (dd, *J*=17.2, 1.2 Hz, 1H), 5.34 (d, *J*=10.6 Hz, 1H), 4.86 ppm (d, *J*=6.1 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 184.4, 162.7, 141.6, 131.3, 130.8, 130.5, 129.2, 120.1, 66.7 ppm; **MS** (Ion trap, EI): m/z (%) = 224 [M^+] (40), 111 (100), 127 (44), 85 (40), 51 (4). **CHN** Anal. Calcd. for $C_{11}H_9ClO_3$: C, 58.8; H, 4.0; found: C, 58.6; H, 4.2.

Synthesis of allyl 2–(4–cyanophenyl)–2–oxoacetate (4.1.2–1ea).

[CAS: 1360924–10–2]

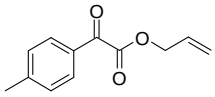


Compound **4.1.2–1ea** was prepared following the standard procedure, starting from 4–cyanophenylglyoxylic acid (**4.1.2–4e**) (1.75 g, 10.00 mmol). After purification **4.1.2–1ea** was isolated as yellow oil (2,15 g, 99%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 8.11 (d, *J*=8.2 Hz, 2H), 7.79 (d, *J*=8.2 Hz, 2H), 5.92 – 6.03 (m, 1H), 5.42 (d, *J*=17.2 Hz, 1H), 5.33 (d, *J*=10.2 Hz, 1H), 4.85 ppm (d, *J*=5.9 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 184.0, 161.8, 135.3, 132.4, 130.2, 120.2, 117.7, 117.4, 66.9 ppm; **MS** (Ion trap, EI): m/z (%) = 215 [M^+] (1), 130 (100), 102 (36), 75 (8), 51 (4); **CHN** Anal. Calcd. for $C_{12}H_{12}NO_3$: C, 66.9; H, 4.2; N, 6.5; found: C, 70.3; H, 4.3; N, 6.5.

Synthesis of allyl–2–oxo–2–(4–tolyl)acetate (4.1.2–1ba).

[CAS: 1360924–11–3]

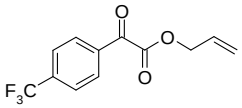


Compound **4.1.2–1ba** was prepared following the standard procedure, starting from 4–methylphenylglyoxylic acid (**4.1.2–4b**) (1.64 g, 10.00 mmol). After purification **4.1.2–1ba** was isolated as brown oil (1.50 g, 63%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.91 (d, *J*=8.2 Hz, 2H), 7.31 (d, J=8.2 Hz, 2H), 5.97 – 6.08 (m, 1H), 5.45 (d, *J*=16.4 Hz, 1H), 5.35 (d, *J*=10.6 Hz, 1H), 4.87 (d, *J*=5.9 Hz, 2H), 2.43 ppm (s, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 185.6, 163.5, 146.2, 130.7, 130.0, 129.9, 129.5, 119.7, 66.3, 21.8 ppm; **MS** (Ion trap, EI): m/z (%) = 204 [M^+] (2), 119 (100), 91 (46), 65 (22), 51 (12); **CHN** Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.5; H, 5.9; found: C, 70.1; H, 5.6.

Synthesis of allyl–2–oxo–2–(4–(trifluoromethyl)phenyl)acetate (4.1.2–1fa).

[CAS: 1360924–12–4]

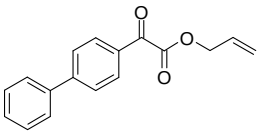


Compound **4.1.2–1fa** was prepared following the standard procedure, starting from 4–trifluoromethylphenylglyoxylic acid (**4.1.2–4f**) (2.18 g, 10.00 mmol). After purification **4.1.2–1fa** was isolated as beige oil (1.8 g, 70%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 8.16 (t, *J*=7.2 Hz, 2H) 7.78 (t, *J*=8.2 Hz, 2H) 5.96 – 6.07 (m, 1H) 5.45 (d, *J*=17.2 Hz, 1H) 5.29 – 5.40 (m, 1H) 4.88 ppm (d, *J*=5.9 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 184.6 162.4 135 (q, $^{1}J_{C-F}$= 272 Hz) 130.4, 130.0, 125.9, 125.9, 125.8 (q, $^{2}J_{C-F}$= 27.2 Hz), 121.9, 118.7, 67.0 ppm; **MS** (Ion trap, EI): m/z (%) = 258 [M^+] (13), 239 (22), 173 (100), 145 60), 125 (32); **CHN** Anal. Calcd. for $C_{11}H_9FO_3$: C, 63.4; H, 4.3; found: C, 63.0; H, 4.6.

Synthesis of allyl 2–([1,1'–biphenyl]–4–yl)–2–oxoacetate (4.1.2–1ga).

[CAS: 25789–67–7]

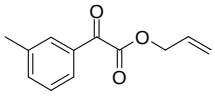


Compound **4.1.2–1ga** was prepared following the standard procedure, starting from 4–biphenylglyoxylic acid (**4.1.2–4g**) (2.26 g, 10.00 mmol). After purification **4.1.2–1ga** was isolated as colourless solid (2.14 g, 79%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 8.09 (d, *J*=8.6 Hz, 2H), 7.71 (d, *J*=8.2 Hz, 2H), 7.61 (d, *J*=7.0 Hz, 2H), 7.38 – 7.49 (m, 3H), 5.35 (m, 1H), 5.47 (d, *J*=18.4 Hz, 1H), 5.35 (d, *J*=9.4 Hz, 1H), 4.89 ppm (d, *J*=5.9 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 185.4, 163.3, 147.4, 139.2, 130.9, 130.7, 130.5(2 C), 128.9 (2 C), 128.5, 127.3(2 C), 127.2 (2 C), 119.8, 66.4 ppm; **CHN** Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30 found: C, 76.49; H, 5.26.

Synthesis of allyl–2–oxo–2–(3–tolyl)acetate (4.1.2–1ha).

[CAS: 1360924–14–6]

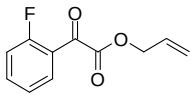


Compound **4.1.2–1ha** was prepared following the standard procedure, starting from 3–methylphenylglyoxylic acid (**4.1.2–4h**) (1.64 g, 10.00 mmol). After purification **4.1.2–1ha** was isolated as brown oil (1.93 g, 93%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.72 – 7.79 (m, 2H), 7.40 – 7.44 (m, 1H), 7.35 (t, *J*=8.0 Hz, 1H), 5.93 – 6.03 (m, 1H), 5.41 (d, *J*=17.2 Hz, 1H), 5.30 (d, *J*=10.6 Hz, 1H), 4.84 (d, *J*=5.9 Hz, 2H), 2.37 ppm (s, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 186.2, 163.5, 138.7, 135.7, 132.2, 130.7, 130.1, 128.6, 127.2, 119.7, 66.3, 21.1 ppm; **MS** (Ion trap, EI): m/z (%) = 204 [M^+] (6), 176 (2), 119 (100), 91 (30), 65(10); **CHN** Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.5; H, 5.9; found: C, 70.8; H, 5.8.

Synthesis of allyl–2–(2–fluorophenyl)–2–oxoacetate (4.1.2–1ia).

[CAS: 1360924–15–7]

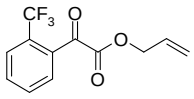


Compound **4.1.2–1ia** was prepared following the standard procedure, starting from 2–fluorophenylglyoxylic acid (**4.1.2–4i**) (1.68 g, 10.00 mmol). After purification **4.1.2–1ia** was isolated as yellow oil (1.73 g, 81%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.89 (t, *J*=7.4 Hz, 1H), 7.61 (q, *J*=6.9 Hz, 1H), 7.23 – 7.30 (m, 1H), 7.09 – 7.18 (m, 1H), 5.91 – 6.02 (m, 1H), 5.40 (d, *J*=17.2 Hz, 1H), 5.30 (d, *J*=10.6 Hz, 1H) 4.82 ppm (d, *J*=5.9 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 183.7, 164.0, 163.7, 161.4, 136.8, 136.8, 130.8, 130.7, 124.9, 124.8, 120.0, 116.7, 116.5, 66.8 ppm; **MS** (Ion trap, EI): m/z (%) = 208 [M^+] (10), 180 (5), 123 (99), 95 (70); **CHN** Anal. Calcd. for $C_{11}H_9FO_3$: C, 63.4; H, 4.3; found: C, 63.2; H, 4.4.

Synthesis of allyl–2–oxo–2–(2–(trifluoromethyl)phenyl)acetate (4.1.2–1ja).

[CAS: 1360924–16–8]

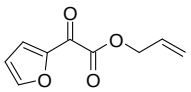


Compound **4.1.2–1ja** was prepared following the standard procedure, starting from 2–trifluoromethylphenylglyoxylic acid (**4.1.2–4j**) (2.18 g, 10.00 mmol). After purification **4.1.2–1ja** was isolated as beige oil (1.60 g, 62%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.72 – 7.76 (m, 1H), 7.58 – 7.69 (m, 3H), 5.89 – 6.00 (m, *J*=16.9, 11.0, 5.8, 5.5 Hz, 1H), 5.27 – 5.37 (m, 2H), 4.80 ppm (d, *J*=6.0 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 186.4, 160.7, 134.2, 132.0, 131.8, 130.4, 128.6 (q, $^{2}J_{C–F}$= 30 Hz), 126.9 (q, $^{3}J_{C–F}$= 3 Hz), 123.5 (q, $^{1}J_{C–F}$= 273 Hz), 67.3 ppm; **MS** (Ion trap, EI): m/z (%) = 258 [M^+] (3), 174 (90), 146 (32), 125 (41), 75 (33).

Synthesis of allyl 2–(furan–2–yl)–2–oxoacetate (4.1.2–1ka).

[CAS: 1246524–59–3]

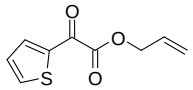


Compound **4.1.2–1ka** was prepared following the standard procedure, starting from 2–furylglyoxylic acid (**4.1.2–4k**) (1.40 g, 10.00 mmol). After purification **4.1.2–1ka** was isolated as beige oil (1.31 g, 72%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.68 (s, 1H), 7.60 (d, *J*=3.8 Hz, 1H), 6.51 – 6.55 (m, 1H), 5.88 (ddd, *J*=16.9, 11.3, 5.3 Hz, 1H), 5.32 (d, *J*=17.4 Hz, 1H), 5.21 (d, *J*=10.3 Hz, 1H), 4.72 ppm (d, *J*=5.8 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 170.5, 160.4, 149.5, 149.4, 130.4, 124.6, 119.7, 112.8, 66.7 ppm; **MS** (Ion trap, EI): m/z (%) = 180 [M^+] (8), 124 (13), 95 (100), 67 (33); **CHN** Anal. Calcd. for $C_9H_8O_4$: C, 60.0; H, 4.5; found: C, 59.8; H, 4.3.

Synthesis of allyl 2–(thionyl–2–yl)–2–oxoacetate (4.1.2–1la).

[CAS: 135386–31–1]

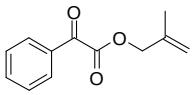


Compound **4.1.2–1la** was prepared following the standard procedure, starting from 2–thionylglyoxylic acid (**4.1.2–1la**) (1.59 g, 10.00 mmol). After purification **4.1.2–1la** was isolated as brown oil (1.60 g, 81%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 8.02 – 8.07 (m, 1H), 7.78 (d, *J*=5.0 Hz, 1H), 7.10 – 7.15 (m, 1H), 5.90 – 6.01 (m, *J*=16.9, 10.7, 5.8, 5.8 Hz, 1H), 5.38 (dd, *J*=17.2, 1.1 Hz, 1H), 5.28 (d, *J*=10.6 Hz, 1H), 4.79 ppm (d, *J*=5.8 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 175.9, 161.1, 138,.8 137.4, 137.1, 130.5, 128.6, 119.9, 66.8 ppm; **MS** (Ion trap, EI): m/z (%) = 196 [M^+] (11), 111 (100), 83 (65), 57 (32); **CHN** Anal. Calcd. for $C_9H_8O_3S$: C, 55.1; H, 4.1; found: C, 55.5; H, 4.0.

Synthesis of 2–methylallyl 2–oxo–2–phenylacetate (4.1.2–1ab).

[CAS: 1360924–17–9]



Compound **4.1.2–1ab** was prepared following the standard procedure, starting from phenylglyoxylic acid (**4.1.2–4a**) (1.50 g, 10.00 mmol) and 2–methyl–2–propen–2–ol (0.736 mg, 10 mmol). After purification **4.1.2–1ab** was isolated as yellow oil (1.76 g, 86%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.98 (d, *J*=7.8 Hz, 2H), 7.63 (t, *J*=7.4 Hz, 1H), 7.49 (t, *J*=7.8 Hz, 2H), 5.08 (s, 1H), 5.00 (s, 1H), 4.78 (s, 2H), 1.80 ppm (s, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 186.0, 163.5, 138.5, 134.9, 132.3, 129.9, 128.8, 114.5, 69.0, 19.4 ppm; **MS** (Ion trap, EI): m/z (%) = 205 [M^+] (1), 159 (2), 105 (100), 77 (12), 51 (6); **CHN** Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.5; H, 5.9; found: C, 70.2; H, 6.1.

6.2.5. Synthesis of α,β–unsaturated ketones

Standard procedure for the synthesis of α,β–unsaturated ketones (Method A).

A 20 mL crimp cap vessel was charged with tris(dibenzylideneacetone)dipalladium(0) (22.8 mg, 0.024 mmol) and tri–*p*–tolylphosphine (77.6 mg, 0.25 mmol). After the vessel was flushed with alternating vacuum and nitrogen purge cycles, a solution of **1** in toluene (4 mL) was added via syringe. The reaction mixture was stirred at 100 °C for 12 h and then cooled to room temperature. The solvent was removed by Kugelrohr distillation ($6x10^{-2}$ mbar) at 30–35 °C. The residue was further purified by flash chromatography (SiO_2, ethyl acetate/hexane (1:10)), yielding the corresponding products **4.1.2–3** in 62–99%.

Standard procedure for the synthesis of α,β–unsaturated ketones from α–oxo–carboxylic acids (Method B).

A 20 mL crimp cap vessel was charged with tris(dibenzylideneacetone)dipalladium(0) (11.4 mg, 0.012 mmol), tri–*p*–tolylphosphine (38.8 mg, 0.125 mmol), potassium carbonate (69.1 mg, 0.50 mmol) and molecular sieves 4 A (250 mg). After the vessel was flushed with alternating vacuum and nitrogen purge cycles, a solution of the *α*–oxo–carboxylic acid (**4.1.2–4**) (0.50 mmol) in mesitylene (4 mL) and the allyl chloride (**4.1.2–6a)** (57.4 mg, 0.75 mmol) were added via syringe. The reaction mixture was stirred at 150 °C for 12 h and then cooled to room temperature. The reaction mixture was filtered over celite and washed with 1N NaOH aqueous solution. After drying ($MgSO_4$), the solvent was removed by Kugelrohr distillation ($6x10^{-2}$ mbar) at 30–35 °C. The residue was further purified by flash chromatography (SiO_2, ethyl acetate/hexane (1:10)) yielding the corresponding products **4.1.2–3** (60–98%).

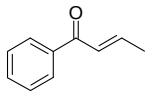
Preparative–scale procedure for the synthesis (E)–1–phenylbut–2–en–1–one (4.1.2–3aa).

An oven–dried, nitrogen–flushed, 100 mL vessel was charged with tris(dibenzylideneacetone)dipalladium(0) (458 mg, 0.5 mmol) and tri–*p*–tolylphosphine (776 mg, 2.5 mmol). After the vessel was flushed with alternating vacuum and nitrogen purge cycles, a degassed solution of **4.1.2–1aa** (1.92 g, 10 mmol) in toluene (60 mL) was added via *syringe*. The reaction mixture was stirred at 100 °C for 12 h and then cooled to room

temperature. The mixture was distilled trap–to–trap (4–6 x10^{-2} mbar, 26 °C) and the residue was further purified by flash chromatography (SiO_2, ethyl acetate/hexane (1:10)) yielding the (E)–1–phenylbut–2–en–1–one (3aa) 76% (1.12 g).

Synthesis of (E)–1–phenylbut–2–en–1–one (4.1.2–3aa).

[CAS: 35845–66–0]

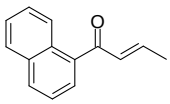


Compound **4.1.2–3aa** was prepared following Method A, starting from ally–2–oxo–2–phenylacetate (**4.1.2–1aa**) (190 mg, 1.00 mmol). After purification **4.1.2–3aa** was isolated as beige oil (145 mg, 99%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 7.94 (m, 2H), 7.52 (m, 1H), 7.45 (m, 2H), 7.07 (m, 1H), 6.93 (dq, *J*=1.6 Hz, 1H), 2.01 ppm (dd, *J*=6.8, 1.6 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 190.4, 144.9, 137.4, 132.2, 128.4 (4 C), 126.9, 18.5 ppm; **CHN** Anal. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.19; found: C, 82.29; H, 6.32. Alternatively **4.1.2–3aa** was also prepared from (**4.1.2–4a**) (75 mg, 0.5 mmol) following Method B in 60% yield (50 mg).

Synthesis of (E)–1–(naphthalen–1–yl)but–2–en–1–one (4.1.2–3ca).

[CAS: 880075–91–2]



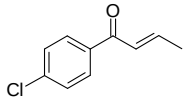
Compound **4.1.2–3ca** was prepared following Method A, starting from allyl 2–(1–naphthyl)–2–oxoacetate (**4.1.2–1ca**) (240 mg, 1.00 mmol). After purification **4.1.2–3ca** was isolated as brown oil (191 mg, 97%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 8.13 (d, *J*=7.8 Hz, 1H), 7.72 – 7.92 (m, 2H), 7.53 (d, *J*=7.0 Hz, 1H), 7.33 – 7.45 (m, 3H), 6.76 (dd, *J*=15.5, 6.8 Hz, 1H), 6.49 – 6.56 (m, 1H), 1.91 ppm (d, *J*=7.0 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 196.7, 147.9, 136.8, 132.9, 132.7, 131.1, 130.3, 128.9, 128.4, 128.3, 127.2, 125.6, 124.3, 18.5 ppm; **MS** (Ion trap, EI): m/z (%) = 196

[M^+] (63), 181 (100), 153 (23), 127 (96), 101 (11); **CHN** Anal. Calcd. for $C_{14}H_{12}O$: C, 85.6; H, 6.1; found: C, 85.8; H, 6.0.

Synthesis of (E)–1–(4–chlorophenyl)but–2–en–1–one (4.1.2–3da).

[CAS: 95826–96–3]

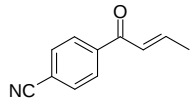


Compound **4.1.2–3da** was prepared following Method A, starting from 2–(4–chlorphenyl)–2–oxoacetate (**4.1.2–1ea**) (225 mg, 1.00 mmol). After purification **4.1.2–3da** was isolated as yellow oil (132 mg, 73%).

^{1}H–NMR (600 MHz, $CDCl_3$) δ= 7.88 (d, *J*=8.4 Hz, 2H), 7.44 (d, 8.5 Hz, 2H), 7.09 (dd, *J*=15.3, 7.0 Hz, 1H), 6.88 (dq, *J*=15.3, 1.8 Hz, 1H), 2.01 ppm (dd, *J*=6.9 Hz, 3H); **^{13}C–NMR** (151 MHz, $CDCl_3$) δ= 189.3, 144.6, 139.3, 136.5, 129.7 (2 C), 128.3 (2 C), 127.1, 18.4 ppm; **CHN** Anal. Calcd. for $C_{10}H_9ClO$: C, 66.49; H, 5.02; found: C, 66.62; H, 5.35. Alternatively **4.1.2–3da** was also prepared from (**4.1.2–4d**) (92 mg, 0.5 mmol) following Method B in 98% yield (89 mg).

Synthesis of (E)–4–but–2–enoylbenzonitrile (4.1.2–3ea).

[CAS: 959311–24–1]



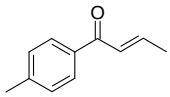
Compound **4.1.2–3ea** was prepared following Method A, starting from allyl 2–(4–cyanophenyl)–2–oxoacetate (**4.1.2–1ea**) (215 mg, 1.00 mmol). After purification **4.1.2–3ea** was isolated as yellow solid (165 mg, 96%).

m.p. 60–61 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ= 7.91 (d, *J*=7.6 Hz, 2H), 7.68 (d, *J*=7.6 Hz, 2H), 6.98 – 7.07 (m, 1H), 6.78 (d, *J*=15.4 Hz, 1H), 1.94 ppm (d, *J*=6.8 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 189.1, 147.0, 141.0, 132.2, 128.7 (2C), 126.8 (2C), 117.8, 115.5, 18.6 ppm;

MS (Ion trap, EI): m/z (%) = 171 [M^+] (85), 156 (44), 130 (100), 102 (79), 69 (99); **CHN** Anal. Calcd. for $C_{11}H_9NO$: C, 77.1; H, 5.3; found: C, 77.5; H, 5.7.

Synthesis of (E)–1–p–tolylbut–2–en–1–one (4.1.2–3ba).

[CAS: 604006–99–7]

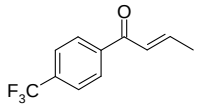


Compound **4.1.2–3ba** was prepared following Method A, starting from allyl–2–oxo–2–(p–tolyl)acetate (**4.1.2–1ba**) (204 mg, 1.00 mmol). After purification **4.1.2–3ba** was isolated as beige oil (100 mg, 62%).

^{1}H–NMR (600 MHz, $CDCl_3$) δ= 7.86 (m, *J*=8.2 Hz, 2H), 7.25 (m, *J*=7.9 Hz, 2H), 7.04 (m, 1H), 6.88 (dq, *J*=15.3, 1.6 Hz, 1H), 2.39 (s, 3H), 1.99 ppm (dd, *J*=6.7, 1.5 Hz, 3H); **^{13}C–NMR** (151 MHz, $CDCl_3$) δ= 190.5, 144.2, 143.1, 135.6, 129.1 (2 C), 128.8 (2 C), 127.3, 21.7, 18.5 ppm; **CHN** Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55; found: C, 82.28; H, 7.83.

Synthesis of (E)–1–(4–(trifluoromethyl)phenyl)but–2–en–1–one (4.1.2–3fa).

[CAS: 201164–24–1]

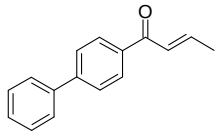


Compound **4.1.2–3fa** was prepared following Method A, starting from allyl–2–oxo–2–(4–(trifluoromethyl)phenyl)acetate (**4.1.2–1fa**) (258 mg, 1.00 mmol). After purification **3fa** was isolated as beige oil (167 mg, 78%).

^{1}H–NMR (600 MHz, $CDCl_3$) δ= 8.02 (d, *J*= 8.2 Hz, 2H), 7.76 (d, *J*=8.2 Hz, 2H), 7.14 (m, 1H), 6.87 (dq, *J*=15.3, 1.8 Hz, 1H), 2.03 ppm (dd, *J*=6.9, 1.6 Hz, 3H); **^{13}C–NMR** (151 MHz, $CDCl_3$) δ= 189.9, 146.6, 140.5, 133.3 (q, J_{CF}=33.3 Hz), 128.7 (2 C), 127.6 (2 C), 126.3 (q, J_{CF}=270.5 Hz), 125.7 (q, J_{CF}=4.2 Hz), 18.7 ppm; **CHN** Anal. Calcd. for $C_{11}H_9F_3O$: C, 61.68; H, 4.24; found: C, 61.34; H, 4.41.

Synthesis of (E)–1–(biphenyl–4–yl)but–2–en–1–one (4.1.2–3ga).

[CAS: 1360924–05–5]

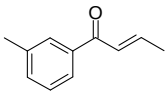


Compound **4.1.2–3ga** was prepared following Method A, starting from 2–([1,1'–biphenyl]–4–yl)–2–oxoacetate (**4.1.2–1ga**) (266 mg, 1.00 mmol). After purification **4.1.2–3ga** was isolated as beige oil (222 mg, 99%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 7.99 – 8.06 (m, 2H), 7.61 – 7.73 (m, 4H), 7.37 – 7.53 (m, 3H), 7.13 (dd, *J*=15.4, 6.8 Hz, 1H), 6.91–7.04 (dq, *J*=15.3, 1.6 Hz, 1H), 2.04 ppm (dd, *J*=6.8, 1.5 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 190.4, 144.1, 139.0, 136.6, 132.3, 132.0, 129.1 (2 C), 128.9 (2 C), 128.3, 127.5 (2 C), 127.3 (2 C), 18.6 ppm; **CHN** Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35; found: C, 86.53; H, 6.29.

Synthesis of (E)–1–m–tolylbut–2–en–1–one (4.1.2–3ha).

[CAS: 944344–73–4]

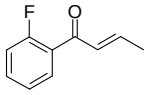


Compound **4.1.2–3ha** was prepared following Method A, starting from allyl–2–oxo–2–(*p*–tolyl)acetate (**4.1.2–1ha**) (148 mg, 1.00 mmol). After purification **4.1.2–3ha** was isolated as brown oil (111 mg, 70%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.81 (s, 1H), 7.75 (d, *J*=6.7 Hz, 1H), 7.32 – 7.40 (m, 2H), 7.00 – 7.19 (m, 1H), 6.75 – 6.83 (m, 1H), 2.46 (s, 3H), 1.98 (d, *J*=5.5 Hz, 2H), 1.97 ppm (s, 1H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 190.9, 144.8, 138.3, 137.9, 133.3, 129.0, 128.3, 127.6, 125.7, 21.3, 18.5 ppm; **MS** (Ion trap, EI): m/z (%) = 160 [M^+] (4), 119 (100), 91 (43), 65 (26); **CHN** Anal. Calcd. for $C_{11}H_{12}O$: C, 82.4; H, 7.5; found: C, 82.6; H, 7.8.

Synthesis of (E)–1–(2–fluorophenyl)but–2–en–1–one (4.1.2–3ia).

[CAS: 1360924–06–6]

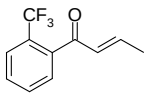


Compound **4.1.2–3ia** was prepared following Method A, starting from allyl–2–(2–fluorophenyl)–2–oxoacetate (**4.1.2–1ia**) (208 mg, 1.00 mmol). After purification **4.1.2–3ia** was isolated as brown oil (135 mg, 82%).

^{1}H–NMR (600 MHz, $CDCl_3$) δ= 7.65 (td, *J*=7.5, 1.8 Hz, 1H), 7.43 (ddd, *J*=15.6, 5.2, 1.8 Hz, 1H), 7.17 (t, *J*=7.5 Hz, 1H), 7.07 (dd, *J*=10.6, 9.1 Hz, 1H), 6.95 (ddd, *J*=15.4, 6.9, 1.8 Hz, 1H), 6.67 – 6.73 (m, 1H), 1.93 ppm (dd, *J*=6.9, 1.6 Hz, 3H); **^{13}C–NMR** (151 MHz, $CDCl_3$) δ= 189.4, 161.6, 160.0, 145.5, 133.5, 133.4, 131.0, 131.0, 130.6, 126.9, 126.8, 124.2, 116.3, 116.2, 18.4 ppm; **MS** (Ion trap, EI): m/z (%) = 164 [M^+] (54), 123 (100), 95 (40), 69 (59); **CHN** Anal. Calcd. for $C_{10}H_9FO$: C, 73.1; H, 5.5; found: C, 73.3; H, 5.2.

Synthesis of (E)–1–(2–(trifluoromethyl)phenyl)but–2–en–1–one (4.1.2–3ja).

[CAS: 1360924–07–7]

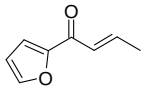


Compound **4.1.2–3ja** was prepared following Method A, starting from allyl–2–oxo–2–(2–(trifluoromethyl)phenyl)acetate (**4.1.2–1ja**) (258 mg, 1.00 mmol). After purification **4.1.2–3ja** was isolated as yellow oil (218 mg, 99%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.70 (d, *J*=7.8 Hz, 1H), 7.51 – 7.62 (m, 2H), 7.35 (d, *J*=7.4 Hz, 1H), 6.51 – 6.61 (m, 1H), 6.37 – 6.45 (m, 1H), 1.94 ppm (d, *J*=6.7 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 195.2, 149.2, 143.2, 138.6, 132.6, 130.0 (q, $^{2}J_{C-F}$= 34 Hz), 128.9, 128.3, 127.9, 127.8, 127.5, 126 (q, $^{3}J_{C-F}$= 3 Hz), 123.6 (q, $^{1}J_{C-F}$= 273 Hz) 122.2 18.5 ppm; **MS** (Ion trap, EI): m/z (%) = 214 [M^+] (20), 194 (8), 173 (43), 145 (47), 126 (8), 69 (100); **CHN** Anal. Calcd. for $C_{11}H_9F_3O$: C, 61.6; H, 4.2; found: C, 61.8; H, 4.3.

Synthesis of (E)–1–(furan–2–yl)but–2–en–1–one (4.1.2–3ka).

[CAS: 131323–45–0]

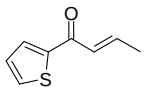


Compound **4.1.2–3ka** was prepared following Method A, starting from 2–(furan–2–yl)–2–oxoacetate (**4.1.2–1ka**) (180 mg, 1.00 mmol). After purification **4.1.2–3ka** was isolated as beige oil (120 mg, 88%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.53 (m, 1H), 7.15 – 7.31 (m, 2H), 6.89 (dq, *J*=15.4, 1.7 Hz, 1H), 6.68 (dd, *J*=3.7, 1.7 Hz, 1H), 2.01 ppm (dd, *J*=7.0, 1.6 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 170,3, 154.0, 145.6, 144.9, 126.3, 118.1, 111.9, 18.5 ppm; **CHN** Anal. Calcd. for $C_8H_8O_2$: C, 70.57; H, 5.92; found: C, 70.48; H, 5.73.

Synthesis of (E)–1–(thiophen–2–yl)but–2–en–1–one (4.1.2–3la).

[CAS: 13196–29–7]

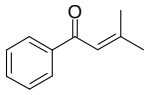


Compound **4.1.2–3la** was prepared following Method A, starting from allyl 2–(thionyl–2–yl)–2–oxoacetate (**4.1.2–1la**) (196 mg, 1.00 mmol). After purification **4.1.2–3la** was isolated as beige oil (117 mg, 77%).

^{1}H–NMR (600 MHz, $CDCl_3$) δ= 7.80 (dd, *J*=3.8, 0.9 Hz, 1H), 7.61 (dd, *J*=5.0, 0.9 Hz, 1H), 7.13 (m, 1H), 7.10 (d, *J*=6.7 Hz, 1H), 6.86 (dq, *J*=15.3, 1.8 Hz, 1H), 1.98 ppm (dd, *J*=7.0, 1.8 Hz, 3H); **^{13}C–NMR** (151 MHz, $CDCl_3$) δ= 182.9, 145.6, 144.7, 132.6, 130.8, 128.1, 125.7, 18.6 ppm; **CHN** Anal. Calcd. for C_8H_8OS: C, 63.13; H, 5.30; found: C, 63.21; H, 5.46.

Synthesis of 1–phenyl–3–methylbut–2–en–1–one (4.1.2–3ab).

[CAS: 5650–07–7]

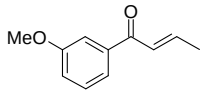


Compound **4.1.2–3ab** was prepared following Method A, starting from (**4.1.2–1ab**) (205 mg, 1.00 mmol). After purification **4.1.2–3ab** was isolated as brown oil (166 mg, 78%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 7.64 – 7.80 (m, 2H), 7.30 – 7.42 (m, 2H), 7.08 (m, 1H), 6.86 (m, 1H), 2.42 (s, 3H), 2.01 ppm (d, *J*=1.2 Hz, 3H); **^{13}C–NMR** (151 MHz, $CDCl_3$) δ = 190.1, 145.5, 137.6, 137.0, 133.2, 128.7, 128.1, 127.2, 124.7, 22.6, 18.6 ppm; **CHN** Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55; found: C, 82.29; H, 7.41.

Synthesis of (E)–1–(3–methoxyphenyl)but–2–en–1–one (4.1.2–3ma).

[CAS: 1087399–25–4]



Compound **4.1.2–3ma** was prepared following Method B, starting from 2–(3–methoxyphenyl)–2–oxoacetic acid (**4.1.2–4m**) (180 mg, 1.00 mmol). After purification **4.1.2–3ma** was isolated as brown oil (120 mg, 68%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.52 (m, 2H), 7.19 (m, 1H), 6.97 – 7.12 (m, 2H), 6.78 (dq, *J*=15.3 Hz, 1H), 3.53 (s, 3H), 1.97 ppm (d, *J*=7.0 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 191.0, 159.2, 145.4, 139.7, 128.1, 127.3, 121.0, 118.6, 112.7, 56.2, 18.5 ppm; **CHN** Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; found: C, 74.83; H, 6.80.

6.3. Decarboxylative Allylation of Glyoxylic Acids with Diallyl Carbonate

6.3.1. General Methods.

Dioxane was dried by fractional distillation from sodium prior to use. Compounds **4.1.3–1a**, **4.1.3–1f**, **4.1.3–1i**, **4.1.3–1k**, **4.1.3–1n**, **4.1.3–1o, 4.1.3–1p, 4.1.3–1q**, and **4.1.3–1r** are commercially available. The other derivatives, **4.1.3–1b** [CAS: 7163–50–0],[28] **4.1.3–1c** [CAS: 26153–26–4],[28] **4.1.3–1d** [CAS: 5449–21–8],[28] **4.1.3–1e** [CAS: 577744–48–0],[292] **4.1.3–1g** [CAS: 79477–86–4],[28] **4.1.3–1h** [CAS: 76590–50–6],[292] **4.1.3–1j** [CAS: 577744–34–4],[292] **4.1.3–1l** [CAS: 467435–08–1],[292] **4.1.3–1m** [CAS: 79477–86–4],[292] were synthesised following known synthetic procedures in 61–98% yields. All other compounds were commercially available and used without further purification.

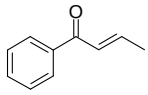
6.3.2. Synthesis of α,β–unsaturated ketones

Standard procedure for the synthesis of α,β–unsaturated ketones from α–oxocarboxylic acids.

A 20 mL crimp cap vessel was charged with tetrakis(triphenylphosphine)palladium(0) (57.6 mg, 0.05 mmol) and tri–*p*–tolylphosphine (77.6 mg, 0.25 mmol). A solution of the *α*–oxocarboxylic acid (1.00 mmol) in 1,4–dioxane (8 mL) and diallyl carbonate (**2**) (144 µL, 1.00 mmol) were added via syringe. The reaction mixture was stirred at 100 °C for 12 h and then cooled to room temperature. The solvent was removed *in vacuo* (40 °C, 107 mbar) and the remaining residue was further purified by flash chromatography (SiO_2, ethyl acetate/hexane (1:10)) yielding the corresponding products **4.1.3–3a–p** (52–99%).

Synthesis of (E)–1–phenylbut–2–en–1–one (4.1.3–3a)

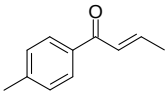
[CAS: 495–41–0]



Compound **4.1.3–3a** was prepared following the standard procedure, starting from phenylglyoxylic acid (**4.1.3–1a**) (150 mg, 1.00 mmol). After purification, **4.1.3–3a** was isolated as yellow oil (145 mg, 99%). The spectroscopic data matched those reported for **4.1.2–3aa**.

Synthesis of (E)–1–(4–tolyl)but–2–en–1–one (4.1.3–3b)

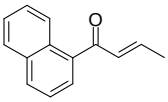
[CAS: 3837–95–4]



Compound **4.1.3–3b** was prepared starting from 4–tolylglyoxylic acid (**4.1.3–1b**) (164 mg, 1.00 mmol). After purification **4.1.3–3b** was isolated as yellow oil (127 mg, 79%). The spectroscopic data matched those reported for **4.1.2–3ba**.

Synthesis of (E)–1–(naphthalen–1–yl)but–2–en–1–one (4.1.3–3c)

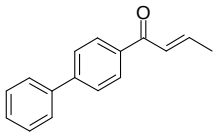
[CAS: 128113–46–2]



Compound **4.1.3–3c** was prepared starting from 1–napthtylglyoxylic acid (**4.1.3–1c**) (200 mg, 1.00 mmol). After purification **4.1.3–3c** was isolated as light yellow oil (185 mg, 94%). The spectroscopic data matched those reported for **4.1.2–3ca**.

Synthesis of (E)–1–([1,1'–biphenyl]–4–yl)but–2–en–1–one (4.1.3–3d)

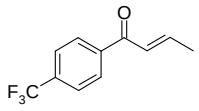
[CAS: 71823–67–1]



Compound **4.1.3–3d** was prepared starting from 4–biphenylglyoxylic acid (**4.1.3–1d**) (226 mg, 1.00 mmol). After purification **4.1.3–3d** was isolated as yellow solid (215,2 mg, 97%). The spectroscopic data matched those reported for **4.1.2–3ga**.

Synthesis of (E)–1–(4–(trifluoromethyl)phenyl)but–2–en–1–one (4.1.3–3e)

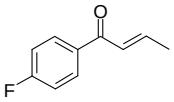
[CAS: 201164–24–1]



Compound **4.1.3–3e** was prepared starting from 4–(trifluoromethyl)phenylglyoxylic acid (**1e**) (218 mg, 1.00 mmol). After purification **4.1.3–3e** was isolated as dark yellow oil (155 mg, 73%). The spectroscopic data matched those reported for **4.1.2–3fa**.

Synthesis of (E)–1–(4–fluorophenyl)but–2–en–1–one (4.1.3–3f)

[CAS: 28122–15–8]

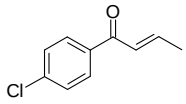


Compound **4.1.3–3f** was prepared starting from 4–flourophenylglyoxylic acid (**4.1.3–1f**) (168 mg, 1.00 mmol). After purification **4.1.3–3f** was isolated as brown oil (120 mg, 73%).

^{1}H–NMR (600 MHz, $CDCl_3$) δ= 7.98 – 7.95 (m, 2H), 7.12 – 7.15 (m, 2H), 7.07 (m, 1H), 6.91 (dq, *J*=15.3, 1.8 Hz, 1H), 2.02 ppm (dd, *J*=6.9, 1.6 Hz, 3H); **^{13}C–NMR** (151 MHz, $CDCl_3$) δ= 189.0, 165.5 (d, J_{CF}=253,8 Hz), 145.2, 134.1 (d, J_{CF}=2.77 Hz), 131.1 (2C) (d, J_{CF}=9.7 Hz), 127.0 (2 C), 115.5 (d, J_{CF} =22.2 Hz), 18.6 ppm; **CHN** Anal. Calcd. for $C_{10}H_9FO$: C, 73.16; H, 5.53; found: C, 73.18; H, 5.56.

Synthesis of (E)–1–(4–chlorophenyl)but–2–en–1–one (4.1.3–3g)

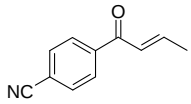
[CAS: 67864–02–2]



Compound **4.1.3–3g** was prepared starting from 4–chlorophenylglyoxylic acid (**4.1.3–1g**) (185 mg, 1.00 mmol). After purification **4.1.3–3g** was isolated as light yellow oil (144 mg, 80%). The spectroscopic data matched those reported for **4.1.2–3da**.

Synthesis of (E)–4–(but–2–enoyl)benzonitrile (4.1.3–3h)

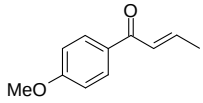
[CAS: 959311–24–1]



Compound **4.1.3–3h** was prepared starting from 4–cyanophenylglyoxylic acid (**4.1.3–1h**) (175 mg, 1.00 mmol). After purification **4.1.3–3h** was isolated as yellow solid (97 mg, 57%, m.p.: 61–62 °C). The spectroscopic data matched those reported for **4.1.2–3ea**.

Synthesis of (E)–1–(4–methoxyphenyl)but–2–en–1–one (4.1.3–3i)

[CAS: 97060–29–2]

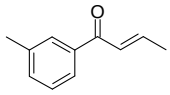


Compound **4.1.3–3i** was prepared starting from 4–methoxyphenylglyoxylic acid (**4.1.3–1i**) (180 mg, 1.00 mmol). After purification **3i** was isolated as brown oil (132 mg, 75%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.94 – 7.97 (m, 2H), 7.07 (m, 1H), 6.93 – 6.96 (m, 3H), 3.88 (s, 3H), 1.99 ppm (dd, *J*=6.7, 1.6 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 189.0, 163.3, 143.9, 130.8, 128.5 (2 C), 127.1 (2 C), 113.7, 55.4, 18.5 ppm; **CHN** Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; found: C, 74.86; H, 6.90.

Synthesis of (E)–1–(3–tolyl)but–2–en–1–one (4.1.3–3j)

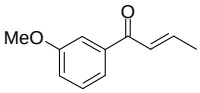
[CAS: 944344–73–4]



Compound **4.1.3–3j** was prepared starting from 3–methylphenylglyoxylic acid (**4.1.3–1j**) (164 mg, 1.00 mmol). After purification **4.1.3–3j** was isolated as yellow oil (133 mg, 83%). The spectroscopic data matched those reported for **4.1.2–3ha**.

Synthesis of (E)–1–(3–methoxyphenyl)but–2–en–1–one (4.1.3–3k)

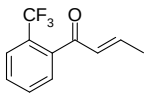
[CAS: 1087399–25–4]



Compound **4.1.3–3k** was prepared starting from 3–methoxyphenylglyoxylic acid (**4.1.3–1k**) (180 mg, 1.00 mmol). After purification **4.1.3–3k** was isolated as brown oil (148 mg, 84%). The spectroscopic data matched those reported for **4.1.2–3ma**.

Synthesis of (E)–1–(2–(trifluoromethyl)phenyl)but–2–en–1–one (4.1.3–3l).

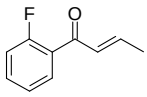
[CAS: 1360924–07–7]



Compound **4.1.3–3l** was prepared starting from 2–trifluoromethylphenylglyoxylic acid (**4.1.3–1l**) (218 mg, 1.00 mmol). After purification **4.1.3–3l** was isolated as yellow oil (178 mg, 83%). The spectroscopic data matched those reported for **4.1.2–3ja**.

Synthesis of (E)–1–(2–fluorophenyl)but–2–en–1–one (4.1.3–3m)

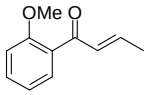
[CAS: 79477–86–4]



Compound **4.1.3–3m** was prepared starting from 2–fluorophenylglyoxylic acid (**4.1.3–1m**) (168 mg, 1.00 mmol). After purification **4.1.3–3m** was isolated as brown oil (117 mg, 71%). The spectroscopic data matched those reported for **4.1.2–3ia**.

Synthesis of (E)–1–(2–methoxyphenyl)but–2–en–1–one (4.1.3–3n)

[CAS: 40872–81–9]

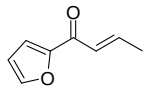


Compound **4.1.3–3n** was prepared starting from 2–methoxyphenylglyoxylic acid (**4.1.3–1n**) (180 mg, 1.00 mmol). After purification **4.1.3–3n** was isolated as dark brown oil (92.4 mg, 52%).

^{1}H–NMR (600 MHz, $CDCl_3$) δ= 7.93 – 8.02 (m, 2H), 7.09 (m, 1H), 6.90 – 7.02 (m, 3H), 3.89 (s, 3H), 2.01 ppm (dd, *J*=6.7, 1.6 Hz, 3H); **^{13}C–NMR** (151 MHz, $CDCl_3$) δ= 190.3, 159.7, 145.0, 139.2, 129.4, 127.4, 121.0, 119.0, 112.7, 55.3, 18.5 ppm; **CHN** Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; found: C, 74.99; H, 6.83.

Synthesis of (E)–1–(furan–2–yl)but–2–en–1–one (4.1.3–3o)

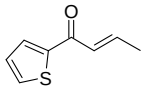
[CAS: 64677–61–8]



Compound **4.1.3–3o** was prepared starting from furan–2–glyoxylic acid (**4.1.3–1o**) (140 mg, 1.00 mmol). After purification **4.1.3–3o** was isolated as dark yellow oil (107 mg, 79%). The spectroscopic data matched those reported for **4.1.2–3ka**.

Synthesis of (E)–1–(thiophen–2–yl)but–2–en–1–one (4.1.3–3p)

[CAS: 13196–29–7]



Compound **4.1.3–3p** was prepared starting from thiophen–2–glyoxylic acid (**4.1.3–1p**) (159 mg, 1.00 mmol). After purification **4.1.3–3p** was isolated as brown oil (126 mg, 83%). The spectroscopic data matched those reported for **4.1.2–3la**.

6.4. Decarboxylative allylation of arylglyoxylic acids with allyl alcohol

6.4.1. General Methods

Compounds **4.1.4–1b** [CAS: 5449–21–8], **4.1.4–1c** [CAS: 7163–50–0], **4.1.4–1d** [CAS: 14289–45–3], **4.1.4–1e** [CAS: 26153–26–4], **4.1.4–1f** [CAS: 7099–88–9], **4.1.4–1g** [CAS: 2251–76–5], **4.1.4–1h** [CAS: 79477–86–4], **4.1.4–1i** [CAS: 26767–10–2] and **4.1.4–1l** [CAS: 39684–36–1] were synthesised in 61–98% yield following known synthetic procedures.[28,292] All other compounds were commercially available and used without further purification.

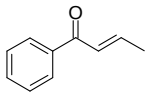
6.4.2. Synthesis of α,β–unsaturated ketones

Standard procedure for the synthesis of α,β–unsaturated ketones from α–oxocarboxylic acids.

A 20 mL crimp–cap vessel was charged with bis(dibenzylideneacetone)palladium(0) (28.8 mg, 0.05 mmol) and triphenylphosphine (91.8 mg, 0.35 mmol). A solution of the α–oxocarboxylic acid (**4.1.4–1a–l**) (1.00 mmol) in 1,4–dioxane (8 mL) and allyl alcohol (**4.1.4–2**) (104 µL, 1.50 mmol) were added via syringe. The reaction mixture was stirred at 100 °C for 16 h and was then cooled to room temperature. The solvent was removed *in vacuo* (40 °C, 100 mbar) and the remaining residue was further purified by flash chromatography (SiO_2, ethyl acetate/hexane (1:10)), yielding the corresponding ketones **4.1.4–4a–l** (63–96%).

Synthesis of (E)–1–phenylbut–2–en–1–one (4.1.4–4a)

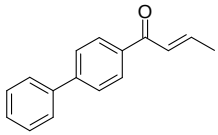
[CAS: 495–41–0]



Compound **4.1.4–4a** was prepared following the standard procedure, starting from phenylglyoxylic acid (**4.1.4–1a**) (155 mg, 1.00 mmol). After purification, **4.1.4–4a** was isolated as colourless oil (129 mg, 88%). The spectroscopic data matched those reported for **4.1.2–3aa**.

Synthesis of (E)–1–([1,1'–biphenyl]–4–yl)but–2–en–1–one (4.1.4–4b)

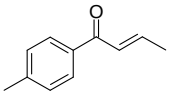
[CAS: 71823–67–1]



Compound **4.1.4–4b** was prepared following the standard procedure, starting from 4–biphenylglyoxylic acid (**4.1.4–1b**) (226 mg, 1.00 mmol). After purification, **4.1.4–4b** was isolated as beige solid (189 mg, 85%). The spectroscopic data matched those reported for **4.1.2–3ga**.

Synthesis of (E)–1–(4–tolyl)but–2–en–1–one (4.1.4–4c)

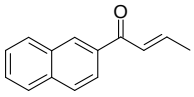
[CAS: 3837–95–4]



Compound **4.1.4–4c** was prepared following the standard procedure, starting from 4–tolylglyoxylic acid (**4.1.4–1c**) (164 mg, 1.00 mmol). After purification, **4.1.4–4c** was isolated as colourless oil (129 mg, 81%). The spectroscopic data matched those reported for **4.1.2–3ba**.

Synthesis of (E)–1–(naphthalen–2–yl)but–2–en–1–one (4.1.4–4d)

[CAS: 128113–44–0]



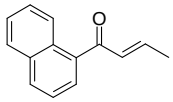
Compound **4.1.4–4d** was prepared following the standard procedure, starting from 2–napththylglyoxylic acid (**4.1.4–1d**) (200 mg, 1.00 mmol). After purification, **4.1.4–4d** was isolated as colourless solid (168 mg, 86%).

m.p. = 57–58 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ = 8.43 (s, 1H), 8.03 (dd, *J*=8.8 Hz, 1.8 Hz, 1H), 7.94 (d, *J*=8.0 Hz, 1H), 7.88 (d, *J*=8.8 Hz, 1H), 7.85 (d, *J*=8.0 Hz, 1H), 7.55 (m, 2H), 7.20 –

7.03 (m, 2H), 2.02 ppm (dd, *J*=6.4 Hz, 1.1 Hz, 3H); **^{13}C–NMR** (151 MHz, $CDCl_3$) δ= 190.2, 144.7, 135.2, 135.0, 132.4, 129.8, 129.3, 128.3, 128.1, 127.6, 127.3, 126.5, 124.3, 18.5 ppm; **IR** ν= 1665 (m), 1613 (vs), 1292 (s), 1188 (m), 1126 (m), 963 (m), 904 (m), 875 (m), 813 (vs), 746 cm^{-1} (vs); **MS** (Ion trap, EI): m/z (%) = 196 [M^+] (43), 195 (100), 181 (21), 155 (10), 127 (32), 126 (13), 69 (15); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{14}H_{12}O$, 196.0888; found, 196.0882; **CHN** Anal. Calcd. for $C_{14}H_{12}O$: C 85.68, H 6.16; found: C 85.54, H 6.16.

Synthesis of (E)–1–(naphthalen–1–yl)but–2–en–1–one (4.1.4–4e)

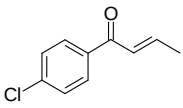
[CAS: 128113–46–2]



Compound **4.1.4–4e** was prepared following the standard procedure, starting from 1–napththylglyoxylic acid (**4.1.4–1e**) (200 mg, 1.00 mmol). After purification, **4.1.4–4e** was isolated as yellow solid (170 mg, 87%). The spectroscopic data matched those reported for **4.1.2–3ca**.

Synthesis of (E)–1–(4–chlorophenyl)but–2–en–1–one (4.1.4–4f)

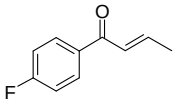
[CAS: 67864–02–2]



Compound **4.1.4–4f** was prepared following the standard procedure, starting from 4–chlorophenylglyoxylic acid (**4.1.4–1f**) (185 mg, 1.00 mmol). After purification, **4.1.4–4f** was isolated as colourless solid (156 mg, 86%). The spectroscopic data matched those reported for **4.1.2–3da**.

Synthesis of (E)–1–(4–fluorophenyl)but–2–en–1–one (4.1.4–4g)

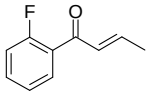
[CAS: 28122–15–8]



Compound **4.1.4–4g** was prepared following the standard procedure, starting from 4–flourophenylglyoxylic acid (**4.1.4–1g**) (168 mg, 1.00 mmol). After purification, **4.1.4–4g** was isolated as colourless oil (158 mg, 96%). The spectroscopic data matched those reported for **4.1.3–3f**.

Synthesis of (E)–1–(2–fluorophenyl)but–2–en–1–one (4.1.4–4h)

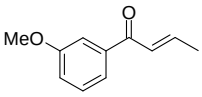
[CAS: 79477–86–4]



Compound **4.1.4–4h** was prepared following the standard procedure, starting from 2–fluorophenylglyoxylic acid (**4.1.4–1h**) (168 mg, 1.00 mmol). After purification, **4.1.4–4h** was isolated as colourless oil (135 mg, 82%). The spectroscopic data matched those reported for **4.1.2–3ia**.

Synthesis of (E)–1–(3–methoxyphenyl)but–2–en–1–one (4.1.4–4i)

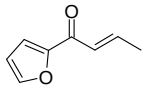
[CAS: 1087399–25–4]



Compound **4.1.4–4i** was prepared following the standard procedure, starting from 3–methoxyphenylglyoxylic acid (**4.1.4–1i**) (180 mg, 1.00 mmol). After purification, **4.1.4–4i** was isolated as yellow oil (135 mg, 77%). The spectroscopic data matched those reported for **4.1.2–3ma**.

Synthesis of (E)–1–(furan–2–yl)but–2–en–1–one (4.1.4–4j)

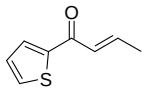
[CAS: 131323–45–0]



Compound **4.1.4–4j** was prepared following the standard procedure, starting from furanyl–2–glyoxylic acid (**4.1.4–1j**) (140 mg, 1.00 mmol). After purification, **4.1.4–4j** was isolated as yellow solid (109 mg, 80%). The spectroscopic data matched those reported for **4.1.2–3ka**.

Synthesis of (E)–1–(thiophen–2–yl)but–2–en–1–one (4.1.4–4k)

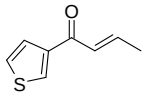
[CAS: 13196–29–7]



Compound **4.1.4–4k** was prepared following the standard procedure, starting from thiophenyl–2–glyoxylic acid (**4.1.4–1k**) (156 mg, 1.00 mmol). After purification, **4.1.4–4k** was isolated as yellow oil (111 mg, 73%). The spectroscopic data matched those reported for **4.1.2–3la**.

Synthesis of (E)–1–(thiophen–3–yl)but–2–en–1–one (4.1.4–4l)

[CAS: 1308249–57–1]



Compound **4.1.4–4l** was prepared following the standard procedure, starting from thiophenyl–3–glyoxylic acid (**4.1.4–1l**) (156 mg, 1.00 mmol). After purification, **4.1.4–4l** was isolated as colourless solid (95.5 mg, 63%).

m.p. = 42–43°C; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ = 8.05 (dd, *J*=2.8, 1.2 Hz, 1H), 7.58 (dd, *J*=5.1, 1.3 Hz, 1H), 7.31 (dd, *J*=5.1, 2.8 Hz, 1H), 7.08 (dq, *J*=15.1, 6.8 Hz, 1H), 6.79 (dq, *J*=15.3, 1.4 Hz, 1H), 1.97 ppm (dd, *J*=6.8, 1.5 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 183.9, 144.0,

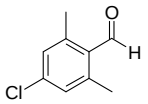
142.6, 131.8, 127.9, 127.3, 126.2, 18.3 ppm (2 C; *C*H_3); **IR** ν = 3105 (s), 2909 (m), 1667 (vs), 1619 (vs), 1511 (m), 1443 (m), 1411 (m), 1291 (m), 1231 (m), 1179 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 152 [M^+] (20), 151 (100), 136 (27), 91 (11), 69 (25), 45 (20), 41 (20); **CHN** Anal. Calcd. for C_8H_8OS: C 63.13, H 5.30, S 21.07; found: C 63.43, H 5.50, S 20.90.

6.5. Synthesis of Arylacetates from Benzylic Alcohols and Oxalate Esters through Decarboxylative Coupling

6.5.1. Synthesis of the benzyl alcohols

Synthesis of 4–chloro–2,6–dimethylbenzaldehyde

[CAS: 6045–90–5]

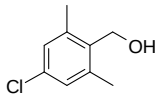


A solution of 2–bromo–5–chloro–1,3–dimethylbenzene (6.65 g, 30.0 mmol, 4.30 mL) in THF (50 mL) was cooled to –100°C and *n*–butyllithium (12.6 mL, 31.5 mmol, 2.5 mol/L in hexane) was added within 10 min. The mixture was stirred for 2h at –100°C and dimethylformamide (4.41 g, 60.0 mmol, 4.66 mL) was added to the slightly orange suspension. The resulting yellow solution was then allowed to reach room temperature over night while stirring under N_2. Water (10 mL) was added and the mixture was stirred for another 10 min, whereupon the solvent was removed *in vacuo* (200 mbar, 40°C). The remaining gel was dissolved in dichloromethane (100 mL) and water (100 mL) and the separated aqueous layer was extracted with dichloromethane (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated (700 mbar, 40°C) and the crude product was thermally recrystallized from hexane/ethyl acetate 3:1. Cooling the saturated solution to 4°C gave the title compound as colourless needles (4.82 g, 28.6 mmol, 95%) that were separated from the mother liquor, smashed and dried *in vacuo* (10^{-3} mbar) for 6 h.

m.p. 57–58 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ = 10.54 (s, 1 H; C*H*O), 7.08 (s, 2H), 2.58 ppm (s, 6 H; 2 C*H*$_3$); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 192.2 (*C*HO), 143.0 (2 C), 138.6, 130.7, 129.5 (2 C), 20.4 ppm (2 C; *C*H_3); **IR** ν = 1683 (s), 1582 (s), 1563 (s), 1380 (vs), 1251 (s), 1191 (s), 1096 (s), 886 (s), 853 (vs), 763 cm^{-1} (vs); **MS** (Ion trap, EI): m/z (%) = 170 [M^+] (22), 169 (38), 168 (71), 167 (100), 141 (11), 139 (34), 105 (13), 103 (21), 77 (21), 51 (9); **CHN** Anal. Calcd. for C_9H_9ClO: C 64.11, H 5.38; found: C 64.00, H 5.48.

Synthesis of 4–chloro–2,6–dimethylbenzyl alcohol (4.1.5–1m)

[CAS: 332179–32–5]

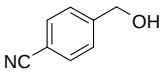


Sodium borohydride (1.15 g, 29.7 mmol) was added to a stirred solution of 4–chloro–2,6–dimethylbenzaldehyde (4.55 g, 27.0 mmol) in methanol (100 mL). After stirring for 2 h, the reaction mixture was concentrated *in vacuo* (100 mbar, 40°C) and the residue dissolved in dichloromethane (100 mL). The organic layer was washed with water (3 × 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* (700 mbar, 40 °C) to give the crude benzyl alcohol as colourless solid. Recrystallization from hexane/ethyl acetate 3:1 afforded the desired product as colourless crystals (3.93 g, 23.0 mmol, 85%).

m.p. 111–112 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ = 7.00 (s, 2H), 4.58 (d, ^3J (H,H) = 4.9 Hz, 2 H; CH_2OH), 2.34 (s, 6 H; 2 CH_3), 2.25 ppm (t, ^3J (H,H) = 5.1 Hz, 1 H; O*H*); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 139.2, 134.8 (2 C), 133.1, 127.9 (2 C), 58.4 (*C*H_2OH), 19.2 ppm (2 C, *C*H_3); **IR** ν = 3278 (br), 1585 (m), 1474 (w), 1443 (w), 1259 (w), 993 (vs), 880 (vs), 863 (m), 856 (vs), 774 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 172 [M^+] (13), 170 (41), 155 (24), 154 (34), 153 (23), 152 (100), 117 (37), 115 (24), 105 (21), 91 (45); **CHN** Anal. Calcd. for $C_9H_{11}ClO$: C 63.35, H 6.50; found: C 63.51, H 6.54.

Synthesis of 4–(hydroxymethyl)benzonitrile (4.1.5–1q)

[CAS: 874–89–5]



Sodium borohydride (0.85 g, 22.0 mmol) was added to a stirred solution of 4–cyanobenzaldehyde (2.62 g, 20.0 mmol) in methanol (75 mL). After stirring for 2 h, the reaction mixture was concentrated *in vacuo* (100 mbar, 40°C) and the residue dissolved in dichloromethane (75 mL). The organic layer was washed with water (3 × 75 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* (700 mbar, 40 °C) to give the crude benzyl alcohol as

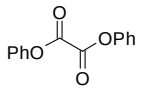
colourless solid. Recrystallization from hexane/ethyl acetate 3:1 afforded the desired product as colourless crystals (2.54 g, 19.1 mmol, 95%).

m.p. 42–43 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ = 7.56 (d, ^{3}J (H,H) = 8.4 Hz, 2H), 7.42 (d, ^{3}J (H,H) = 8.4 Hz, 2H), 4.70 (s, 2 H; CH_2OH), 3.25 ppm (s, 1 H; O*H*); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 146.5, 132.0 (2 C), 126.8 (2 C), 118.7, 110.4 (*C*N), 63.7 ppm (*C*H2OH); **IR** ν = 3312 (br), 2232 (s), 1739 (w), 1415 (m), 1346 (m), 1208 (m), 1028 (m), 1018 (s), 833 (s), 817 cm^{-1} (vs); **MS** (Ion trap, EI): m/z (%) = 133 [M^+] (37), 132 (43), 104 (100), 105 (24), 102 (11), 78 (9), 77 (29), 76 (11), 75 (8), 51 (10); **CHN** Anal. Calcd. for C_8H_7NO: C 72.17, H 5.30, N 10.52; found: C 71.92, H 5.42, N 10.55.

6.5.2. Synthesis of the alkyl− and aryl oxalates

Synthesis of diphenyl oxalate (4.1.5–2d)

[CAS: 3155–16–6]



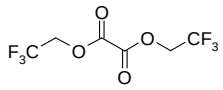
A solution of phenol (9.41 g, 100 mmol) in diethyl ether (100 mL) was cooled to 0° and triethylamine (10.1 g, 100 mmol, 13.9 mL) was added. Oxalyl chloride (6.98 g, 100 mmol, 5.23 mL) was then added with stirring during 30 min using an ice bath to maintain the reaction temperature between 10 and 25°C. The resulting yellow slurry was stirred for 3 h and washed with water (3 × 50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* (700 mbar, 40°C) and the crude product was thermally recrystallized from hexane/ethyl acetate 3:1. Cooling the saturated solution to 4°C gave the title compound as colourless needles (8.30 g, 34.3 mmol, 69%) that were separated from the mother liquor, smashed and dried *in vacuo* (10^{-3} mbar) for 6 h.

m.p. 138–139 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ = 7.44 (t, ^{3}J (H,H) = 8.0 Hz, 4H), 7.31 (t, ^{3}J (H,H) = 7.6 Hz, 2H), 7.26 ppm (d, ^{3}J (H,H) = 8.0 Hz, 4H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 155.6 (2 C; *C*O_2Ph), 149.9 (2 C), 129.7 (4 C), 126.9 (2 C), 120.9 ppm (4 C); **IR** (NaCl) ν = 3043 (w), 1775 (vs, C=O), 1586 (m), 1483 (m), 1305 (s), 1164 (vs), 1144 (vs, C–O–C), 934 (m), 846 (m), 751 cm^{-1} (vs); **MS** (Ion trap, EI): m/z (%) = 242 [M^+] (8), 215 (10), 214 (60), 170 (28), 169

(35), 142 (42), 141 (71), 94 (9), 77 (100), 65 (30); **CHN** Anal. Calcd. for $C_{14}H_{10}O_4$: C 69.42, H 4.16; found: C 69.54, H 4.39.

Synthesis of bis(2,2,2–trifluoroethyl) oxalate (4.1.5–2e)

[CAS: 466684–90–2]

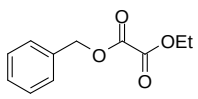


A solution of 2,2,2–trifluoroethanol (12.5 g, 125 mmol) in dichloromethane (50 mL) was cooled to 0°. Triethylamine (13.3 g, 125 mmol, 18.3 mL), 4–Dimethylaminopyridine (611 mg, 5.00 mmol) and oxalyl chloride (6.35 g, 50 mmol, 4.75 mL) were subsequently added with stirring using an ice bath to maintain the reaction temperature between 0°C and 10°C. The resulting yellow slurry was stirred for another 18 h and brine (20 mL) was added to quench the reaction. The mixture was extracted with diethyl ether (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* (700 mbar, 40 °C) to give the crude product. Distillation under reduced pressure gave the title compound as colourless liquid (8.95 g, 35.2 mmol, 70%).

b.p. 70 °C/50 mbar; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ = 4.67 ppm (q, ^3J (H,F) = 8.0 Hz, 4H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 154.7 (2 C; *C*O_2R), 122.0 (q, ^1J (C,F) = 277.9 Hz, 2 C; *C*F_3), 62.3 ppm (q, ^1J (C,F) = 38.1 Hz, 2 C; *C*H_2CF_3); **^{19}F–NMR** (376.5 MHz, $CDCl_3$) δ = -73.5 ppm (t, ^3J (F,H) = 6.8 Hz, 6 F); **IR** (NaCl) ν = 2989 (m), 1795 (vs), 1775 (vs), 1420 (m), 1285 (vs), 1271 (vs), 1173 (vs), 978 (m), 844 (w), 775 cm^{-1} (w); **CHN** Anal. Calcd. for $C_6H_4F_6O_4$: C 28.36, H 1.59; found: C 28.41, H 1.42.

Synthesis of benzyl ethyl oxalate (4.1.5–2f)

[CAS: 75406–29–0]



A stirred solution of benzyl alcohol (3.24 g, 30.0 mmol, 3.11 mL) and pyridine (2.41 g, 30.3 mmol, 2.46 mL) in dichloromethane (15 mL) was cooled in an ice bath and ethyl oxalyl chloride (4.22 g, 30.3 mmol, 3.44 mL) was added over 1 h. The mixture was stirred at 0°C for 4 h, then at

room temperature overnight and was then washed with water (2 × 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* (700 mbar, 40°C) to give the crude oxalate. Kugelrohr distillation under reduced pressure gave the title compound as colourless liquid (5.48 g, 26.3 mmol, 88%).

b.p. 90 °C/2×10^{-2} mbar,; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ = 7.45 – 7.36 (m, 5H), 5.32 (s, 2 H; C*H*$_2$Ph), 4.36 (q, ^3J (H,H) = 7.1 Hz, 2 H; C*H*$_2$CH$_3$), 1.38 ppm (t, ^3J (H,H) = 7.1 Hz, 3 H; C*H*$_3$); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 157.7, 157.6, 134.2, 128.8, 128.7 (2 C), 128.7 (2 C), 68.5, 63.2, 13.9 ppm (*C*H$_3$); **IR** (NaCl) ν = 2985 (vs), 1774 (vs), 1736 (vs), 1458 (m), 1381 (m), 1309 (m), 1183 (s), 1158 (s), 1018 (w), 946 cm^{-1} (w); **MS** (Ion trap, EI): m/z (%) = 208 [M$^+$] (1), 180 (7), 107 (13), 92 (8), 91 (100), 89 (2), 79 (2), 77 (4), 65 (8), 63 (2); **CHN** Anal. Calcd. for $C_{11}H_{12}O_4$: C 63.45, H 5.81; found: C 63.48, H 5.82.

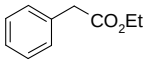
6.5.3. Synthesis of the arylacetic esters from benzyl alcohols

Standard procedure for the synthesis of arylacetic esters from benzyl alcohols and dialkyl or –aryl oxalates.

An oven–dried 20 mL crimp cap vessel was charged with palladium (II) acetate (4.58 mg, 0.02 mmol), 1,3–bis(diphenylphosphino)propane (12.4 mg, 0.03 mmol), 1,4–diazabicyclo[2.2.2]octane (11.2 mg, 0.10 mmol) and a Teflon–coated stirrer bar and brought under an atmosphere of dry nitrogen. A solution of the benzyl alcohol (1.00 mmol) in NMP (2 mL) and the oxalate (1.20 mmol) were added via syringe. The reaction mixture was stirred at 150 °C for 16 h and then cooled to room temperature. The pressure was released and ethyl acetate (20 mL) was added. The mixture was washed with water (20 mL) and a saturated aqueous bicarbonate solution (20 mL). The organic layer was separated, dried over $MgSO_4$, filtered and the solvents were removed *in vacuo* (40 °C, 200 mbar). The remaining residue was further purified by flash chromatography (SiO_2, ethyl acetate/hexane (1:10)), yielding the corresponding esters (41–95%).

Synthesis of ethyl 2–phenylacetate (4.1.5–4a)

[CAS: 101–97–3]

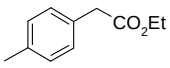


Compound **4.1.5–4a** was prepared following the standard procedure, starting from benzyl alcohol (**4.1.5–1a**) (108 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4a** was isolated as colourless liquid (156 mg, 0.95 mmol, 95%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.38 – 7.26 (m, 5H), 4.18 (q, ^3J (H,H) = 7.2 Hz, 2 H; CH_2CH$_3$), 3.64 (s, 2 H; CH_2Ph), 1.28 ppm (t, ^3J (H,H) = 7.1 Hz, 3 H; CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 171.6 (*C*O$_2$Et), 134.1, 129.2 (2 C), 128.5 (2 C), 127.0, 60.8 (O*C*H$_2$CH$_3$), 41.4, 14.1 ppm (*C*H$_3$); **IR** (NaCl) ν= 3032 (m), 2983 (s), 1736 (vs), 1498 (m), 1456 (m), 1368 (s), 1254 (s), 1159 (vs), 1030 (s), 946 cm^{-1} (w); **MS** (Ion trap, EI): m/z (%) = 164 [M$^+$] (22), 119 (2), 105 (2), 92 (11), 91 (100), 90 (3), 89 (4), 65 (10), 63 (3); **CHN** Anal. Calcd. for $C_{10}H_{12}O_2$: C 73.15, H 7.37; found: C 72.88, H 7.24.

Synthesis of ethyl 2–(p–tolyl)acetate (4.1.5–4b)

[CAS: 14062–19–2]



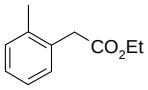
Compound **4.1.5–4b** was prepared following the standard procedure, starting from (4–methylphenyl)methyl alcohol (**4.1.5–1b**) (125 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4b** was isolated as colourless liquid (165 mg, 0.93 mmol, 93%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.20 (d, ^3J (H,H) = 8.2 Hz, 2H), 7.15 (d, ^3J (H,H) = 8.2 Hz, 2H), 4.17 (q, ^3J (H,H) = 7.2 Hz, 2 H; OCH_2CH$_3$), 3.59 (s, 2H), 2.35 (s, 3 H; CH_3), 1.27 ppm (t, ^3J (H,H) = 7.1 Hz, 3 H; OCH$_2$CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 171.8 (*C*O$_2$Et), 136.6, 131.1, 129.2 (2 C), 129.0 (2 C), 60.7 (O*C*H$_2$CH$_3$), 41.0, 21.0 (*C*H$_3$), 14.1 ppm (OCH$_2$*C*H$_3$); **IR** (NaCl) ν= 2983 (vs), 2927 (s), 1736 (vs), 1517 (s), 1466 (m), 1368 (m), 1256 (s), 1156 (s), 1034

(s), 810 cm^{-1} (w); **MS** (Ion trap, EI): m/z (%) = 178 [M^+] (22), 106 (10), 105 (100), 103 (7), 79 (6), 78 (4), 77 (10); **CHN** Anal. Calcd. for $C_{11}H_{14}O_2$: C 74.13, H 7.92; found: C 74.05, H 7.87.

Synthesis of ethyl 2–(o–tolyl)acetate (4.1.5–4c)

[CAS: 40291–39–2]

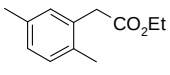


Compound **4.1.5–4c** was prepared following the standard procedure, starting from (2–methylphenyl)methyl alcohol (**4.1.5–1c**) (125 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4c** was isolated as colourless liquid (156 mg, 0.88 mmol, 88%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.24 – 7.16 (m, 4H), 4.18 (q, ^3J (H,H) = 7.0 Hz, 2 H; OCH_2CH_3), 3.65 (s, 2H), 2.34 (s, 3 H; CH_3), 1.27 ppm (t, ^3J (H,H) = 7.1 Hz, 3 H; OCH_2CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 171.5 (CO_2Et), 136.8, 132.9, 130.3, 130.1, 127.3, 126.1, 60.7 (OCH_2CH_3), 39.2, 19.5 (CH_3), 14.1 ppm (OCH_2CH_3); **IR** (NaCl) ν= 2982 (m), 1736 (vs), 1460 (w), 1368 (m), 1253 (s), 1156 (s), 1099 (m), 1033 (m), 747 (m), 728 cm^{-1} (w); **MS** (Ion trap, EI): m/z (%) = 178 [M^+] (23), 132 (11), 106 (10), 105 (100), 104 (23), 103 (10), 91 (4), 79 (9), 78 (6), 77 (13); **CHN** Anal. Calcd. for $C_{11}H_{14}O_2$: C 74.13, H 7.92; found: 74.01, H 7.79.

Synthesis of ethyl 2–(2,5–dimethylphenyl)acetate (4.1.5–4d)

[CAS: 58358–37–5]



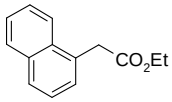
Compound **4.1.5–4d** was prepared following the standard procedure, starting from (2,5–dimethylphenyl)methyl alcohol (**4.1.5–1d**) (140 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4d** was isolated as colourless liquid (155 mg, 0.81 mmol, 81%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.11 (d, ^3J = (H,H) = 7.5 Hz, 1H), 7.07 (s, 1H), 7.04 (d, ^3J (H,H) = 7.5 Hz, 1H), 4.20 (q, ^3J (H,H) = 7.0 Hz, 2 H; OCH_2CH_3), 3.64 (s, 2H), 2.35 (s, 3 H,

C*H*$_3$), 2.32 (s, 3 H, C*H*$_3$), 1.30 ppm (t, ^3J (H,H) = 7.2 Hz, 3 H; OCH$_2$C*H*$_3$); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 171.5 (*C*O$_2$Et), 135.4, 133.5, 132.6, 130.8, 130.1, 127.9, 60.6 (O*C*H$_2$CH$_3$), 39.1, 20.8 (*C*H$_3$), 19.0 (*C*H$_3$), 14.1 ppm (OCH$_2$*C*H$_3$); **IR** (NaCl) ν = 2981 (vs), 1737 (vs), 1508 (m), 1475 (m), 1367 (m), 1332 (m), 1252 (s), 1162 (s), 1034 (s), 811 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 192 [M$^+$] (35), 146 (6), 120 (10), 119 (100), 118 (38), 117 (9), 115 (6), 103 (5), 91 (13), 77 (5); **CHN** Anal. Calcd. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.81, H 8.18.

Synthesis of ethyl 2–(naphthalen–1–yl)acetate (4.1.5–4e)

[CAS: 2122–70–5]

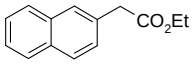


Compound **4.1.5–4e** was prepared following the standard procedure, starting from 1–naphthylenemethanol (**4.1.5–1e**) (161 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4e** was isolated as colourless liquid (127 mg, 0.59 mmol, 59%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 8.05 (d, ^3J (H,H) = 8.6 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.86 – 7.80 (m, 1H), 7.60 – 7.44 (m, 4H), 4.19 (q, ^3J (H,H) = 7.2 Hz, 2 H; OC*H*$_2$CH$_3$), 4.10 (s, 2H), 1.26 ppm (t, ^3J (H,H) = 7.1 Hz, 3 H; OCH$_2$C*H*$_3$); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 171.5 (*C*O$_2$Et), 133.8, 132.1, 130.7, 128.7, 128.0, 127.9, 126.2, 125.7, 125.4, 123.8, 60.9 (O*C*H$_2$CH$_3$), 39.2, 14.1 ppm (OCH$_2$*C*H$_3$); **IR** (NaCl) ν = 2982 (s), 1735 (vs), 1599 (w), 1511 (m), 1368 (m), 1266 (m), 1174 (s), 1030 (m), 792 (m), 781 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 214 [M$^+$] (31), 142 (13), 141 (100), 140 (3), 139 (10), 116 (2), 115 (21), 89 (2), 70 (2); **CHN** Anal. Calcd. for $C_{14}H_{14}O_2$: C 78.48, H 6.59; found: C 78.62, H 6.50.

Synthesis of ethyl 2–(naphthalen–2–yl)acetate (4.1.5–4f)

[CAS: 2876–70–2]

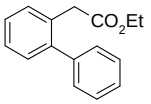


Compound **4.1.5–4f** was prepared following the standard procedure, starting from 2–naphthylenemethanol (**4.1.5–1f**) (161 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4f** was isolated as colourless liquid (124 mg, 0.58 mmol, 58%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.87 – 7.81 (m, 3H), 7.77 (s, 1H), 7.52 – 7.43 (m, 3H), 4.21(q, ^{3}J (H,H) = 7.2 Hz, 2 H; OCH_2CH$_3$), 3.81 (s, 2H), 1.29 ppm (t, ^{3}J (H,H) = 7.1 Hz, 3 H; OCH$_2$CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 171.5 (CO$_2$Et), 133.4, 132.4, 131.6, 128.1, 127.9, 127.6, 127.6, 127.3, 126.1, 125.7, 60.9 (OCH$_2$CH$_3$), 41.6, 14.1 ppm (OCH$_2$$CH_3$); **IR** (NaCl) ν= 3057 (m), 2982 (m), 1736 (vs), 1369 (m), 1329 (m), 1272 (s), 1260 (s), 1181 (s), 1160 (vs), 1033 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 214 [M^{+}] (75), 142 (13), 141 (100), 140 (4), 139 (8), 115 (24); **CHN** Anal. Calcd. for $C_{14}H_{14}O_2$: C 78.48, H 6.59; found: C 78.52, H 6.56.

Synthesis of ethyl 2–([1,1'–biphenyl]–2–yl)acetate (4.1.5–4g)

[CAS: 854624–08–1]



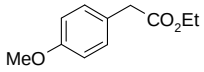
Compound **4.1.5–4g** was prepared following the standard procedure, starting from 2–hydroxymethylbiphenyl (**4.1.5–1g**) (188 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4g** was isolated as colourless liquid (204 mg, 0.85 mmol, 85%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.35 – 7.16 (m, 9H), 4.00 (q, ^{3}J (H,H) = 7.0 Hz, 2 H; OCH_2CH$_3$), 3.51 (s, 2H), 1.11 ppm (t, ^{3}J (H,H) = 7.2 Hz, 3 H; OCH$_2$CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 171.9 (CO$_2$Et), 142.4, 141.1, 131.9, 130.3, 130.1, 129.2 (2 C), 128.1 (2 C), 127.5, 127.1 (2 C), 60.7 (OCH$_2$CH$_3$), 39.0, 14.1 ppm (OCH$_2$$CH_3$); **IR** (NaCl) ν= 3061 (m), 3024

(m), 2982 (s), 1736 (vs), 1481 (s), 1334 (s), 1248 (vs), 1209 (vs), 1158 (vs), 1032 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 240 [M^+] (100), 194 (13), 167 (63), 166 (20), 165 (37), 152 (14); **CHN** Anal. Calcd. for $C_{16}H_{16}O_2$: C 79.97, H 6.71; found: C 79.88, H 6.69.

Synthesis of ethyl 2–(4–methoxyphenyl)acetate (4.1.5–4h)

[CAS: 14062–18–1]

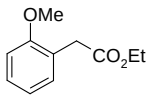


Compound **4.1.5–4h** was prepared following the standard procedure, starting from (4–methoxyphenyl)methanol (**4.1.5–1h**) (140 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4h** was isolated as colourless liquid (160 mg, 0.82 mmol, 82%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 7.24 – 7.19 (m, 2H), 6.90 – 6.86 (m, 2H), 4.16 (q, ^3J (H,H) = 7.0 Hz, 2 H; OCH_2CH_3), 3.79 (s, 3 H; OCH_3), 3.56 (s, 2H), 1.26 ppm (t, ^3J (H,H) = 7.2 Hz, 3 H; OCH_2CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 171.7 (CO_2Et), 158.5, 130.1 (2 C), 126.1, 113.8 (2 C), 60.6 (OCH_2CH_3), 55.0 (OCH_3), 40.3, 14.0 ppm (OCH_2CH_3); **IR** (NaCl) ν = 2983 (vs), 2938 (s), 1736 (vs), 1615 (s), 1515 (vs), 1466 (m), 1302 (s), 1249 (vs), 1156 (s), 1034 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 194 [M^+] (21), 122 (9), 121 (100), 91 (3), 89 (2), 78 (7), 77 (6), 52 (2), 51 (2); **CHN** Anal. Calcd. for $C_{11}H_{14}O_3$: C 68.02, H 7.27; found: C 67.67, H 7.28.

Synthesis of ethyl 2–(2–methoxyphenyl)acetate (4.1.5–4i)

[CAS: 6056–23–1]

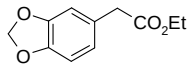


Compound **4.1.5–4i** was prepared following the standard procedure, starting from (2–methoxyphenyl)methanol (**4.1.5–1i**) (140 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4i** was isolated as colourless liquid (146 mg, 0.75 mmol, 75%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 7.27 (td, *J* (H,H) = 7.8, 1.8 Hz, 1H), 7.20 (dd, *J* (H,H) = 7.4, 1.6 Hz, 1H), 6.93 (td, *J* (H,H) = 7.5, 1.0 Hz, 1H), 6.89 (d, ^{3}J (H,H) = 8.2 Hz, 1H), 4.17 (q, ^{3}J (H,H) = 7.2 Hz, 2 H; OC*H*$_2$CH$_3$), 3.83 (s, 3 H; OC*H*$_3$), 3.63 (s, 2H), 1.26 ppm (t, ^{3}J (H,H) = 7.1 Hz, 3 H; OCH$_2$C*H*$_3$); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 171.9 (*C*O$_2$Et), 157.5, 130.8, 128.5, 123.2, 120.5, 110.4, 60.5 (O*C*H$_2$CH$_3$), 55.4 (O*C*H$_3$), 36.0, 14.2 ppm (OCH$_2$*C*H$_3$); **IR** (NaCl) ν = 2982 (m), 1736 (vs), 1604 (m), 1498 (vs), 1466 (s), 1248 (vs), 1157 (vs), 1114 (s), 1031 (vs), 755 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 194 [M^{+}] (51), 148 (6), 122 (10), 121 (100), 93 (7), 91 (64), 78 (9), 77 (6), 65 (9); **CHN** Anal. Calcd. for $C_{11}H_{14}O_3$: C 68.02, H 7.27; found: C 67.95, H 7.38.

Synthesis of ethyl 2–(benzo[d][1,3]dioxol–5–yl)acetate (4.1.5–4j)

[CAS: 26664–86–8]

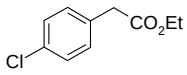


Compound **4.1.5–4j** was prepared following the standard procedure, starting from Piperonylalcohol (**4.1.5–1j**) (155 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4j** was isolated as colourless liquid (137 mg, 0.66 mmol, 66%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 6.81 – 6.70 (m, 3H), 5.94 (s, 2 H; OC*H*$_2$O), 4.15 (q, ^{3}J (H,H) = 7.2 Hz, 2 H; O*C*H$_2$CH$_3$), 3.52 (s, 2H), 1.26 ppm (t, ^{3}J (H,H) = 7.2 Hz, 3 H; OCH$_2$C*H*$_3$); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 171.6 (*C*O$_2$Et), 147.7, 146.6, 127.6, 122.3, 109.6, 108.2, 100.9 (O*C*H$_2$O), 60.8 (O*C*H$_2$CH$_3$), 40.9, 14.1 ppm (OCH$_2$*C*H$_3$); **IR** (NaCl) ν = 2981 (vs), 2902 (vs), 1736 (s), 1492 (s), 1445 (s), 1249 (s), 1159 (m), 1037 (m), 931 (m), 873 cm^{-1} (w); **MS** (Ion trap, EI): m/z (%) = 208 [M^{+}] (28), 136 (9), 135 (100), 105 (4), 79 (3), 78 (2), 77 (12), 67 (2), 51 (7); **CHN** Anal. Calcd. for $C_{11}H_{12}O_4$: C 63.45, H 5.81; found: C 63.34, H 5.90.

Synthesis of ethyl 2–(4–chlorophenyl)acetate (4.1.5–4k)

[CAS: 14062–24–9]

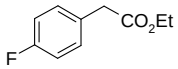


Compound **4.1.5–4k** was prepared following the standard procedure, starting from (4–chlorophenyl)methanol (**4.1.5–1k**) (144 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4k** was isolated as colourless liquid (147 mg, 0.74 mmol, 74%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.32 – 7.27 (m, 2H), 7.24 – 7.20 (m, 2H), 4.16 (q, ^{3}J (H,H) = 7.0 Hz, 2 H; OCH_2CH_3), 3.58 (s, 2H), 1.26 ppm (t, ^{3}J (H,H) = 7.2 Hz, 3 H; OCH_2CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 171.1 (CO_2Et), 132.9, 132.5, 130.6 (2 C), 128.6 (2 C), 60.9 (OCH_2CH_3), 40.6, 14.1 ppm (OCH_2CH_3); **IR** (NaCl) ν= 2984 (vs), 2939 (m), 1736 (vs), 1492 (s), 1369 (s), 1334 (s), 1160 (vs), 1092 (vs), 1031 (vs), 1018 cm^{-1} (vs); **MS** (Ion trap, EI): m/z (%) = 200 [M^+] (6), 198 (19) [M^+], 128 (3), 127 (31), 126 (8), 125 (100), 99 (4), 90 (5), 89 (15), 63 (6); **CHN** Anal. Calcd. for $C_{10}H_{11}ClO_2$: C 60.46, H 5.58; found: C 60.54, H 5.71.

Synthesis of ethyl 2–(4–fluorophenyl)acetate (4.1.5–4l)

[CAS: 587–88–2]



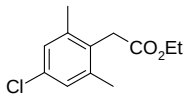
Compound **4.1.5–4l** was prepared following the standard procedure, starting from (4–fluorophenyl)methanol (**4.1.5–1l**) (130 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4l** was isolated as colourless liquid (163 mg, 0.90 mmol, 90%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.18 – 7.12 (m, 2H), 6.94 – 6.87 (m, 2H), 4.05 (q, ^{3}J (H,H) = 7.0 Hz, 2 H; OCH_2CH_3), 3.48 (s, 2H), 1.15 ppm (t, ^{3}J (H,H) = 7.2 Hz, 3 H; OCH_2CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 171.3 (CO_2Et), 161.9 (d, ^{1}J (C,F) = 245 Hz, 1 C), 130.7 (d, ^{3}J (C,F) = 8.1 Hz, 2 C), 129.8 (d, ^{4}J (C,F) = 2.9 Hz, 1 C), 115.3 (d, ^{2}J (C,F) = 22.0 Hz, 2 C), 60.8 (OCH_2CH_3), 40.4, 14.0 ppm (OCH_2CH_3); **^{19}F–NMR** (376.5 MHz, $CDCl_3$) δ= -115.9 ppm; **IR**

(NaCl) ν = 2985 (m), 1737 (vs), 1609 (m), 1511 (vs), 1370 (m), 1256 (s), 1225 (vs), 1173 (s), 1157 (vs), 1033 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 182 [M^+] (18), 110 (9), 109 (100), 108 (3), 107 (5), 89 (1), 83 (9), 63 (2), 57 (2); **CHN** Anal. Calcd. for $C_{10}H_{11}FO_2$: C 65.92, H 6.09; found: C 66.05, H 6.10.

Synthesis of ethyl 2–(4–chloro–2,6–dimethylphenyl)acetate (4.1.5–4m)

[CAS: 1315482–74–6]

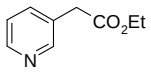


Compound **4.1.5–4m** was prepared following the standard procedure, starting from 4–chloro–2,6–dimethylbenzyl alcohol (**4.1.5–1m**) (171 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4m** was isolated as colourless liquid (126 mg, 0.56 mmol, 56%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 7.04 (s, 2H), 4.15 (q, ^3J (H,H) = 7.2 Hz, 2 H; OCH_2CH_3), 3.64 (s, 2H), 2.31 (s, 6 H; 2 CH_3), 1.25 ppm (t, ^3J (H,H) = 7.1 Hz, 3 H; OCH_2CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 170.8 (CO_2Et), 139.0 (2 C), 132.2, 130.3, 127.8 (2 C), 60.8 (OCH_2CH_3), 35.0, 20.2 (2 C; 2 CH_3), 14.2 ppm (OCH_2CH_3); **IR** (NaCl) ν = 2981 (vs), 1736 (s), 1587 (m), 1450 (s), 1368 (m), 1329 (m), 1157 (m), 1031 (m), 889 (m), 860 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 228 [M^+] (9), 226 (28), 180 (6), 155 (34), 154 (17), 153 (100), 152 (22), 117 (7), 115 (14), 91 (7); **CHN** Anal. Calcd. for $C_{12}H_{15}ClO_2$: C 63.58, H 6.67; found: C 63.68, H 6.61.

Synthesis of ethyl 2–(pyridin–3–yl)acetate (4.1.5–4n)

[CAS: 39931–77–6]

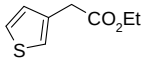


Compound **4.1.5–4n** was prepared following the standard procedure, starting from 3–hydroxymethyl–pyridine (**4.1.5–1n**) (109 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4n** was isolated as colourless liquid (68.0 mg, 0.41 mmol, 41%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 8.49 – 8.45 (m, 2H), 7.59 (dt, *J* (H,H) = 7.9, 1.9 Hz, 1H), 7.21 (dd, *J* (H,H) = 7.8, 4.6 Hz, 1H), 4.12 (q, ^{3}J (H,H) = 7.1 Hz, 2 H; OCH_2CH_3), 3.57 (s, 2H), 1.21 ppm (t, ^{3}J (H,H) = 7.1 Hz, 3 H; OCH_2CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 170.5 (CO_2Et), 150.2, 148.3, 136.6, 129.7, 123.2, 61.0 (OCH_2CH_3), 38.3, 14.0 ppm (OCH_2CH_3); **IR** (NaCl) ν = 2984 (vs), 1739 (vs), 1578 (m), 1481 (s), 1428 (s), 1370 (s), 1333 (s), 1235 (s), 1180 (s), 1029 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 165 [M^+] (34), 121 (7), 120 (7), 93 (35), 92 (100), 91 (5), 66 (4), 65 (25), 64 (5), 63 (7); **HRMS** (GC/EI): *m/z* calcd for $C_9H_{11}NO_2$: 165.0790; found: 165.0795.

Synthesis of ethyl 2–(thiophen–3–yl)acetate (4.1.5–4o)

[CAS: 37784–63–7]

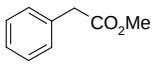


Compound **4.1.5–4o** was prepared following the standard procedure, starting from 3–hydroxymethyl–thiophene (**4.1.5–1o**) (116 mg, 1.00 mmol) and diethyl oxalate (**4.1.5–2a**) (175 mg, 1.20 mmol, 164 µL). After purification, **4.1.5–4o** was isolated as colourless liquid (94.0 mg, 0.55 mmol, 55%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 7.29 (dd, *J* (H,H) = 4.9, 2.9 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.06 (dd, *J* (H,H) = 4.9, 1.2 Hz, 1H), 4.18 (q, ^{3}J (H,H) = 7.3 Hz, 2 H; OCH_2CH_3), 3.66 (s, 2H), 1.28 ppm (t, ^{3}J (H,H) = 7.1 Hz, 3 H; OCH_2CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 171.0 (CO_2Et), 133.7, 128.4, 125.6, 122.7, 60.8 (OCH_2CH_3), 35.8, 14.1 ppm (OCH_2CH_3); **IR** (NaCl) ν = 3105 (m), 2982 (s), 1736 (vs), 1368 (m), 1331 (s), 1153 (s), 1032 (s), 860 (m), 834 (w), 765 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 170 [M^+] (59), 98 (14), 97 (100), 69 (5), 53 (12), 45 (15); **CHN** Anal. Calcd. for $C_8H_{10}O_2S$: C 56.45, H 5.92, S 18.84; found: C 56.28, H 6.05, S 18.77.

Synthesis of methyl 2–phenylacetate (4.1.5–4p)

[CAS: 101–41–7]

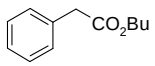


Compound **4.1.5–4p** was prepared following the standard procedure, starting from benzyl alcohol (**4.1.5–1a**) (108 mg, 1.00 mmol) and dimethyl oxalate (**4.1.5–2b**) (143 mg, 1.20 mmol). After purification, **4.1.5–4p** was isolated as colourless liquid (126 mg, 0.84 mmol, 84%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.26 (m, 5H), 3.71 (s, 3 H; OC*H*$_3$), 3.65 ppm (s, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 172.0 (*C*O_2CH_3), 134.0, 129.2 (2 C), 128.6 (2 C), 127.1, 52.0 (CO_2*C*H_3), 41.2 ppm; **IR** (NaCl) ν = 2953 (s), 1736 (vs), 1498 (s), 1457 (s), 1438 (s), 1343 (m), 1162 (s), 1014 (m), 698 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 150 [M$^+$] (38), 92 (8), 91 (100), 90 (3), 89 (6), 65 (11), 63 (4), 59 (4), 51 (3); **CHN** Anal. Calcd. for $C_9H_{10}O_2$: C 71.98, H 6.71; found: C 71.76, H 7.05.

Synthesis of butyl 2–phenylacetate (4.1.5–4q)

[CAS: 122–43–0]

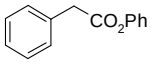


Compound **4.1.5–4q** was prepared following the standard procedure, starting from benzyl alcohol (**4.1.5–1a**) (108 mg, 1.00 mmol) and dibutyl oxalate (**4.1.5–2c**) (245 mg, 1.20 mmol). After purification, **4.1.5–4q** was isolated as colourless liquid (170 mg, 0.88 mmol, 88%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.26 (m, 5H), 4.12 (t, ^{3}J (H,H) = 6.7 Hz, 2 H; OC*H*$_2$), 3.63 (s, 2H), 1.62 (m, 2 H; $OCH_2CH_2CH_2$), 1.37 (m, 2 H; $CH_2CH_2CH_3$), 0.93 ppm (t, ^{3}J (H,H) = 7.3 Hz, 3 H; CH_2CH_3); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 171.6 (*C*O_2Bu), 134.1, 129.2 (2 C), 128.4 (2 C), 126.9, 64.6 (O*C*H$_2$), 41.4, 30.5 ($OCH_2CH_2CH_2$), 19.0 ($CH_2CH_2CH_3$), 13.6 ppm (CH_2CH_3); **IR** (NaCl) ν = 2961 (vs), 2875 (s), 1736 (vs), 1498 (m), 1457 (m), 1251 (m), 1152 (m), 1022 (w), 762 (w), 697 cm^{-1} (w); **MS** (Ion trap, EI): m/z (%) = 192 [M$^+$] (8), 137 (5), 136 (27), 119 (4), 92 (32), 91 (100), 89 (5), 65 (14), 63 (3), 57 (26); **CHN** Anal. Calcd. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.96, H 8.44.

Synthesis of phenyl 2–phenylacetate (4.1.5–4r)

[CAS: 722–01–0]

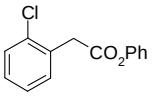


Compound **4.1.5–4r** was prepared following the standard procedure, starting from benzyl alcohol (**4.1.5–1a**) (108 mg, 1.00 mmol) and diphenyl oxalate (**4.1.5–2d**) (291 mg, 1.20 mmol). After purification, **4.1.5–4r** was isolated as colourless solid (89.0 mg, 0.42 mmol, 42%).

m.p. 42–43 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ = 7.44 – 7.36 (m, 6H), 7.33 (t, ^{3}J (H,H) = 6.6 Hz, 1H), 7.24 (t, ^{3}J (H,H) = 7.0 Hz, 1H), 7.08 (d, ^{3}J (H,H) = 8.1 Hz, 2H), 3.89 ppm (s, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 170.0 (CO_2Ph), 150.7, 133.4, 129.4, 129.3 (2 C), 128.7 (2 C), 127.3 (2 C), 125.8, 121.4 (2 C), 41.4 ppm; **IR** (NaCl) ν = 1761 (s), 1592 (w), 1492 (m), 1456 (w), 1339 (w), 1217 (m), 1196 (m), 1127 (vs), 747 (m), 696 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 212 [M^+] (1), 119 (10), 118 (100), 92 (8), 91 (98), 90 (11), 89 (6), 65 (19), 63 (5), 51 (3); **CHN** Anal. Calcd. for $C_{14}H_{12}O_2$: C 79.23, H 5.70; found: C 79.28, H 5.90.

Synthesis of phenyl 2–(2–chlorophenyl)acetate (4.1.5–4s)

[CAS: 1497382–97–4]



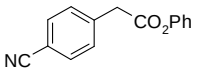
Compound **4.1.5–4s** was prepared following the standard procedure, starting from 2–Chlorobenzylalcohol (**4.1.5–1p**) (144 mg, 1.00 mmol) and diphenyl oxalate (**4.1.5–2d**) (291 mg, 1.20 mmol). After purification, **4.1.5–4s** was isolated as colourless solid (173 mg, 0.70 mmol, 70%).

m.p. 38–39 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ = 7.49 – 7.37 (m, 4H), 7.33 – 7.23 (m, 3H), 7.16 – 7.12 (m, 2H), 4.05 ppm (s, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 169.0 (CO_2Ph), 150.7, 134.6, 132.0, 131.5, 129.6, 129.4 (2 C), 128.9, 127.0, 125.9, 121.4 (2 C), 39.4 ppm; **IR** (NaCl) ν = 3062 (vs), 2925 (s), 1752 (vs), 1592 (s), 1492 (s), 1476 (s), 1445 (s), 1341 (m), 1194 (s), 1136 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 248 [M^+] (1), 246 (1), 154 (35), 153 (9), 152 (100),

127 (27), 126 (8), 125 (79), 124 (6), 89 (19); **CHN** Anal. Calcd. for $C_{14}H_{11}ClO_2$: C 68.16, H 4.49; found: C 68.09, H 4.66.

Synthesis of phenyl 2–(4–cyanophenyl)acetate (4.1.5–4t)

[CAS: 1497382–99–6]

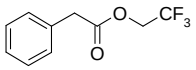


Compound **4.1.5–4t** was prepared following the standard procedure, starting from 4–cyanobenzyl alcohol (**4.1.5–1q**) (136 mg, 1.00 mmol) and diphenyl oxalate (**4.1.5–2d**) (291 mg, 1.20 mmol). After purification, **4.1.5–4t** was isolated as colourless solid (128 mg, 0.54 mmol, 54%).

m.p. 61.2°C; **^{1}H–NMR** (400 MHz, $CDCl_3$) δ= 7.68 (m, 2H), 7.52 (d, ^3J (H,H) = 8.4 Hz, 2H), 7.39 (m, 2H), 7.25 (m, 1H), 7.07 (m, 2H), 3.94 ppm (s, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 168.8 (*C*O_2Ph), 150.4, 138.7, 132.4 (2 C), 130.2 (2 C), 129.5 (2 C), 126.1, 121.2 (2 C), 118.6, 111.4 (*C*N), 41.2 ppm; **IR** (NaCl) ν= 2228 (m), 1751 (vs), 1492 (m), 1342 (s), 1218 (s), 1147 (vs), 940 (m), 869 (m), 772 (s), 695 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 237 [M^+] (4), 144 (12), 143 (100), 117 (9), 116 (88), 115 (13), 94 (74), 89 (21), 65 (10), 63 (7); **CHN** Anal. Calcd. for $C_{15}H_{11}NO_2$: C 75.94, H 4.67, N 5.90, found: C 75.83, H 4.59, N 6.06.

Synthesis of 2,2,2–trifluoroethyl 2–phenylacetate (4.1.5–4u)

[CAS: 1524–11–4]



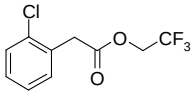
Compound **4.1.5–4u** was prepared following the standard procedure, starting from benzyl alcohol (**4.1.5–1a**) (108 mg, 1.00 mmol) and bis(2,2,2–trifluoroethyl) oxalate (**4.1.5–2e**) (305 mg, 1.20 mmol). After purification, **4.1.5–4u** was isolated as colourless liquid (163 mg, 0.75 mmol, 75%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ= 7.39 – 7.34 (m, 2H), 7.33 – 7.28 (m, 3H), 4.49 (q, ^3J (H,F) = 8.4 Hz, 2 H; OC$H_2$$CF_3$), 3.74 ppm (s, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ= 170.0 (*C*O_2R),

132.8, 129.2 (2 C), 128.7 (2 C), 127.5, 122.9 (q, ^{1}J (C,F) = 276.1 Hz, 1 C; OCH_2CF_3), 60.6 (q, ^{2}J (C,F) = 36.3 Hz, 1 C; OCH_2CF_3), 40.5 ppm; **^{19}F–NMR** (376.5 MHz, $CDCl_3$) δ = -73.8 ppm (t, ^{3}J (F,H) = 8.2 Hz, 3 F; OCH_2CF_3); **IR** (NaCl) ν = 1758 (vs), 1458 (m), 1412 (m), 1283 (s), 1170 (s), 1137 (s), 980 (m), 842 (w), 724 (w), 696 cm^{-1} (w); **MS** (Ion trap, EI): m/z (%) = 218 [M^+] (27), 119 (2), 92 (8), 91 (100), 90 (3), 89 (4), 83 (3), 65 (10), 63 (4); **CHN** Anal. Calcd. for $C_{10}H_9F_3O_2$: C 55.05, H 4.16; found: C 55.12, H 4.15.

Synthesis of 2,2,2–trifluoroethyl 2–(2–chlorophenyl)acetate (4.1.5–4v)

[CAS: 1497383–01–3]



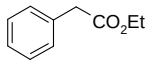
Compound **4.1.5–4v** was prepared following the standard procedure, starting from 2–Chlorobenzylalcohol (**4.1.5–1p**) (144 mg, 1.00 mmol) and bis(2,2,2–trifluoroethyl) oxalate (**4.1.5–2e**) (305 mg, 1.20 mmol). After purification, **4.1.5–4v** was isolated as colourless liquid (205 mg, 0.81 mmol, 81%).

^{1}H–NMR (400 MHz, $CDCl_3$) δ = 7.46 – 7.41 (m, 1H), 7.34 – 7.26 (m, 3H), 4.54 (q, ^{3}J (H,F) = 8.3 Hz, 2 H; OCH_2CF_3), 3.91 ppm (s, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$) δ = 169.0 (CO_2R), 134.6, 131.4, 131.3, 129.6, 129.1, 127.0, 122.8 (q, ^{1}J (C,F) = 285.2 Hz, 1 C; OCH_2CF_3), 60.6 (q, ^{2}J (C,F) = 36.3 Hz, 1 C; OCH_2CF_3), 38.4 ppm; **^{19}F–NMR** (376.5 MHz, $CDCl_3$) δ = -73.8 ppm (t, ^{3}J (F,H) = 8.2 Hz, 3 F; OCH_2CF_3); **IR** (NaCl) ν = 2976 (s), 1762 (vs), 1477 (s), 1448 (s), 1413 (s), 1285 (s), 1170 (s), 1146 (s), 1057 (m), 981 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 254 [M^+] (6), 252 (19), 218 (6), 217 (55), 127 (32), 126 (8), 125 (100), 89 (19), 83 (6), 63 (8); **CHN** Anal. Calcd. for $C_{10}H_8ClF_3O_2$: C 47.55, H 3.19; found: C 47.68, H 3.23.

6.5.4. Preparative scale synthesis

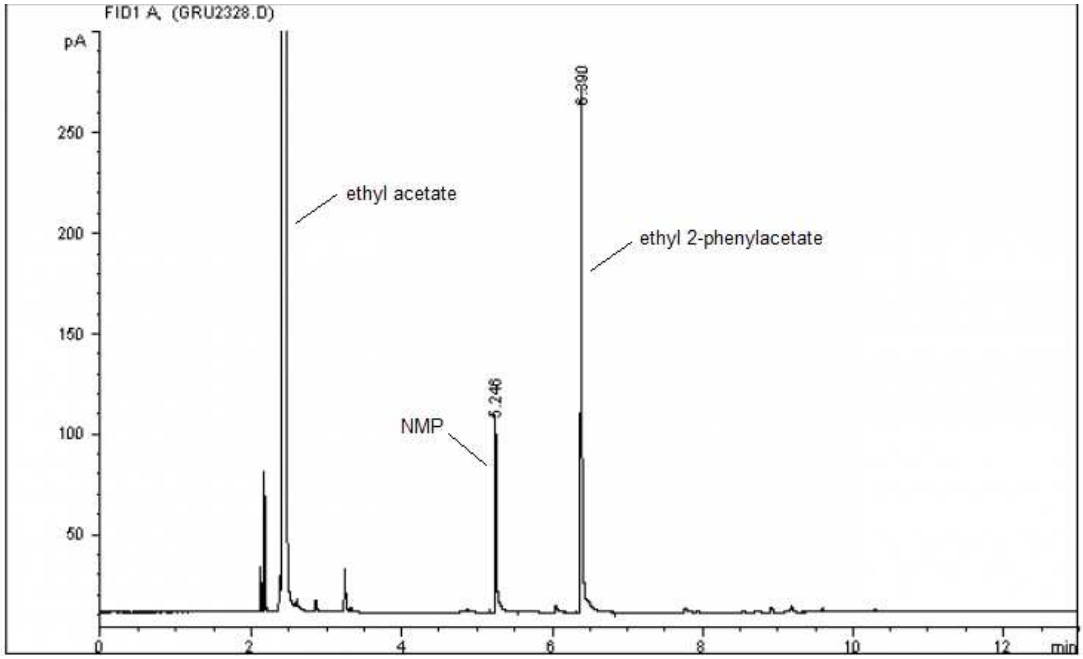
Preparative scale synthesis of ethyl 2–phenylacetate (4.1.5–4a)

[CAS: 101–97–3]



Palladium (II) acetate (115 mg, 0.50 mmol), 1,3–bis(diphenylphosphino)propane (309 mg, 0.75 mmol) and 1,4–diazabicyclo[2.2.2]octane (561 mg, 5.00 mmol) were added to a dry 100 mL three–necked round bottomed flask with equipped reflux condenser and kept *in vacuo* for 10 min. After three nitrogen–vacuum cycles, the degassed distilled NMP (50 mL), benzyl alcohol (**4.1.5–1a**) (5.46 g, 50.0 mmol, 5.23 mL) and diethyl oxalate (**4.1.5–2a**) (8.77 g, 60.0 mmol, 8.20 mL) were added. The reaction mixture was heated to 150 °C for 16 h and was then allowed to cool to room temperature. A sample of 0.1 mL was taken, diluted with ethyl acetate (3 mL) and washed with a saturated aqueous sodium bicarbonate solution (3 mL). The layers were separated and the organic layer was dried over $MgSO_4$, filtered and analysed by GC, indicating the full conversion of the starting materials.

Gas chromatography after the aqueous workup:



The GC sample was reunited with the reaction mixture that was then diluted with ethyl acetate (100 mL) and washed with a saturated aqueous sodium bicarbonate solution (100 mL). The phases were separated and the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* (200 mbar, 40°C) to give a yellow solution of the desired product, NMP and catalyst. The colourless mixture of the product and NMP was completely distilled off by Kugelrohr distillation (50 mbar, 130 °C), leaving the remains of the catalyst as brownish tar. The product mixture was then washed with an aqueous lithium chloride solution (2%, 2 × 50 mL) to remove the NMP. The organic layer was dried over $MgSO_4$, filtered and the filter cake was rinsed with diethyl ether (10 mL). The ether was removed *in vacuo* (100 mbar, 40 °C) to get the pure product as colourless liquid (7.78 g, 47.4 mmol, 95%). The analytical data matched the ones described before.

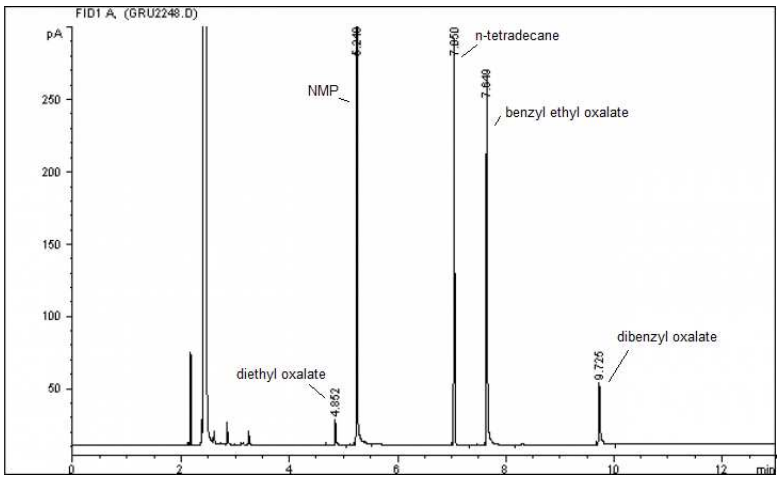
6.5.5. Mechanistic investigations

Standard procedure for the mechanistic investigations

A solution of benzyl ethyl oxalate (**4.1.5–2f**) (104 mg, 0.50 mmol), the relevant catalyst component and the internal GC standard *n*–tetradecane (50 µL) in NMP (1 mL) was stirred at 150°C for 16 h and then cooled to room temperature. A 0.5 mL sample was taken, diluted with ethyl acetate (3 mL) and washed with a saturated aqueous sodium bicarbonate solution (3 mL). The organic layer was separated, dried over $MgSO_4$, filtered and analysed by GC.

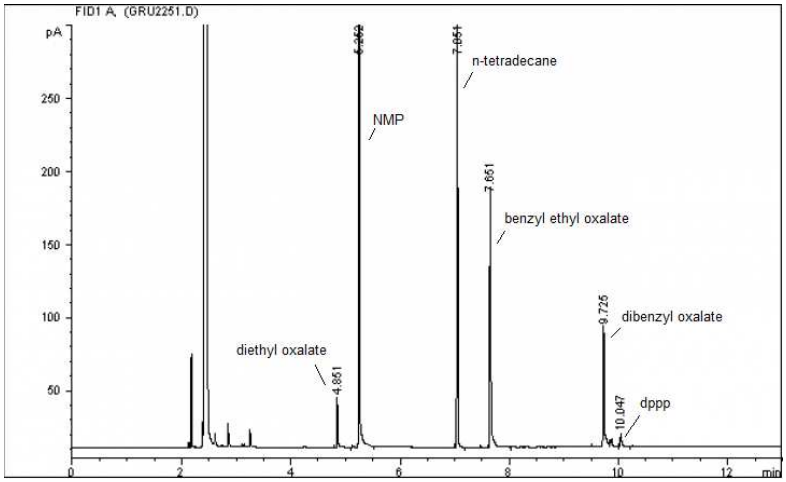
Experiment 1

The **oxalate** was heated to 150°C without any catalyst.



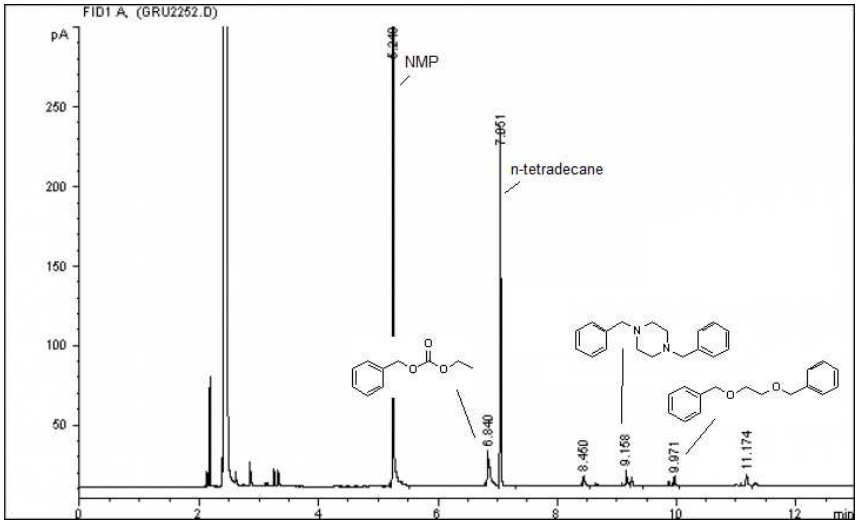
Experiment 2

The **oxalate** was heated to 150°C in the presence of **dppp** (6.19 mg, 1.50 µmol).



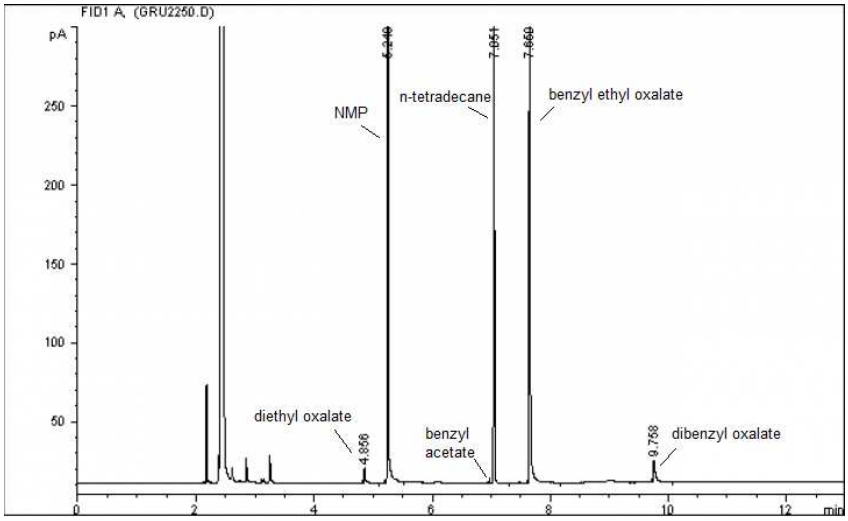
Experiment 3

The **oxalate** was heated to 150°C in the presence of **DABCO** (5.61 mg, 0.05 mmol).



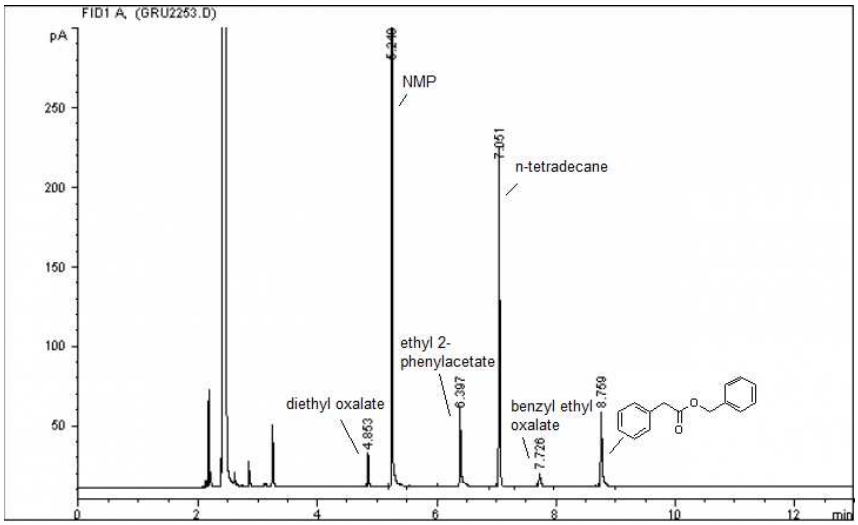
Experiment 4

The **oxalate** was heated to 150°C in the presence of **$Pd(OAc)_2$** (2.29 mg, 0.01 mmol).



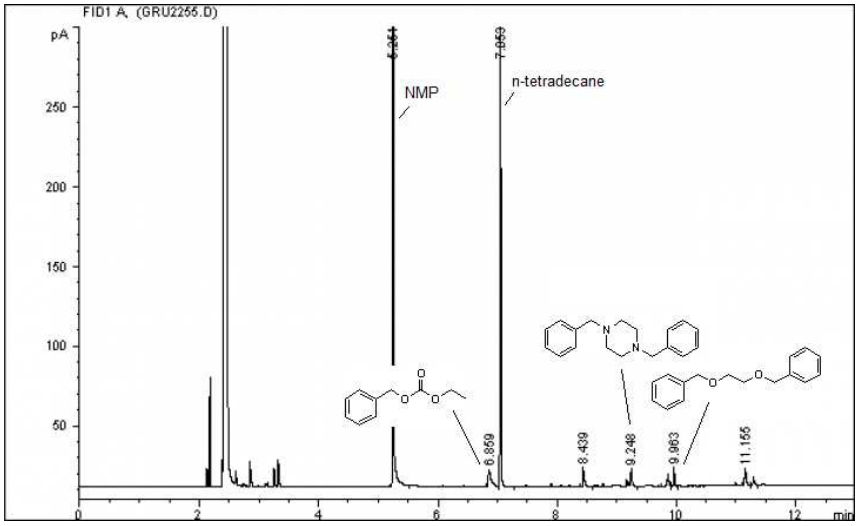
Experiment 5

The **oxalate** was heated to 150°C in the presence of **$Pd(OAc)_2$** (2.29 mg, 0.01 mmol) and **dppp** (6.19 mg, 1.50 µmol).



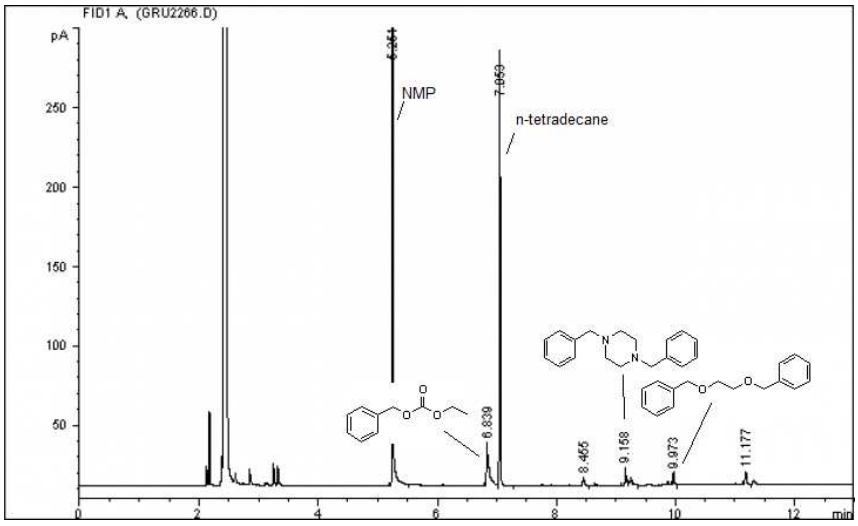
Experiment 6

The **oxalate** was heated to 150°C in the presence of **dppp** (6.19 mg, 1.50 µmol) and **DABCO** (5.61 mg, 0.05 mmol).



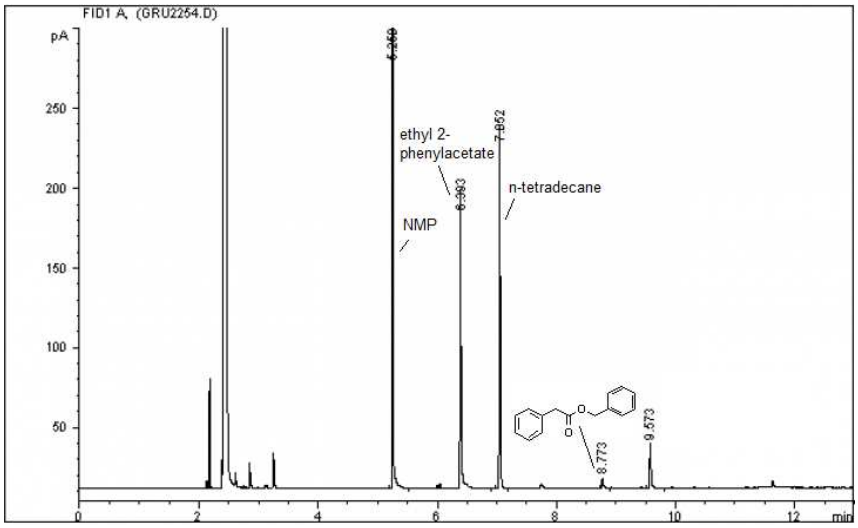
Experiment 7

The **oxalate** was heated to 150°C in the presence of **$Pd(OAc)_2$** (2.29 mg, 0.01 mmol) and **DABCO** (5.61 mg, 0.05 mmol).



Experiment 8

The **oxalate** was heated to 150°C in the presence of **$Pd(OAc)_2$** (2.29 mg, 0.01 mmol), **dppp** (6.19 mg, 1.50 µmol) and **DABCO** (5.61 mg, 0.05 mmol).



6.6. Decarboxylierende Allylierung von Allylbenzoaten

6.6.1. Synthesis of the allyl and cinnamyl esters

Standard procedure for the synthesis of the allyl esters

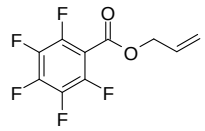
4–Dimethylaminopyridine (247 mg, 2.00 mmol), the corresponding carboxylic acid (20.0 mmol) and allyl alcohol (2.35 g, 40.0 mmol, 2.76 mL) were dissolved in CH_2Cl_2 (30 mL). At 0 °C a solution of *N*,*N'*–Dicyclohexylcarbodiimide (4.54 g, 22 mmol) in CH_2Cl_2 (10 mL) was slowly added. The mixture was stirred at room temperature for 16 h, diluted with *n*–pentane (200 mL), filtered and concentrated *in vacuo*. The residue was dissolved in Et_2O (50 mL), washed with a saturated aqueous solution of $NaHCO_3$ (30 mL), brine (20 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, Et_2O/*n*–pentane gradient) and subsequent Kugelrohr distillation.

Standard procedure for the synthesis of the cinnamyl esters

4–Dimethylaminopyridine (185 mg, 1.50 mmol), the corresponding carboxylic acid (15.8 mmol) and the cinnamyl alcohol (15.0 mmol) were dissolved in CH_2Cl_2 (50 mL). At 0 °C a solution of *N*,*N'*–Dicyclohexylcarbodiimide (3.44 g, 16.5 mmol) in CH_2Cl_2 (10 mL) was slowly added. The mixture was stirred at room temperature for 16 h, diluted with *n*–hexane (200 mL), filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc (50 mL), washed with a saturated aqueous solution of $NaHCO_3$ (30 mL), brine (20 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, Et_2O/*n*–pentane gradient).

Synthesis of allyl 2,3,4,5,6–pentafluorobenzoate (4.1.6–1a)

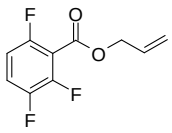
[CAS: 99483–18–8].



A mixture of 2,3,4,5,6–pentafluorobenzoic acid (49.3 g, 230 mmol), allyl alcohol (67.5 g, 1.15 mol, 79.4 mL) and sulfuric acid (4.51 g, 46 mmol, 2.46 mL) was heated to reflux for 12 h. The cooled reaction mixture was diluted with Et_2O (200 mL), washed with a saturated aqueous solution of $NaHCO_3$ (3 x 100 mL), water (80 mL), brine (50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* and the remaining red solution was fractionally distilled under vacuum (57 °C/10^{-2} mbar). **4.1.6–1a** was obtained as a colourless liquid (24.0 g, 95.2 mmol, 41%).

b.p. 70 °C/10^{-3} mbar; **^{1}H–NMR** (400 MHz, Chloroform–*d*) δ= 5.99 (m, 1H), 5.44 (dd, *J*=17.2 Hz, 1.2 Hz, 1H), 5.33 (dd, *J*=10.6 Hz, 1.0 Hz, 1H), 4.87 ppm (d, *J*=5.8 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*) δ= 158.7, 145.4 (dm, *J*=258.0 Hz, 2C), 143.2 (dm, *J*=259.9 Hz, 1C), 137.7 (dm, *J*=251.5 Hz, 2C), 130.8, 119.4, 108.1 (m, 1C), 67.1 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*) δ= -138.2 (m, 2F), –148.7 (tt, *J*=20.6 Hz, 4.1 Hz, 1F), -160.5 ppm (m, 2F); **MS** (Ion trap, EI): m/z (%) = 252 [M^+] (3), 196 (10), 195 (100), 167 (5), 165 (3), 117 (9), 41 (4); **IR** ν = 1745 (vs), 1654 (m), 1526 (vs), 1500 (vs), 1424 (m), 1364 (m), 1328 (s), 1225 (s), 1104 (w), 1008 cm^{-1} (s); **CHN** Anal. Calcd. for $C_{10}H_5F_5O_2$: C 47.64, H 2.00; found: C 47.87, H 2.20.

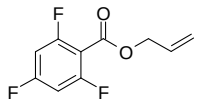
Synthesis of allyl 2,3,6–trifluorobenzoate (4.1.6–1b)



Following the general procedure, 2,3,6–trifluorobenzoic acid (986 mg, 5.60 mmol) was reacted with allyl alcohol (657 mg, 11.2 mmol, 773 µL). **4.1.6–1b** was obtained as a colourless liquid (970 mg, 4.48 mmol, 80%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.27 (qd, *J*=9.1 Hz, 4.9 Hz, 1H), 6.91 (tdd, *J*=9.0 Hz, 3.5 Hz, 2.2 Hz, 1H), 5.94–6.06 (m, 1H), 5.44 (dq, *J*=17.1 Hz, 1.5 Hz, 1H), 5.32 (dd, *J*=10.3 Hz, 1.2 Hz, 1H), 4.87 ppm (dt, *J*=5.7 Hz, 1.4 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 160.1–160.2 (m), 155.8 (dm, *J*=253.41 Hz), 148.6 (dm, *J*=258.85 Hz), 147.0 (dm, *J*=247.96 Hz), 131.1, 119.7 (ddd, *J*=19.98 Hz, 9.99 Hz, 1.82 Hz), 119.0, 112.5 (dd, *J*=19.98 Hz, 14.53 Hz), 111.4–111.9 (m), 66.6 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -115.62 – -115.30 (m, 1F), -133.52 – -133.23 (m, 1F), -141.19 – -140.83 ppm (m, 1F); **MS** (Ion trap, EI): m/z (%) = 216 [M^+] (3), 159 (100), 131 (14), 81 (9), 57 (3); **IR** (NaCl) ν = 2120, 1742, 1637, 1497, 1458, 1362, 1282, 1241, 1188, 1181, 1129, 1029, 985, 937, 818, 736, 708, 623 cm^{-1}; **CHN** Anal. Calcd. for $C_{10}H_7F_3O_2$: C, 55.57; H, 3.26; found C, 55.52; H, 3.22.

Synthesis of allyl 2,4,6–trifluorobenzoate (4.1.6–1c)

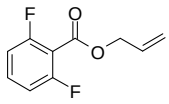


Following the general procedure, 2,4,6–trifluorobenzoic acid (986 mg, 5.60 mmol) was reacted with allyl alcohol (657 mg, 11.2 mmol, 773 µL). **4.1.6–1c** was obtained as a colourless liquid (970 mg, 4.49 mmol, 80%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 6.68–6.77 (m, 2H), 5.94–6.06 (m, 1H), 5.43 (dq, *J*=17.1 Hz, 1.5 Hz, 1H), 5.30 (dd, *J*=10.3 Hz, 1.2 Hz, 1H), 4.84 ppm (dt, *J*=5.6 Hz, 1.3 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 165.5 (t, *J*=15.40 Hz, 1C), 161.8 (dm, 2C), 131.2, 118.8, 107.6 (td, *J*=17.61 Hz, 4.40 Hz, 1C), 100.6–101.4 (m, 2C), 66.4 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -101.83 (t, *J*=8.2 Hz, 1F), -106.06 ppm (d, *J*=8.2 Hz, 2F); **MS** (Ion trap, EI): m/z (%) = 216 [M^+] (1), 159 (100), 131 (9), 81 (7), 57 (2); **IR** (NaCl) ν = 2944, 2893, 2845, 1739, 1734, 1616, 1594, 1583, 1473, 1456, 1440, 1307, 1287, 1261, 1244, 1110, 1086, 1064, 997, 963, 943, 822, 791, 762, 739, 724, 620, 523 cm^{-1}; **CHN** Anal. Calcd. for $C_{10}H_7F_3O_3$: C, 55.57; H, 3.26; found C, 55.42; H, 3.36.

Synthesis of allyl 2,6–difluorobenzoate (4.1.6–1d)

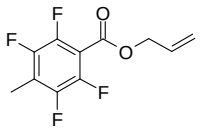
[CAS: 99483–18–8]



Following the general procedure, 2,6–difluorobenzoic acid (6.45 g, 40.0 mmol) was reacted with allyl alcohol (4.69 g, 80.0 mmol, 5.52 mL). **4.1.6–1d** was obtained as a colourless liquid (6.94 g, 35.0 mmol, 88%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.42 (tt, *J*=8.5 Hz, 6.2 Hz, 1H), 6.96 (t, *J*=8.3 Hz, 2H), 5.95–6.08 (m, 1H), 5.44 (dd, *J*=17.2 Hz, 1.3 Hz, 1H), 5.31 (dd, *J*=10.4 Hz, 1.1 Hz, 1H), 4.86 ppm (d, *J*=5.6 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 160.9, 160.4 (dd, *J*=256 Hz, 6.4 Hz, 2C), 132.6 (t, *J*=10.4 Hz), 131.2, 118.4, 111.6–112.0 (m, 2C), 110.8 (t, *J*=18.17 Hz), 66.1 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -110.56 (t, *J*=6.8 Hz, 2F) ppm; **MS** (Ion trap, EI): m/z (%) = 198 [M^+] (2), 141 (100), 113 (11), 63 (6); **IR** (NaCl) ν = 1739, 1626, 1594, 1574, 1471, 1361, 1299, 1289, 1263, 1237, 1116, 1058, 1015, 939, 824, 799, 769, 702, 516 cm^{-1}; **CHN** Anal. Calcd. for $C_{10}H_8F_2O_2$: C, 60.61; H, 4.07; found C, 60.80; H, 4.25.

Synthesis of allyl 2,3,5,6–tetrafluoro–4–methylbenzoate (4.1.6–1e)

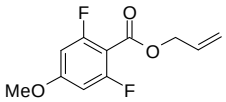


Following the general procedure, 2,3,5,6–tetrafluoro–*p*–toluic acid (4.99 g, 23.5 mmol) was reacted with allyl alcohol (2.67 g, 47.0 mmol, 3.24 mL). **4.1.6–1e** was obtained as a colourless liquid (4.11 g, 16.6 mmol, 71%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 5.94–6.06 (m, 1H), 5.44 (dq, *J*=17.1 Hz, 1.5 Hz, 1H), 5.32 (dq, *J*=10.5 Hz, 1.3 Hz, 1H), 4.87 (dt, *J*=5.6 Hz, 1.4 Hz, 2H), 2.32 ppm (t, *J*=2.3 Hz, 3H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 159.5–159.8 (m), 144.8 (dm, *J*=246.5 Hz, 2C), 144.5 (dm, *J*=256.0 Hz, 2C), 131.0, 120.0 (t, *J*=19.1 Hz), 119.1, 109.9 (t, *J*=15.4 Hz), 66.7, 7.8–7.9 ppm (m); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -140.87 – -140.73 (m, 2F), -142.51 – -142.26 ppm (m, 2F); **MS** (Ion trap, EI): m/z (%) = 248 [M^+] (30), 247 (95), 191 (100), 162

(74), 142 (55), 57 (41), 41 (57); **IR** (NaCl) ν = 1743, 1655, 1487, 1451, 1359, 1307, 1215, 1071, 971, 935, 788, 760 cm^{-1}; **CHN** Anal. Calcd. for $C_{11}H_8F_4O_2$: C, 53.24; H, 3.25; found C, 53.13; H, 3.50.

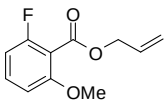
Synthesis of allyl 2,6–difluoro–4–methoxybenzoate (4.1.6–1f)



Following the general procedure, 2,6–difluoro–*p*–anisic acid (1.98 g, 10.5 mmol) was reacted with allyl alcohol (1.23 g, 21.0 mmol, 1.45 mL). **4.1.6–1f** was obtained as a colourless liquid (2.26 g, 9.90 mmol, 94%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 6.41–6.47 (m, 2H), 5.97 (ddt, *J*=17.2 Hz, 10.6 Hz, 5.4 Hz, 1H), 5.39 (dq, *J*=17.2 Hz, 1.6 Hz, 1H), 5.25 (dq, *J*=10.4 Hz, 1.3 Hz, 1H), 4.79 (dt, *J*=5.4 Hz, 1.4 Hz, 2H), 3.78 ppm (s, 3H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 163.3 (t, *J*=14.5 Hz), 162.3 (dd, *J*=256.1 Hz, 8.17 Hz), 161.0–161.1 (m), 131.6, 118.2, 102.8, (t, *J*=16.4 Hz), 98.1–98.7 (m, 2C), 65.7, 55.8 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -107.64 ppm (d, *J*=9.5 Hz, 2F); **MS** (Ion trap, EI): m/z (%) = 228 [M^+] (5), 171 (100), 144 (4) 128 (7); **IR** (NaCl) ν = 1730, 1636, 1582, 1503, 1466, 1445, 1354, 1268, 1204, 1155, 1113, 1049, 1033, 841, 649, 626, 524 cm^{-1}; **CHN** Anal. Calcd. for $C_{11}H_{10}F_2O_3$: C, 57.90; H, 4.42; found C, 57.93; H, 4.42.

Synthesis of allyl 2–fuoro–6–methoxybenzoate (4.1.6–1g)

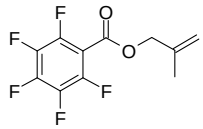


Following the general procedure, 2–fluoro–6–methoxybenzoic acid (2.55 g, 15.0 mmol) was reacted with allyl alcohol (1.76 g, 30.0 mmol, 2.07 mL). **4.1.6–1g** was obtained as a colourless liquid (2.36 g, 11.2 mmol, 75%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.22 (td, *J*=8.4, 6.7 Hz, 1H), 6.59–6.66 (m, 2H), 5.86–5.99 (m, 1H), 5.35 (dq, *J*=17.3 Hz, 1.5 Hz, 1H), 5.19 (dd, *J*=10.5 Hz, 1.2 Hz, 1H), 4.77 (dt, *J*=5.6 Hz, 1.4 Hz, 2H), 3.73 ppm (s, 3H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 163.1, 159.8 (d, *J*=249.8 Hz), 157.7 (d, *J*=7.3 Hz), 131.6, 131.4 (d, *J*=7.3 Hz), 117.8, 111.6 (d, *J*=19.1

Hz), 107.6 (d, *J*=21.8 Hz), 106.6 (d, *J*=3.6 Hz), 65.6, 55.8 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -114.44 ppm (dd, *J*=9.5 Hz, 6.8 Hz, 1F); **MS** (Ion trap, EI): m/z (%) = 210 [M^+] (12), 153 (100), 139 (9), 110 (10), 95 (6), 82 (3); **IR** (NaCl) ν = 2944, 2893, 2845, 1739, 1734, 1616, 1594, 1583, 1473, 1456, 1440, 1307, 1287, 1261, 1244, 1110, 1086, 1064, 997, 963, 943, 822, 791, 762, 739, 724, 620, 523 cm^{-1}; **CHN** Anal. Calcd. for $C_{11}H_{11}FO_3$: C, 62.85; H, 5.27; found C, 62.85; H, 5.33.

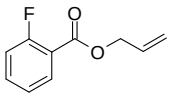
Synthesis of 2–methylallyl 2,3,4,5,6–pentafluorobenzoate (4.1.6–1h)



Following the general procedure, 2,3,4,5,6–pentafluorobenzoic acid (4.28 g, 20.0 mmol) was reacted with 2–methyl–2–propen–1–ol (2.94 g, 40.0 mmol, 3.45 mL). **4.1.6–1h** was obtained as a colourless liquid (3.87 g, 14.5 mmol, 73%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 5.10 (s, 1H), 5.03 (s, 1H), 4.80 (s, 2H), 1.83 ppm (s, 3H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 158.7, 145.4 (dm, *J*=259.0 Hz), 143.2 (dm, *J*=259.7 Hz), 138.6, 137.7 (dm, *J*=256.0 Hz), 114.5, 107.9–108.3 (m), 70.0, 19.3 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -138.27 – -137.92 (m, 2F), -148.70 – -148.39 (m, 1F), -160.56 – -160.21 ppm (m, 2F); **MS** (Ion trap, EI): m/z (%) = 266 [M^+] (3), 195 (100), 167 (13), 117 (9), 55 (8); **IR** (NaCl) ν = 1743, 1655, 1523), 1499, 1455, 1423, 1367, 1327, 1219, 1103, 1007, 951, 812, 752 cm^{-1}; **CHN** Anal. Calcd. for $C_{11}H_7F_5O_2$: C, 49.64; H, 2.65; found C, 49.59; H, 2.75.

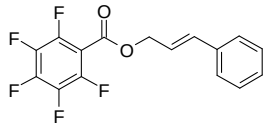
Synthesis of allyl 2–fluorobenzoate (4.1.6–1i)



Following the general procedure, 2–fluorobenzoic acid (4.25 g, 30.0 mmol) was reacted with allyl alcohol (3.52 g, 60.0 mmol, 4.14 mL). **4.1.6–1i** was obtained as a colourless liquid (3.97 g, 22.0 mmol, 73%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.87 (td, *J*=7.6, 2.0 Hz, 1H), 7.42 (dddd, *J*=8.2 Hz, 7.3 Hz, 5.2 Hz, 1.8 Hz, 1H), 7.00–7.14 (m, 2H), 5.96 (ddt, *J*=17.2 Hz, 10.7 Hz, 5.5 Hz, 1H), 5.36 (dq, *J*=17.2 Hz, 1.6 Hz, 1H), 5.21 (dq, *J*=10.4 Hz, 1.3 Hz, 1H), 4.76 ppm (dt, *J*=5.6 Hz, 1.4 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 163.5 (d, *J*=3.6 Hz), 161.6 (d, *J*=259.8 Hz), 134.2 (d, *J*=9.1 Hz), 131.7 (d, *J*=18.2 Hz), 123.6 (d, *J*=3.6 Hz), 118.3 (d, *J*=10.0 Hz), 117.8, 116.7, 116.5, 65.4 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -109.38 – -109.18 ppm (m, 1F); **MS** (Ion trap, EI): m/z (%) = 180 [M^+] (3), 123 (100), 95 (15), 75 (7); **IR** (NaCl) ν = 1732, 1720, 1614, 1490, 1458, 1362, 1301, 1273, 1251, 1159, 1129, 1081, 1034, 997, 969, 935, 861, 791, 757, 693, 656, 652 cm^{-1}; **CHN** Anal. Calcd. for $C_{10}H_9FO_2$: C, 66.66; H, 5.03; found C, 66.66; H, 5.10.

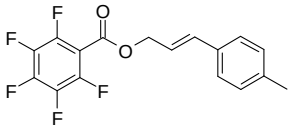
Synthesis of cinnamyl 2,3,4,5,6–pentafluorobenzoate (4.1.6–1j)



Following the general procedure, 2,3,4,5,6–pentafluorobenzoic acid (3.21 g, 15.0 mmol) was reacted with cinnamyl alcohol (4.03 g, 30.0 mmol). After recrystallization (EtOAc/*n*–hexane) **4.1.6–1j** was obtained as a colourless solid (3.80 g, 11.6 mmol, 77%).

m.p. 97–98 °C. **^{1}H–NMR** (400 MHz, Chloroform–*d*): δ = 7.41–7.46 (m, 2H), 7.28–7.39 (m, 3H), 6.78 (d, *J*=16.1 Hz, 1H), 6.37 (dt, *J*=15.8 Hz, 6.5 Hz, 1H), 5.05 ppm (dd, *J*=6.5 Hz, 1.3 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 158.8 (m), 145.4 (dm, *J*=258.2 Hz), 143.1 (dm, *J*=259.7 Hz), 137.8 (dm, *J*=253.1 Hz), 135.8, 135.5, 128.6 (2C), 128.4, 126.7 (2C), 121.5, 108.1 (td, *J*=15.8 Hz, 3.7 Hz), 67.2 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -138.21 – -137.78 (m, 2F), -148.68 – -148.30 (m, 1F), -160.51 – -160.09 (m, 2F) ppm; **MS** (Ion trap, EI): m/z (%) = 328 [M^+] (21), 195 (89), 167 (39), 133 (97), 117 (80), 116 (34), 115 (100), 105 (70); **IR** (neat) ν = 3071, 2970, 2948, 1720, 1653, 1525, 1495, 1451, 1420, 1322, 1240, 1220, 1002, 978, 943 cm^{-1}; **CHN** Anal. Calcd. for $C_{16}H_9F_5O_2$: C, 58.55; H, 2.76; found C, 58.61; H, 2.88.

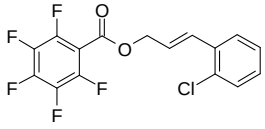
Synthesis of (*E*)–3–(*p*–tolyl)allyl 2,3,4,5,6–pentafluorobenzoate (4.1.6–1k)



Following the general procedure, 2,3,4,5,6–pentafluorobenzoic acid (1.35 g, 6.30 mmol) was reacted with *p*–methylcinnamyl alcohol (805 mg, 6.00 mmol). After recrystallization (EtOAc/*n*–hexane) **4.1.6–1k** was obtained as a colourless solid (1.53 g, 4.47 mmol, 75%).

m.p. 87–88 °C. **^{1}H–NMR** (400 MHz, Chloroform–*d*): δ = 7.33 (d, *J*=8.0 Hz, 2H), 7.16 (d, *J*=8.0 Hz, 2H), 6.75 (d, *J*=15.8 Hz, 1H), 6.31 (dt, *J*=15.8 Hz, 6.7 Hz, 1H), 5.03 (dd, *J*=6.5 Hz, 1.0 Hz, 2H), 2.36 ppm (s, 3H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 158.9 (m), 145.7 (dm, *J*=258.2 Hz), 142.7 (dm, *J*=259.7 Hz), 138.4, 137.4 (dm, *J*=259.0 Hz), 135.7, 133.0, 129.3, 126.6, 120.4, 108.1–108.4 (m), 67.4, 21.2 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -138.19 – -137.88 (m, 2F), -148.67 – -148.36 (m, 1F), -160.50 – -160.17 (m, 2F) ppm; **MS** (Ion trap, EI): m/z (%) = 342 [M^+] (78), 195 (79), 147 (100), 131 (92), 119 (83), 115 (58), 91 (56); **IR** (neat) ν = 3031, 2928, 1720, 1652, 1526, 1497, 1321, 1239, 1222, 1004, 945, 793, 771 cm^{-1}; **CHN** Anal. Calcd. for $C_{17}H_{11}F_5O_2$: C, 59.66; H, 3.24; found C, 59.63; H, 3.34.

Synthesis of (*E*)–3–(2–chlorophenyl)allyl 2,3,4,5,6–pentafluorobenzoate (4.1.6–1l)

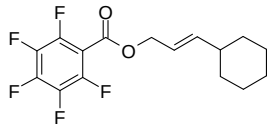


Following the general procedure, 2,3,4,5,6–pentafluorobenzoic acid (1.35 g, 6.30 mmol) was reacted with *o*–chlorocinnamyl alcohol (985 mg, 6.00 mmol). After recrystallization (EtOAc/*n*–hexane) **4.1.6–1l** was obtained as a colourless solid (1.55 g, 4.27 mmol, 71%).

m.p. 64–65 °C. **^{1}H–NMR** (400 MHz, Chloroform–*d*): δ = 7.53–7.59 (m, 1H), 7.35–7.41 (m, 1H), 7.21–7.29 (m, 2H), 7.17 (d, *J*=16.1 Hz, 1H), 6.35 (dt, *J*=15.9 Hz, 6.4 Hz, 1H), 5.08 ppm (dd, *J*=6.3 Hz, 1.3 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 158.8 (m), 145.4 (dm, *J*=259.0 Hz), 143.3 (dm, *J*=259.0 Hz), 137.8 (dm, *J*=255.3 Hz), 134.0, 133.4, 131.3, 129.8, 129.3, 127.0, 126.9, 124.4, 107.6–108.4 (m), 66.9 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -138.10 – -137.69 (m, 2F), -148.36 – -148.09 (m, 1F), -160.44 – -160.11 ppm (m, 2F); **MS** (Ion trap, EI): m/z (%) = 362 [M^+] (1), 195.0 (100), 167.0 (62), 139.1 (21), 117.0 (16), 116.2

(15), 115.2 (42), 103.2 (17); **IR** (neat) ν = 2915, 2873, 1727, 1649, 1527, 1491, 1381, 1321, 1226, 1114, 1042, 1002, 979, 940, 751, 707 cm^{-1}; **CHN** Anal. Calcd. for $C_{16}H_8ClF_5O_2$: C, 52.99; H, 2.22; found C, 52.98; H, 2.34.

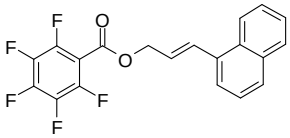
Synthesis of (*E*)–3–cyclohexylallyl 2,3,4,5,6–pentafluorobenzoate (4.1.6–1m)



Following the general procedure, 2,3,4,5,6–pentafluorobenzoic acid (1.35 g, 6.30 mmol) was reacted with (*E*)–3–cyclohexylprop–2–en–1–ol (805 mg, 6.00 mmol). **4.1.6–1m** was obtained as a colourless liquid (1.39 g, 4.16 mmol, 69%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 5.84 (dd, *J*=15.6, 6.5 Hz, 1H), 5.54–5.65 (m, 1H), 4.82 (d, *J*=6.5 Hz, 2H), 1.95–2.08 (m, 1H), 1.62–1.80 (m, 5H), 1.02–1.36 ppm (m, 5H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 158.8 (m), 145.1 (dm, *J*=257.5 Hz), 143.8, 142.9 (dm, *J*=259.0 Hz), 137.9 (dm, *J*=253.1 Hz), 120.0, 108.1–108.9 (m), 67.7, 40.3, 32.4 (2C), 26.0, 25.9 ppm (2C); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -138.49 – -138.17 (m, 2F), -149.10 – -148.88 (m, 1F), -160.69 – -160.36 ppm (m, 2F); **IR** (neat) ν = 2927, 2854, 1739, 1652, 1523, 1496, 1450, 1326, 1216, 996, 971, 943, 752 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^+] Calcd. for $C_{16}H_{15}F_5O_2$: 334.0992; found 334.0976; **CHN** Anal. Calcd. for $C_{16}H_{15}F_5O_2$: C, 57.59; H, 4.52; found C, 57.46; H, 4.56.

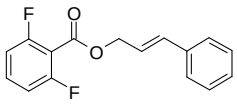
Synthesis of (*E*)–3–(1–naphthyl)allyl 2,3,4,5,6–pentafluorobenzoate (4.1.6–1n)



Following the general procedure, 2,3,4,5,6–pentafluorobenzoic acid (1.80 g, 8.40 mmol) was reacted with (*E*)–3–(1–naphthyl)prop–2–en–1–ol (1.31 g, 8.00 mmol). After recrystallization (EtOAc/*n*–hexane) **4.1.6–1n** was obtained as a colourless solid (830 mg, 2.19 mmol, 27%).

m.p. 124–125 °C. **^{1}H–NMR** (400 MHz, Chloroform–*d*): δ = 8.11 (d, *J*=8.0 Hz, 1H), 7.80–7.91 (m, 2H), 7.64 (d, *J*=7.0 Hz, 1H), 7.45–7.60 (m, 4H), 6.40 (dt, *J*=15.6 Hz, 6.4 Hz, 1H), 5.17 ppm (dd, *J*=6.4 Hz, 1.4 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 158.8 (m), 145.9 (dm, *J*=257.5 Hz), 143.0 (dm, *J*=259.7 Hz), 137.8 (dm, *J*=251.6 Hz), 133.6, 133.5, 132.8, 131.1, 128.7, 128.6, 126.3, 125.9, 125.5, 124.7, 124.2, 123.5, 107.9–108.4 (m), 67.3 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -138.11 – -137.82 (m, 1F), -148.44 – -148.17 (m, 1F), -160.38 – -160.00 ppm (m, 1F); **MS** (Ion trap, EI): m/z (%) = 378 [M^+] (63), 195 (42), 167 (56), 166 (59), 165 (100), 153 (14), 152 (19); **IR** (neat) ν = 3063, 2934, 1720, 1649, 1489, 1323, 1211, 1002, 958, 779 cm^{-1}; **CHN** Anal. Calcd. for $C_{20}H_{11}F_5O_2$: C, 63.50; H, 2.93; found C, 63.48; H, 3.10.

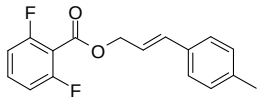
Synthesis of cinnamyl 2,6–difluorobenzoate (4.1.6–1o)



Following the general procedure, 2,6–difluorobenzoic acid (2.55 g, 15.8 mmol) was reacted with cinnamyl alcohol (2.05 g, 15.0 mmol). **4.1.6–1o** was obtained as a colourless liquid (3.90 g, 14.2 mmol, 95%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.26–7.46 (m, 6H), 6.93 – 7.00 (m, 2H), 6.78 (d, *J*=15.8 Hz, 1H), 6.40 (dt, *J*=15.8 Hz, 6.4 Hz, 1H), 5.04 ppm (dd, *J*=6.4 Hz, 1.4 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 161.2–161.3 (m), 160.6 (dd, *J*=256.8 Hz, 6.60 Hz), 136.0, 134.7, 132.7 (t, *J*=11.0 Hz), 128.5 (2C), 128.1, 126.6 (2C), 122.3, 111.8–112.2 (m, 2C), 111.0 (t, *J*=18.0 Hz), 66.3 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -110.11 ppm (s, 2F); **MS** (Ion trap, EI): m/z (%) = 274 [M^+] (3), 245 (10), 141 (100), 133 (33), 117 (23), 115 (32), 113 (13), 63 (19); **IR** (neat) ν = 3028, 1730, 1624, 1468, 1285, 1259, 1234, 1107, 1012, 966, 795, 743, 691 cm^{-1}; **CHN** Anal. Calcd. for $C_{16}H_{12}F_2O_2$: C, 70.07; H, 4.41; found C, 70.06; H, 4.52.

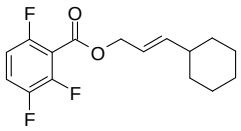
Synthesis of (*E*)–3–(*p*–tolyl)allyl 2,6–difluorobenzoate (4.1.6–1p)



Following the general procedure, 2,6–difluorobenzoic acid (1.03 g, 6.30 mmol) was reacted with (*E*)–3–(p–tolyl)prop–2–en–1–ol (889 mg, 6.00 mmol). **4.1.6–1p** was obtained as a colourless liquid (1.72 g, 5.96 mmol, 99%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.42 (tt, *J*=8.5 Hz, 6.2 Hz, 1H), 7.34 (d, *J*=8.0 Hz, 2H), 7.16 (d, *J*=7.8 Hz, 2H), 6.93–7.01 (m, 2H), 6.75 (d, *J*=15.8 Hz, 1H), 6.35 (dt, *J*=15.8 Hz, 6.5 Hz, 1H), 5.03 (dd, *J*=6.5 Hz, 1.3 Hz, 2H), 2.36 ppm (s, 3H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 161.3–161.4 (m), 160.7 (dd, *J*=256.8 Hz, 5.87 Hz), 138.0, 134.8, 133.3, 132.7 (t, *J*=10.3 Hz), 129.3, 126.6, 121.2, 111.8–112.2 (m), 111.1 (t, *J*=18.3 Hz) 66.5, 21.2 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -110.15 ppm (s, 2F); **MS** (Ion trap, EI): m/z (%) = 288 [M^+] (8), 147 (60), 141 (100), 131 (30), 115 (27), 113 (16), 91 (21), 63 (20); **IR** (neat) ν = 3025, 1730, 1624, 1469, 1285, 1259, 1235, 1107, 1057, 1012, 968, 792, 767 cm^{-1}; **CHN** Anal. Calcd. for $C_{17}H_{14}F_2O_2$: C, 70.83; H, 4.89; found C, 70.77; H, 5.04.

Synthesis of (*E*)–3–cyclohexylallyl 2,3,6–trifluorobenzoate (4.1.6–1q).

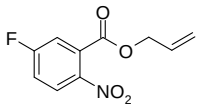


Following the general procedure, 2,3,6–trifluorobenzoic acid (1.12 g, 6.30 mmol) was reacted with (*E*)–3–cyclohexylprop–2–en–1–ol (985 mg, 6.00 mmol). **4.1.6–1q** was obtained as a colourless liquid (1.65 g, 5.53 mmol, 92%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.25 (qd, *J*=9.0 Hz, 4.8 Hz, 1H), 6.90 (tdd, *J*=9.0 Hz, 3.5 Hz, 2.3 Hz, 1H), 5.83 (dd, *J*=15.4 Hz, 6.7 Hz, 1H), 5.61 (dtd, *J*=15.6 Hz, 6.5 Hz, 1.3 Hz, 1H), 4.81 (d, *J*=6.5 Hz, 2H), 2.01 (dtd, *J*=10.8 Hz, 7.3 Hz, 3.3 Hz, 1H), 1.69–1.78 (m, 4H), 1.60–1.69 (m, 1H), 1.02–1.35 ppm (m, 5H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 160.3 (m), 155.1 (dm, *J*=252.4 Hz), 148.5 (ddd, *J*=259.0 Hz, 15.41 Hz, 7.34 Hz), 147.0 (ddd, *J*=247.2 Hz, 13.2 Hz, 4.4 Hz), 143.2, 120.3, 119.4 (ddd, *J*=19.1 Hz, 10.3 Hz, 1.5 Hz), 112.8 (dd, *J*=20.5

Hz, 14.7 Hz), 111.5 (ddd, *J*=24.2 Hz, 5.9 Hz, 4.4 Hz), 67.2, 40.3, 32.4, 26.0, 25.9 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -115.67 (d, *J*=15.0 Hz, 1F), -133.68 – -133.29 (m, 1F), -141.24 – -140.97 ppm (m, 1F); **MS** (Ion trap, EI): m/z (%) = 159 [α–cleavage] (100), 122 (65), 107 (39), 93 (30), 81 (72), 79 (54), 67 (30); **IR** (neat) ν = 2926, 2853, 1734, 1493, 1450, 1278, 1239, 1178, 1126, 1025, 967, 955, 814 cm^{-1}; **CHN** Anal. Calcd. for $C_{16}H_{17}F_3O_2$: C, 64.42; H, 5.74; found C, 64.36; H, 5.79.

Synthesis of allyl 5–fluoro–2–nitrobenzoate (4.1.6–1r)



Following the general procedure, 5–fluoro–2–nitrobenzoic acid (4.67 g, 25.0 mmol) was reacted with allyl alcohol (2.93 g, 50.0 mmol, 3.75 mL). **4.1.6–1r** was obtained as a yellow liquid (4.78 g, 21.2 mmol, 85%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.97 (dd, *J*=8.9 Hz, 4.5 Hz, 1H), 7.34 (dd, *J*=7.8 Hz, 2.7 Hz, 1H), 7.27 (ddd, *J*=8.9 Hz, 7.3 Hz, 2.8 Hz, 1H), 5.87–6.00 (m, 1H), 5.35 (dq, *J*=17.2 Hz, 1.4 Hz, 1H), 5.26 (dq, *J*=10.4 Hz, 1.2 Hz, 1H), 4.78 ppm (dt, *J*=5.9 Hz, 1.3 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 163.8 (d, *J*=1.8 Hz), 164.2 (d, *J*=258.0 Hz), 143.7 (br. s.), 130.7, 130.5 (d, *J*=9.1 Hz), 126.8 (d, *J*=9.1 Hz), 119.5, 118.3 (d, *J*=22.7 Hz), 116.8 (d, *J*=25.4 Hz), 67.1 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -103.53 – -101.38 (m, 1F) ppm; **MS** (Ion trap, EI): m/z (%) = 225 [M^{+}] (0.4), 169 (100), 139 (36), 111 (25), 94 (39), 83 (18), 76 (21); **IR** (NaCl) ν = 3086, 1741, 1592, 1537, 1419, 1351, 1286, 1248, 1212, 1126, 1065, 974, 935, 885, 844, 756, 618 cm^{-1}; **CHN** Anal. Calcd. for $C_{10}H_8FNO_4$: C, 53.34; H, 3.58; N, 6.22; found C, 53.46; H, 3.56; N, 6.25.

6.6.2. Synthesis of the allyl– and cinnamyl benzenes

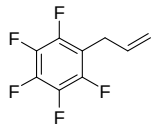
Standard procedure palladium–catalyzed decarboxylative allylation

A 20 mL vessel was charged with $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol) and tri–*p*–tolylphosphine (7.76 mg, 0.025 mmol) and the vessel was brought under an atmosphere of dry nitrogen.

1,4–dioxane (4 mL) and allyl 2,3,4,5,6–pentafluorobenzoate (**4.1.6–1a–p**, 252 mg, 1.00 mmol) were added via syringe and the mixture was stirred at 110 °C for 24 h. After cooling to room temperature, the mixture was diluted with *n*–pentane (20 mL), washed with aqueous 1N NaOH (3 x 20 mL), water (20 mL) and brine (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed at ambient pressure and the products **4.1.6–2a–p** were isolated from the residue by flash column chromatography (SiO_2, Et_2O /*n*–pentane gradient).

Synthesis of allyl 2,3,4,5,6–pentafluorobenzene (4.1.6–2a)

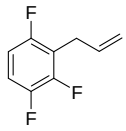
[CAS: 1736–60–3]



Following the general procedure, compound **4.1.6–2a** was synthesised from allyl 2,3,4,5,6–pentafluorobenzoate (**4.1.6–1a**, 252 mg, 1.00 mmol). The product was obtained as a colourless liquid (183 mg, 879 µmol, 88%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 5.82–5.96 (m, 1H), 5.03–5.16 (m, 2H), 3.45 ppm (dt, *J*=6.4 Hz, 1.7 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 145.1 (dm, *J*=246.5 Hz), 139.8 (dm, *J*=251.6 Hz), 137.2 (dm, *J*=250.2 Hz), 132.9, 116.8–117.2 (m), 112.8–113.4 (m), 26.3 ppm (d, *J*=1.5 Hz); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -144.23 – -44.05 (m, 1F), -157.73 – -157.38 (m, 1F), -163.04 – -162.75 ppm (m, 1F); **IR** (NaCl) ν = 1655, 1643, 1503, 1443, 1415, 1315, 1299, 1219, 1123, 1011, 983, 911, 895, 752, 692, 624 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^+] Calcd. for $C_9H_5F_5$: 208.0311; found 208.0319; **CHN** Anal. Calcd. for $C_9H_5F_5$: C, 51.94; H, 2.42; found C, 52.20; H, 2.59.

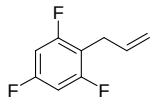
Synthesis of allyl 2,3,6–trifluorobenzene (4.1.6–2b)



Following the general procedure, compound **4.1.6–2b** was synthesised from allyl 2,3,6–trifluorobenzoate (**4.1.6–1b**, 216 mg, 1.00 mmol). The product was obtained as a colourless liquid (118 mg, 683 µmol, 68%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.01 (dq, *J*=9.2 Hz, 5.1 Hz, 1H), 6.81 (tdd, *J*=8.9 Hz, 3.8 Hz, 2.2 Hz, 1H), 5.86–5.99 (m, 1H), 5.10 (s, 1H), 5.06 (dd, *J*=6.6 Hz, 1.0 Hz, 1H), 3.42–3.49 ppm (m, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 156.5 (ddd, *J*=243.4 Hz, 6.4 Hz, 2.7 Hz), 148.9 (ddd, *J*=248.0 Hz, 13.6 Hz, 9.1 Hz), 147.1 (ddd, *J*=243.4 Hz, 12.7 Hz, 2.7 Hz), 133.8, 117.6 (dd, *J*=22.7 Hz, 17.3 Hz), 116.4, 114.4–114.8 (m), 110.3 (dq, *J*=24.5 Hz, 3.6 Hz), 26.5–27.0 ppm (m); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -121.16 – -120.92 (m, 1F), -138.92 – -138.68 (m, 1F), -143.03 – -142.70 ppm (m, 1F); **IR** (NaCl) ν = 1643, 1495, 1463, 1439, 1415, 1303, 1243, 1211, 1143, 1111, 1027, 971, 919, 871, 808, 768, 736, 624 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^{+}] Calcd. for $C_9H_7F_3$: 172.0500; found 172.0511; **CHN** Anal. Calcd. for $C_9H_7F_3$: C, 62.79; H, 4.10; found C, 63.16; H, 4.34.

Synthesis of allyl 2,4,6–trifluorobenzene (4.1.6–2c)



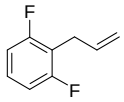
Following the general procedure, compound **4.1.6–2c** was synthesised from allyl 2,4,6–trifluorobenzoate (**4.1.6–1c**, 216 mg, 1.00 mmol). The product was obtained as a colourless liquid (131 mg, 761 µmol, 76%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 6.59–6.70 (m, 2H), 5.91 (ddt, *J*=16.8 Hz, 10.4 Hz, 6.1 Hz, 1H), 4.99–5.10 (m, 2H), 3.38 ppm (d, *J*=6.0 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ =161.3 (dm, *J*=248.7 Hz, 3C), 134.3, 115.9, 111.6 (td, *J*=20.5 Hz, 4.4 Hz), 99.5–100.3 (m, 2C), 26.0 ppm (t, *J*=2.6 Hz); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -111.52 (t, *J*=5.5 Hz, 1F), -113.29 ppm (d, *J*=5.4 Hz, 1F); **IR** (NaCl) ν = 1643, 1623, 1603, 1495, 1443,

1219, 1167, 1115, 1043, 1019, 999, 919, 840, 716 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^+] Calcd. for $C_9H_7F_3$: 172.0500; found 172.0498; **CHN** Anal. Calcd. for $C_9H_7F_3$: C, 62.79; H, 4.10; found C, 63.09; H, 4.31.

Synthesis of allyl 2,6–difluorobenzene (4.1.6–2d)

[CAS: 1028801–61–7]

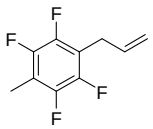


Following the general procedure, compound **4.1.6–2d** was synthesised from allyl 2,6–difluorobenzoate (**4.1.6–1d**, 198 mg, 1.00 mmol). The product was obtained as a colourless liquid (145 mg, 919 µmol, 92%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.17 (tt, *J*=8.3 Hz, 6.6 Hz, 1H), 6.83–6.93 (m, 2H), 5.89–6.03 (m, 1H), 5.01–5.11 (m, 2H), 3.41–3.49 ppm (m, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 161.4 (dd, *J*=247.1 Hz, 9.1 Hz, 2C), 134.5, 127.7 (t, *J*=10.0 Hz), 115.8, 115.6 (t, *J*=20.0 Hz), 110.7–111.3 (m, 2C), 26.4 ppm (t, *J*=2.7 Hz); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -116.01 – -115.79 ppm (m, 2F); **IR** (NaCl) ν = 3081, 2981, 2925, 2853, 1914, 1834, 1623, 1591, 1471, 1439, 1415, 1267, 1239, 1215, 1107, 1059, 1019, 987, 919, 879, 780, 736, 692 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^+] Calcd. for $C_9H_8F_2$: 154.0594; found 154.0608; **CHN** Anal. Calcd. for $C_9H_8F_2$: C, 70.12; H, 5.23; found C, 70.28; H, 5.29.

Synthesis of allyl 2,3,5,6–tetrafluoro–4–methylbenzene (4.1.6–2e)

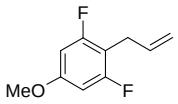
[CAS: 1101449–89–1]



Following the general procedure, compound **4.1.6–2e** was synthesised from allyl 2,3,5,6–tetrafluoro–4–methylbenzoate (**4.1.6–1e**, 248 mg, 1.00 mmol). The product was obtained as a colourless liquid (125 mg, 612 µmol, 61%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ =5.84–5.97 (m, 1H), 5.04–5.13 (m, 2H), 3.40–3.49 (m, 2H), 2.26 ppm (t, *J*=2.1 Hz, 3H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ =144.9 (dm, *J*=244.3 Hz, 2C), 144.6 (dm, *J*=244.3 Hz, 2C), 133.5, 116.5, 115.2 (t, *J*=18.7 Hz), 113.9 (t, *J*=19.1 Hz), 26.6 (t, *J*=1.8 Hz), 7.3 ppm (d, *J*=2.2 Hz); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -145.00 – -144.78 (m, 2F), -146.54 – -146.32 ppm (m, 2F); **IR** (NaCl) ν = 1639, 1487, 1443, 1411, 1295, 1271, 1111, 1063, 991, 947, 923, 891, 859, 748, 688 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^{+}] Calcd. for $C_{10}H_8F_4$: 204.0562; found 204.0563; **CHN** Anal. Calcd. for $C_{10}H_8F_4$: C, 58.83; H, 3.95; found C, 58.63; H, 3.93.

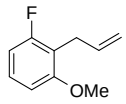
Synthesis of allyl 2,6–difluoro–4–methoxybenzene (4.1.6–2f)



Following the general procedure, compound **4.1.6–2f** was synthesised from allyl 2,6–difluoro–4–methoxybenzoate (**4.1.6–1f**, 228 mg, 1.00 mmol). The product was obtained as a colourless liquid (183 mg, 994 µmol, 99%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 6.41–6.48 (m, 2H), 5.92 (ddt, *J*=17.7 Hz, 9.4 Hz, 6.1 Hz, 1H), 4.99–5.06 (m, 2H), 3.78 (s, 3H), 3.32–3.36 ppm (m, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 161.8 (dd, *J*=245.2 Hz, 12.7 Hz, 2C), 159.3 (t, *J*=13.6 Hz), 135.1, 115.3, 107.4 (t, *J*=21.8 Hz), 97.7 (dd, *J*=20.9 Hz, 8.2 Hz, 2C), 55.7, 25.6–26.4 ppm (m); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -115.06 ppm (d, *J*=9.5 Hz, 2F); **IR** (NaCl) ν = 2845, 1639, 1587, 1503, 1467, 1443, 1347, 1219, 1195, 1143, 1115, 1039, 1015, 991, 919, 840, 820, 632 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^{+}] Calcd. for $C_{10}H_{10}F_2O$: 184.0700; found 184.0701; **CHN** Anal. Calcd. for $C_{10}H_{10}F_2O$: C, 65.21; H, 5.47; found C, 65.26; H, 5.58.

Synthesis of allyl 2–fluoro–6–methoxybenzene (4.1.6–2g)

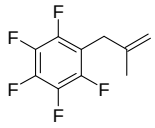


Following the general procedure, compound **4.1.6–2g** was synthesised from allyl 2–fluoro–6–methoxybenzoate (**4.1.6–1g**, 210 mg, 1.00 mmol). The product was obtained as a colourless liquid (109 mg, 656 µmol, 66%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.15 (td, *J*=8.3 Hz, 6.8 Hz, 1H), 6.64–6.73 (m, 2H), 5.97 (dd, *J*=16.8 Hz, 10.4 Hz, 1H), 4.96–5.06 (m, 2H), 3.85 (s, 3H), 3.39–3.46 ppm (m, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 161.6 (d, *J*=243.4 Hz), 158.6 (d, *J*=9.1 Hz), 135.7, 127.4 (d, *J*=10.0 Hz), 115.7 (d, *J*=19.1 Hz), 114.8, 107.8 (d, *J*=23.6 Hz), 106.1 (d, *J*=2.7 Hz), 55.9, 26.7 ppm (d, *J*=3.6 Hz); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -117.53 ppm (t, *J*=8.2 Hz, 1F); **IR** (NaCl) ν = 3077, 2937, 2837, 1639, 1615, 1587, 1471, 1439, 1271, 1243, 1215, 1119, 1087, 1067, 995, 911, 776 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^{+}] Calcd. for $C_{10}H_{11}FO$: 166.0794; found 166.0804; **CHN** Anal. Calcd. for $C_{10}H_{11}FO$: C, 72.27; H, 6.67; found C, 72.30; H, 6.66.

Synthesis of 2–methylallyl 2,3,4,5,6–pentafluorobenzene (4.1.6–2h)

[CAS: 116212–41–0]



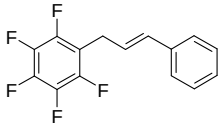
Following the general procedure, compound **4.1.6–2h** was synthesised from 2–methylallyl 2,3,4,5,6–pentafluorobenzoate (**4.1.6–1h**, 266 mg, 1.00 mmol). The product was obtained as a colourless liquid (193 mg, 869 µmol, 87%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 4.83–4.85 (m, 1H), 4.64 (m, 1H), 3.39 (s, 2H), 1.79 ppm (s, 3H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 145.2 (dm, *J*=246.5 Hz), 141.0, 139.7 (dm, *J*=257.5 Hz), 137.3 (dm, *J*=250.2 Hz), 112.8–113.3 (m), 112.3, 30.1, 22.1 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -143.76 – -143.33 (m, 2F), -157.61 – -157.27 (m, 1F), -163.26

– -162.85 ppm (m, 2F); **IR** (NaCl) ν = 1655, 1503, 1447, 1379, 1303, 1211, 1195, 1123, 1047, 983, 951, 907, 748, 676, 656 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^+] Calcd. for $C_{10}H_7F_5$: 222.0468; found 222.0468; **CHN** Anal. Calcd. for $C_{10}H_7F_5$: C, 54.07; H, 3.18; found C, 54.03; H, 3.06.

Synthesis of 1–cinnamyl–2,3,4,5,6–pentafluorobenzene (4.1.6–2j)

[CAS: 474097–66–0]

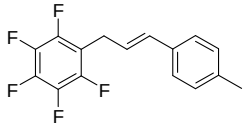


Following the general procedure, compound **4.1.6–2j** was synthesised from cinnamyl 2,3,4,5,6–pentafluorobenzoate (**4.1.6–1j**, 328 mg, 1.00 mmol). The product was obtained as a colourless solid (284 mg, 999 µmol, 99%).

m.p. 65–66 °C; **^{1}H–NMR** (400 MHz, Chloroform–*d*): δ = 7.28–7.43 (m, 5H), 6.56 (d, *J*=15.8 Hz, 1H), 6.30 (dt, *J*=15.8 Hz, 6.8 Hz, 1H), 3.62–3.71 ppm (m, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 145.0 (dm, *J*=246.1 Hz), 140.3 (dm, *J*=247.1 Hz), 136.6, 137.2 (dm, *J*=248.0 Hz), 132.4, 128.5 (2C), 127.6, 126.2 (2C), 124.2, 113.0 – 113.5 (m), 25.5 ppm (m); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -144.21 – -143.90 (m, 2F), -157.58 – -157.34 (m, 1F), -162.82 – -162.51 ppm (m, 2F); **IR** (neat) ν = 3026, 1519, 1501, 1117, 987, 970, 959, 910, 756, 692 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^+] Calcd. for $C_{15}H_9F_5$: 284.0624; found 284.0627; **CHN** Anal. Calcd. for $C_{15}H_9F_5$: C, 63.39; H, 3.19; found C, 63.42; H, 3.13.

Synthesis of (*E*)–1–(3–(*p*–tolyl)allyl)–2,3,4,5,6–pentafluorobenzene (4.1.6–2k)

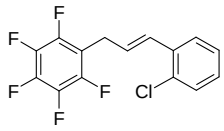
[CAS: 1289638–88–5]



Following the general procedure, compound **4.1.6–2k** was synthesised from (*E*)–3–(*p*–tolyl)allyl 2,3,4,5,6–pentafluorobenzoate (**4.1.6–1k**, 342 mg, 1.00 mmol). The product was obtained as a colourless solid (290 mg, 972 µmol, 97%).

m.p. 76–77 °C; **^{1}H–NMR** (400 MHz, Chloroform–*d*): δ = 7.30 (d, *J*=8.0 Hz, 2H), 7.19 (d, *J*=8.0 Hz, 2H), 6.53 (d, *J*=15.8 Hz, 1H), 6.25 (dt, *J*=15.5 Hz, 6.8 Hz, 1H), 3.65 (dd, *J*=6.8 Hz, 1.3 Hz, 2H), 2.42 ppm (s, 3H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 145.0 (dm, *J*=246.1 Hz), 140.0 (dm, *J*=247.1 Hz), 137.5, 137.4 (dm, *J*=250.7 Hz), 133.8, 132.3, 129.2 (2C), 126.1, (2C), 123.1, 113.1–113.6 (m), 25.5, 21.0 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -144.21 – -143.99 (m, 2F), -157.73 – -157.48 (m, 1F), -162.90 – -162.63 ppm (m, 2F); **IR** (neat) ν = 3030, 2922, 1497, 1117, 1069, 1007, 986, 963, 929, 912, 841, 831, 791, 780 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^{+}] Calcd. for $C_{16}H_{11}F_5$: 298.0781; found 298.0789; **CHN** Anal. Calcd. for $C_{16}H_{11}F_5$: C, 64.43; H, 3.72; found C, 64.57; H, 3.70.

Synthesis of (*E*)–1–(3–(2–chlorophenyl)allyl)–2,3,4,5,6–pentafluorobenzene (4.1.6–2l)

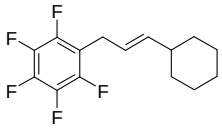


Following the general procedure, compound **4.1.6–2l** was synthesised from (*E*)–3–(2–chlorophenyl)allyl 2,3,4,5,6–pentafluorobenzoate (**4.1.6–1l**, 363 mg, 1.00 mmol). The product was obtained as a colourless solid (292 mg, 916 µmol, 92%).

m.p. 86–87 °C; **^{1}H–NMR** (400 MHz, Chloroform–*d*): δ = 7.48 (dd, *J*=7.4 Hz, 2.1 Hz, 1H), 7.33–7.37 (m, 1H), 7.21 (dquin, *J*=7.4 Hz, 1.9 Hz, 2H), 6.93 (d, *J*=15.6 Hz, 1H), 6.23 (dt, *J*=15.8 Hz, 6.8 Hz, 1H), 3.67 ppm (dd, *J*=6.8 Hz, 1.5 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ =144.9 (dm, *J*=246.1 Hz), 140.0 (dm, *J*=252.5 Hz), 137.2 (dm, *J*=252.5 Hz), 134.7, 132.9, 129.6, 128.8, 128.6, 127.1, 126.8, 126.7, 112.9 (td, *J*=18.6 Hz, 3.6 Hz), 25.8 ppm (m); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -143.97 – -143.72 (m, 2F), -157.28 – -157.00 (m, 1F), -162.69 – -162.42 ppm (m, 2F); **IR** (neat) ν = 3061, 1520, 1501, 1468, 1115, 1068, 985, 974, 959, 916, 755, 692 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^{+}] Calcd. for $C_{15}H_8ClF_5$: 318.0235; found 318.0246; **CHN** Anal. Calcd. for $C_{15}H_8ClF_5$: C, 56.54; H, 2.53; found C, 56.54; H, 2.46.

Synthesis of (*E*)–1–(3–cyclohexylallyl)–2,3,4,5,6–pentafluorobenzene (4.1.6–2m)

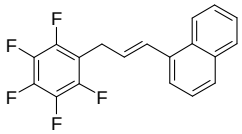
[CAS: 1314581–23–1].



Following the general procedure, compound **4.1.6–2m** was synthesised from (*E*)–3–cyclohexylallyl 2,3,4,5,6–pentafluorobenzoate (**4.1.6–1m**, 334 mg, 1.00 mmol). The product was obtained as a colourless liquid (65.0 mg, 224 µmol, 22%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 5.35–5.56 (m, 2H), 3.37 (d, *J*=6.3 Hz, 2H), 1.84–1.97 (m, 1H), 1.60–1.78 (m, 5H), 0.97–1.31 ppm (m, 5H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 144.9 (dm, *J*=245.2 Hz), 139.4, 140.0 (dm, *J*=250.7 Hz), 137.2 (dm, *J*=251.6 Hz), 121.7, 114.1 (td, *J*=18.9 Hz, 4.1 Hz), 40.4, 32.7, 26.1, 26.0, 25.5 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -144.42 – -144.21 (m, 2F), -158.26 – -157.98 (m, 1F), -163.15 – -162.89 ppm (m, 2F); **IR** (neat) ν = 2925, 2853, 1655, 1500, 1449, 1310, 1121, 990, 957, 905, 666 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^{+}] Calcd. for $C_{15}H_{15}F_5$: 290.1094; found 290.1082; **CHN** Anal. Calcd. for $C_{15}H_{15}F_5$: C, 62.07; H, 5.21; found C, 62.07; H, 5.37.

Synthesis of (*E*)–1–(3–(1–naphthyl)allyl)–2,3,4,5,6–pentafluorobenzene (4.1.6–2n)



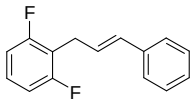
Following the general procedure, compound **4.1.6–2n** was synthesised from (*E*)–3–(1–naphthyl)allyl 2,3,4,5,6–pentafluorobenzoate (**4.1.6–1n**, 378 mg, 1.00 mmol). The product was obtained as a colourless solid (291 mg, 871 µmol, 87%).

m.p. 131–132 °C; **^{1}H–NMR** (400 MHz, Chloroform–*d*): δ = 8.10 (d, *J*=8.3 Hz, 1H), 7.89 (d, *J*=7.8 Hz, 1H), 7.81 (d, *J*=8.3 Hz, 1H), 7.51–7.62 (m, 3H), 7.44–7.50 (m, 1H), 7.29 (d, *J*=14.3 Hz, 1H), 6.22–6.33 (m, 1H), 3.73 ppm (dd, *J*=6.8, 1.8 Hz, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ =144.8 (dm, *J*=246.1 Hz), 139.7 (dm, *J*=251.6 Hz), 137.1 (dm, *J*=250.7 Hz),

134.3, 133.5, 131.0, 129.8, 128.5, 128.0, 127.5, 126.1, 125.8, 125.5, 123.8, 123.5, 112.9–113.4 (m), 26.0 ppm; **^{19}F–NMR** (376 MHz, Chloroform–d): δ = -144.10 – -143.69 (m, 2F), -157.28 – -156.90 (m, 1F), -162.53 – -162.20 ppm (m, 2F); **IR** (neat) ν = 3050, 1517, 1499, 1113, 1072, 974, 955, 913, 794, 774 cm^{-1}; **HRMS–EI** (TOF) m/z: [M$^+$] Calcd. for $C_{19}H_{11}F_5$: 334.0781; found 334.0798; **CHN** Anal. Calcd. for $C_{19}H_{11}F_5$: C, 68.27; H, 3.32; found C, 68.27; H, 3.26.

Synthesis of 1–cinnamyl–2,6–difluorobenzene (4.1.6–2o)

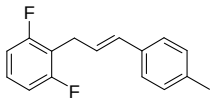
[CAS: 1433415–60–1]



Following the general procedure at 130 °C, compound **4.1.6–2o** was synthesised from cinnamyl 2,6–difluorobenzoate (**4.1.6–1o**, 274 mg, 1.00 mmol). The product was obtained as a colourless liquid (228 mg, 990 µmol, 99%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.20–7.52 (m, 6H), 6.92–7.03 (m, 2H), 6.53–6.62 (m, 1H), 6.37–6.48 (m, 1H), 3.70 ppm (br. s., 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 161.4 (dd, *J*=246.5 Hz, 7.33 Hz, 2C), 137.2, 131.2, 128.4 (2C), 127.7 (t, *J*=9.9 Hz), 127.2, 126.2, 126.1 (2C), 115.7 (t, *J*=20.5 Hz), 111.1 (dd, *J*=19.1 Hz, 7.3 Hz, 2C), 25.7 ppm (t, *J*=2.9 Hz); **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -115.65 – -115.36 ppm (m, 2F); **IR** (neat) ν = 3029, 1625, 1591, 1467, 1264, 1236, 1017, 992, 962, 780, 743, 721, 691 cm^{-1}; **HRMS–EI** (TOF) m/z: [M$^+$] Calcd. for $C_{15}H_{12}F_2$: 230.0907; found 230.0910; **CHN** Anal. Calcd. for $C_{15}H_{12}F_2$: C, 78.25; H, 5.25; found C, 78.27; H, 5.27.

Synthesis of (E)–1–(3–(p–tolyl)allyl)–2,3,4,5,6–pentafluorobenzene (4.1.6–2p)

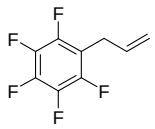


Following the general procedure at 130 °C, compound **4.1.6–2p** was synthesised from (*E*)–3–(*p*–tolyl)allyl 2,6–difluorobenzoate (**4.1.6–1p**, 288 mg, 1.00 mmol). The product was obtained as a colourless liquid (238 mg, 974 µmol, 97%).

^{1}H–NMR (400 MHz, Chloroform–*d*): δ = 7.12–7.32 (m, 5H), 6.88–6.97 (m, 2H), 6.49 (dd, *J*=15.8 Hz, 0.5 Hz, 1H), 6.26–6.38 (m, 1H), 3.60–3.66 (m, 2H), 2.37 ppm (s, 3H); **^{13}C–NMR** (101 MHz, Chloroform–*d*): δ = 161.4 (dd, *J*=247.2 Hz, 8.8 Hz, 2C), 136.9, 134.4, 131.1, 129.1 (2C), 127.7 (t, *J*=9.9 Hz), 126.0 (2C), 125.2, 115.8 (t, *J*=19.8 Hz), 111.1 (dd, *J*=19.1 Hz, 6.6 Hz, 2C), 25.7 (t, *J*=2.9 Hz), 21.1 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*): δ = -115.61 ppm (m, 2F); **IR** (neat) ν = 3027, 2922, 1624, 1591, 1512, 1468, 1263, 1236, 1017, 994, 964, 823, 779, 727 cm^{-1}; **HRMS–EI** (TOF) m/z: [M^{+}] Calcd. for $C_{16}H_{14}F_2$: 244.1064; found 244.1070; **CHN** Anal. Calcd. for $C_{16}H_{14}F_2$: C, 78.67; H, 5.78; found C, 78.87; H, 5.88.

Nickel–catalyzed synthesis of allyl 2,3,4,5,6–pentafluorobenzene (4.1.6–2a)

[CAS: 1736–60–3]

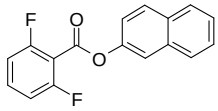


A crimp–cap reaction vessel was charged with nickel(II) chloride (13.0 mg, 0.10 mmol), BINAP (76.2 mg, 0.12 mmol) and zinc powder (65.4 mg, 1.00 mmol). Under an inert atmosphere, the degassed NMP (2 mL) and the allyl pentafluorobenzoate (252 mg, 1.00 mmol, 183 µL) were added via syringe. The reaction mixture was stirred at 100 °C for 16 h and then cooled to room temperature. The slight pressure buildup caused by the partially dissolved CO_2 was carefully released by piercing the septum with a syringe needle before uncapping. Pentane (20 mL) was added and the mixture was washed with water (2 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated (40 °C mbar). The crude product was further purified by flash chromatography (SiO_2, pentane), yielding the allyl benzene as colourless liquid (171 mg, 0.82 mmol, 82%). The analytical data matched those reported before.

6.7. Nickel–katalysierte decarboxylierende Biarylynthese

Synthese von 2,6–Difluorbenzoesäurenaphth–2–ylester (4.1.7–4a)

[CAS: 959079–93–7]

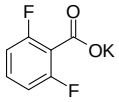


Difluorbenzoesäure (25.0 g, 155 mmol), 2–Naphthol (21.3 g, 148 mmol) und 4–Dimethylaminopyridin (1.83 g, 14.8 mmol) wurden in Dichlormethan (40 mL) gelöst und auf 0 °C gekühlt. *N*,*N'*–Dicyclohexylcarbodiimid (30.8 g, 148 mmol) in Dichlormethan (20 mL) wurde bei 0 °C zugetropft und das Reaktionsgemisch anschließend für 12 h bei Raumtemperatur gerührt. Die gebildete Suspension wurde über Celite (10 g) filtriert und das Filtrat im Vakuum aufkonzentriert (40 °C, 600 mbar). Nach säulenchromatographischer Aufreinigung (SiO_2, Hexan/Ethylacetat = 9:1) wurde das gewünschte Produkt als farbloser Feststoff erhalten. (32.1 g, 113 mmol, 76%).

Schmp. 100–101 °C; **^{1}H–NMR** (400 MHz, Chloroform–*d*) δ= 7.95 (d, *J*=9.0 Hz, 1H), 7.90 (m, 2H), 7.82 (d, *J*=2.3 Hz, 1H), 7.55 (m, 2H), 7.50 – 7.43 (m, 2H), 7.05 ppm (m, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*) δ= 160.9 (dd, *J*=258.0 Hz, 5.5 Hz, 2C), 160.1, 147.9, 133.6, 133.4 (t, *J*=10.9 Hz, 1C), 131.6, 129.5, 127.7, 127.7, 126.6, 125.9, 120.8, 118.6, 112.1 (m, 2C), 110.4 ppm (t, *J*=17.3 Hz, 1C); **^{19}F–NMR** (376 MHz, Chloroform–*d*) δ= -109.4 ppm; **MS** (Ion trap, EI): m/z (%) = 284 [M^+] (12), 283 (65), 141 (7), 140 (100), 113 (15), 89 (4), 63 (16); **IR** ν = 1747 (vs), 1625 (m), 1466 (s), 1288 (s), 1234 (vs), 1087 (vs), 1006 (s), 906 (s), 792 (vs), 761 cm^{-1} (vs); **CHN** Anal. ber. für $C_{17}H_{10}F_2O_2$: C 71.83, H 3.55; gefunden: C 72.08, H 3.76.

Synthese von Kalium–2,6–Difluorbenzoat (4.1.7–8)

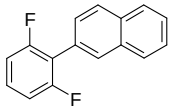
[CAS: 1206164–21–7]



In einem 100 mL Rundkolben wurde 2,6–Difluorbenzoesäure (7.47 g, 60.0 mmol) in siedendem Ethanol (40.0 mL) gelöst, und eine siedende Lösung von Kalium–*tert*–butylat (6.73 g, 60.0 mmol) innerhalb von 5 min zugetropft. Das Reaktionsgemisch wurde auf Raumtemperatur abgekühlt, der ausgefallene Feststoff filtriert, mit Diethylether (2 × 50 mL) gewaschen und im Vakuum (1×10^{-3} mbar) getrocknet. Das gewünschte Benzoat wurde als farbloser Feststoff erhalten (10.7 g, 54.5 mmol, 91%).

^{1}H–NMR (400 MHz, D_2O) δ = 7.31 (tt, *J*=8.5 Hz, 6.6 Hz, 1H), 6.96 ppm (m, 2H); **^{13}C–NMR** (101 MHz, D_2O) δ = 169.2, 158.5 (dd, *J*=245.2 Hz, 9.1 Hz, 2C), 130.1 (t, *J*=10.0 Hz, 1C), 117.1 (t, *J*=24.1 Hz, 1C), 111.6 ppm (dd, *J*=19.1 Hz, 6.4 Hz, 2C); **^{19}F–NMR** (376 MHz, D_2O) δ = -116.0 ppm (s, 2F); **IR** ν = 1608 (vs), 1457 (m), 1379 (m), 1226 (m), 1006 (s), 997 (s), 838 (m), 806 (m), 760 (m), 703 cm^{-1} (s); **CHN** Anal. ber. für $C_7H_3F_2KO_2$: C 42.85, H 1.54; gefunden: C 42.85, H 1.60.

2–(2,6–Difluorphenyl)naphthalin (4.1.7–5)



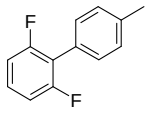
In einem 20 mL Rollrandglas wurden Kalium–2,6–difluorbenzoat (294 mg, 1.50 mmol), 2–Bromnaphthalin (209 mg, 1.00 mmol), Nickel(II)chlorid (13.0 mg, 0.10 mmol), Terpyridin (11.9 mg, 0.05 mmol) und Zinkpulver (65.4 mg, 1.00 mmol) eingewogen, evakuiert (2×10^{-3} mbar) und mit Stickstoff rückbefüllt. Wasserfreies, deoxygeniertes NMP (4 mL) wurde zugegeben und das Reaktionsgemisch für 16 h auf 170 °C erhitzt. Nach dem Abkühlen auf Raumtemperatur wurde Dichlormethan (30 mL) zugegeben und mit Wasser (3 × 20 mL) und einer gesättigten Natriumchlorid–Lösung (20 mL) gewaschen. Die organische Phase wurde über Magnesiumsulfat getrocknet und filtriert. Nach dem Entfernen des Lösungsmittels (40 °C,

600 mbar) wurde das Rohprodukt säulenchromatographisch (SiO_2, Hexan) gereinigt und das gewünschte Produkt als farbloser Feststoff erhalten (124 mg, 0.52 mmol, 52%).

Schmp. 128–129 °C; **^{1}H–NMR** (400 MHz, Chloroform–*d*) δ= 7.98 (br. s, 1H), 7.94 (d, *J*=8.5 Hz, 1H), 7.90 (m, 2H), 7.58 (dq, *J*=8.5 Hz, 1.6 Hz, 1H), 7.54 (m, 2H), 7.33 (tt, *J*=8.4 Hz, 6.3 Hz, 1H), 7.04 ppm (m, 2H); **^{13}C–NMR** (101 MHz, Chloroform–*d*) δ= 160.3 (dd, *J*=248.9 Hz, 7.3 Hz, 2C), 133.1, 132.9, 129.8 (m, 1C), 128.9 (t, *J*=10.0 Hz, 1C), 128.2, 127.8 (m, 1C), 127.8, 127.7, 126.6, 126.5, 126.2, 118.5 (m, 1C), 111.7 ppm (dd, *J*=19.1 Hz, 7.3 Hz, 2C); **^{19}F–NMR** (376 MHz, Chloroform–*d*) δ= -114.3 ppm (s, 1F); **IR** ν = 1583 (w), 1460 (vs), 1431 (w), 1228 (s), 989 (vs), 861 (m), 826 (vs), 782 (vs), 747 (vs), 720 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 241 [M^+] (16), 240 (100), 239 (12), 238 (8), 221 (3), 220 (8), 50 (3); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{16}H_{10}F_2$, 240.0751; found, 240.0750.

2,6–Difluor–4'–methylbiphenyl (4.1.7–12)

[CAS: 906366–93–6]



In einem 20 mL Rollrandglas wurden Kalium–2,6–difluorbenzoat (294 mg, 1.50 mmol), Bis(1,5–cyclooctadiene)nickel(0) (55.0 mg, 0.20 mmol) und Terpyridin (23.8 mg, 0.10 mmol) eingewogen, evakuiert (2×10^{-3} mbar) und mit Stickstoff rückbefüllt. Wasserfreies, deoxygeniertes NMP (4 mL) und 4–Bromtoluol (175 mg, 1.00 mmol, 126 µL) wurde zugegeben und das Reaktionsgemisch für 16 h auf 150 °C erhitzt. Nach dem Abkühlen auf Raumtemperatur wurde Dichlormethan (30 mL) zugegeben und mit Wasser (3 × 20 mL) und einer gesättigten Natriumchlorid–Lösung (20 mL) gewaschen. Die organische Phase wurde über Magnesiumsulfat getrocknet und filtriert. Nach dem Entfernen des Lösungsmittels (40 °C, 600 mbar) wurde das Rohprodukt säulenchromatographisch (SiO_2, Hexan) gereinigt und das gewünschte Produkt als farbloser Feststoff erhalten (81 mg, 0.41 mmol, 41%).

Schmp. 39–40 °C; **^{1}H–NMR** (400 MHz, Chloroform–*d*) δ= 7.25 (m, 2H); 7.15 (d, *J*=7.8 Hz, 2H), 7.09 (m, 1H), 6.83 (m, 2H), 2.28 ppm (s, 3H); **^{13}C–NMR** (101 MHz, Chloroform–*d*) δ= 160.1 (dd, *J*= 248.0 Hz, 7.3 Hz, 2C), 138.1, 130.1 (t, *J*=1.8 Hz, 2C), 129.0 (2C), 128.5 (t, *J*=10.5

Hz, 1C), 126.1, 118.5 (t, *J*=18.7 Hz, 1C), 111.5 (dd, *J*= 19.1 Hz, 7.3 Hz, 2C), 21.2 ppm; **^{19}F–NMR** (376 MHz, Chloroform–*d*) δ = -114.0 ppm (s, 2F); **IR** ν = 1589 (w), 1459 (vs), 1403 (w), 1268 (w), 1227 (s), 992 (vs), 816 (vs), 777 (vs), 726 (s), 711 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 204 [M^+] (100), 203 (41), 201 (6), 184 (11), 183 (27), 63 (6), 50 (6); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{13}H_{10}F_2$, 204.0751; found, 204.0746.

6.8. $[Pd(\mu\text{–}Br)(P^tBu_3)]_2$ as a Highly Active Isomerization Catalyst: Synthesis of Enol Esters from Allylic Esters

6.8.1. General Methods

The catalyst di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) was dissolved in degassed toluene and used as stock solution (0.005 mol/L). Amounts over 1 mol% of catalyst were directly weighed in.

6.8.2. Synthesis of the allylic esters

Method A

The corresponding carboxylic acid **4.1.8–1** (10.0 mmol) was suspended in allyl alcohol (**4.1.8–2a**) (2.35 g, 40.0 mmol, 2.76 mL). After the dropwise addition of concentrated sulfuric acid (0.49 g, 5 mmol, 0.27 mL), the reaction mixture was stirred under reflux for 2–4 h. After full conversion of the carboxylic acid, distilled water (20 mL) was added and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$ and the volatiles were removed *in vacuo* (100 mbar, 40 °C) to afford the corresponding allyl ester, which was further purified by column chromatography (SiO_2, hexane/ ethyl acetate).

Method B

Carbonyldiimidazole (1.95 g, 12.0 mmol) was suspended in THF (15 mL), followed by the addition of the corresponding carboxylic acid **4.1.8–1** (11.0 mmol). The mixture was stirred for 2 h at room temperature until the gas evolution ended and a clear solution was formed. The reaction solution was then concentrated *in vacuo* (100 mbar, 40 °C) to a volume of 5 mL.

In another round bottom flask, sodium (0.35 g, 1.50 mmol) was dissolved completely in a solution of imidazole (0.34 g, 5.00 mmol) in THF (4 mL) under reflux. After cooling to room temperature, the corresponding allylic alcohol **4.1.8–2** (10.0 mmol) in THF (3 mL) was added and stirred for additional 15 min. The initially prepared benzoyl imidazole solution was added and the mixture stirred overnight. After removing the THF *in vacuo* (100 mbar, 40 °C), the residue was mixed with diethyl ether (40 mL) and washed with distilled water (40 mL). The

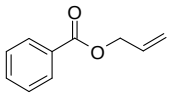
aqueous layer was removed and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with 1M hydrochloric acid (40 mL) and a saturated solution of sodium bicarbonate (40 mL), dried over $MgSO_4$ and the volatiles were removed *in vacuo* (100 mbar, 40 °C) to afford the corresponding allylic ester, which was further purified by column chromatography (SiO_2, hexane/ethyl acetate).

Method C

The corresponding aroyl chloride **4.1.8–1'** (10.0 mmol) was added to a solution of pyridine (12.5 mmol, 1.00 g, 1.01 mL) in THF (4 mL). After cooling to 0 °C, the corresponding allylic alcohol **4.1.8–2** (12.5 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with distilled water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with 2M aqueous hydrochloric acid (30 mL), 10% aqueous sodium hydroxide solution (30 mL), distilled water (2 × 20 mL) and dried over $MgSO_4$. The volatiles were removed *in vacuo* (100 mbar, 40 °C) to afford the corresponding allylic ester, which was further purified by column chromatography (SiO_2, hexane/ ethyl acetate).

Synthesis of allyl benzoate (4.1.8–3a)

[CAS: 583–04–0]



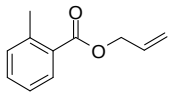
Using method A, compound **4.1.8–3a** was prepared from benzoic acid (**4.1.8–1a**) (1.22 g, 10.0 mmol) yielding **4.1.8–3a** as a colourless liquid (1.39 g, 8.57 mmol, 86%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J*=7.8 Hz, 2H), 7.55 (t, *J*=7.4 Hz, 1H), 7.43 (t, *J*=7.0 Hz, 2H), 6.03 (ddt, *J*=16.5 Hz, 10.3 Hz, 5.5 Hz, 1H), 5.41 (d, *J*=17.2 Hz, 1H), 5.28 (d, *J*=10.6 Hz, 1H), 4.82 ppm (d, *J*=4.7 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 165.9, 132.6, 131.9, 129.8 (2C), 129.3 (2C), 128.0, 117.8, 65.2 ppm; **IR** (NaCl): ν = 3071 (w), 2944 (w), 2881 (w), 1721 (vs), 1601 (w), 1451 (m), 1361 (w), 1272 (vs), 1176 (w), 1112 (m), 1070 (m), 1026 (w), 972 (w), 936 (w), 712 cm^{-1} (s); **MS** (ion trap, EI, 70 eV): m/z (%) = 162 [M^+] (3), 147 (1),

105 (100), 77 (26), 51 (11), 50 (7), 41 (3); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{10}H_{10}O_2$; 162.0681; found, 162.0674.

Synthesis of allyl 2–methylbenzoate (4.1.8–3b)

[CAS: 3609–56–1]

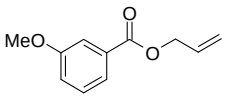


Using method A, compound **4.1.8–3b** was prepared from 2–methylbenzoic acid (**4.1.8–1b**) (1.38 g, 10.0 mmol) yielding **4.1.8–3b** as a colourless liquid (1.41 g, 8.00 mmol, 80%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J*=7.4 Hz, 1H), 7.43 – 7.34 (m, 1H), 7.26 – 7.19 (m, 2H), 6.09 (ddt, *J*=16.2 Hz, 10.6 Hz, 5.4 Hz, 1H), 5.40 (d, *J*=17.2 Hz, 1H), 5.27 (d, *J*=10.6 Hz, 1H), 4.80 (d, *J*=5.9 Hz, 2H), 2.60 ppm (s, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 167.2, 140.2, 132.3, 132.0, 131.7, 130.6, 129.5, 125.7, 118.2, 65.3, 21.7 ppm; **IR** (NaCl): ν = 3077 (m), 2931 (m), 1719 (vs), 1457 (m), 1294 (m), 1254 (vs), 1142 (m), 1078 (m), 934 (w), 738 (m), 664 cm^{-1} (w); **MS** (ion trap, EI, 70 eV): m/z (%) = 176 [M^+] (11), 158 (25), 147 (40), 135 (64), 119 (100), 91 (54), 65 (34); **CHN** Anal. calcd. for $C_{11}H_{12}O_2$: C, 74.98%; H, 6.86%; found: C, 74.69%; H, 6.92%.

Synthesis of allyl 3–methoxybenzoate (4.1.8–3c)

[CAS: 157398–92–0]



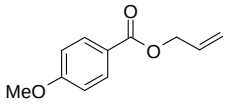
Using method A, compound **4.1.8–3c** was prepared from 3–methoxybenzoic acid (**4.1.8–1c**) (1.52 g, 10.0 mmol) yielding **4.1.8–3c** as a colourless liquid (1.51 g, 7.88 mmol, 79%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J*=7.8 Hz, 1H), 7.56 (s, 1H), 7.36 – 7.29 (m, 1H), 7.08 (d, *J*=8.3 Hz, 1H), 6.07 (ddt, *J*=16.0 Hz, 10.3 Hz, 5.6 Hz, 1H), 5.39 (d, *J*=17.4 Hz, 1H), 5.27 (d, *J*=10.6 Hz, 1H), 4.80 (d, *J*=5.5 Hz, 2H), 3.82 ppm (d, *J*=2.3 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 166.0, 159.5, 132.1, 131.4, 129.3, 121.9, 119.4, 118.1, 114.0, 65.5, 55.3 ppm;

IR (NaCl): ν = 3081 (w), 2943 (m), 2837 (m), 1721 (vs), 1601 (m), 1587 (m), 1489 (m), 1455 (m), 1433 (m), 1278 (vs), 1228 (s), 1182 (m), 1108 (m), 1078 (m), 1046 (m), 980 (m), 934 (w), 788 (w), 756 (m), 684 cm^{-1} (w); **MS** (ion trap, EI, 70 eV): m/z (%) = 192 [M^+] (35), 135 (100), 107 (9), 92 (5), 63 (12), 41 (6); **CHN** Anal. calcd. for $C_{11}H_{12}O_3$: C, 68.74%; H, 6.29%; found: C, 68.48%; H, 6.39%.

Synthesis of allyl 4–methoxybenzoate (4.1.8–3d)

[CAS: 6941–68–0]

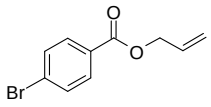


Using method C, compound **4.1.8–3d** was prepared from 4–methoxybenzoic acid (**4.1.8–1d**) (1.55 g, 10.0 mmol) and allyl alcohol (**4.1.8–2a**) (0.59 g, 10.0 mmol) yielding **4.1.8–3d** as a colourless liquid (1.59 g, 8.27 mmol, 83%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.06 – 8.00 (m, 2H), 6.97 – 6.91 (m, 2H), 6.12 (ddt, *J*=16.2 Hz, 10.3 Hz, 5.5 Hz, 1H), 5.41 (dq, *J*=17.2 Hz, 1.6 Hz, 1H), 5.28 (dq, *J*=10.4 Hz, 1.3 Hz, 1H), 4.81 (dt, *J*=5.6 Hz, 1.4 Hz, 2H), 3.87 ppm (s, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 166.0, 163.4, 132.4, 131.6 (2C), 122.5, 117.9, 113.6 (2C), 65.2, 55.4 ppm; **IR** (NaCl): ν = 2937 (m), 1713 (vs), 1605 (vs), 1512 (vs), 1462 (m), 1456 (m), 1444 (m), 1316 (s), 1272 (vs), 1256 (vs), 1168 (vs), 1102 (vs), 1030 (s), 848 (s), 770 cm^{-1} (s); MS (ion trap, EI, 70 eV): m/z (%) = 192 [M^+] (5), 136 (9), 135 (100), 107 (6), 92 (6), 77 (4), 63 (5); **CHN** Anal. calcd. for $C_{11}H_{12}O_3$: C, 68.74%; H, 6.29%; found: C, 68.73%; H, 6.40%.

Synthesis of allyl 4–bromobenzoate (4.1.8–3e)

[CAS: 6420–77–5]

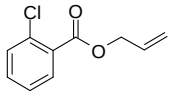


Using method A, compound **4.1.8–3e** was prepared from 4–bromobenzoic acid (**4.1.8–1e**) (2.01 g, 10.0 mmol) yielding **4.1.8–3e** as a colourless liquid (1.43 g, 5.93 mmol, 59%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J*=8.2 Hz, 2H), 7.56 (d, *J*=8.2 Hz, 2H), 6.01 (ddt, *J*=16.9 Hz, 11.1 Hz, 5.7 Hz, 1H), 5.39 (d, *J*=17.2 Hz, 1H), 5.28 (d, *J*=10.6 Hz, 1H), 4.80 ppm (d, *J*=5.9 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 165.4, 131.9, 131.7 (2C), 131.1 (2C), 129.0, 128.1, 118.5, 65.7 ppm; **IR** (NaCl): ν = 3087 (m), 2945 (w), 2880 (w), 1723 (vs), 1649 (w), 1591 (s), 1483 (w), 1453 (w), 1397 (m), 1270 (vs), 1174 (w), 1116 (m), 1102 (m), 1012 (m), 972 (w), 934 (w), 848 (w), 756 (m), 684 cm^{-1} (w); **MS** (ion trap, EI, 70 eV): m/z (%) = 242 [M^+] (4), 240 (4), 185 (100), 183 (26), 157 (3), 155 (2), 76 (7), 50 (5), 41 (10); **CHN** Anal. calcd. for $C_{10}H_9BrO_2$: C, 49.82%; H, 3.76%; found: C, 49.82%; H, 3.86%.

Synthesis of allyl 2–chlorobenzoate (4.1.8–3f)

[CAS: 7506–76–5]

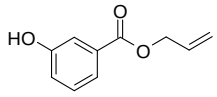


Using method A, compound **4.1.8–3f** was prepared from 2–chlorobenzoic acid (**4.1.8–1f**) (1.57 g, 10.0 mmol) yielding **4.1.8–3f** as a colourless liquid (1.69 g, 8.59 mmol, 86%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, *J*=7.8 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.37 – 7.28 (m, 1H), 6.03 (ddt, *J*=17.2 Hz, 10.4 Hz, 5.7 Hz, 1H), 5.43 (dq, *J*=17.2 Hz, 1.2 Hz, 1H), 5.30 (dq, J=10.5 Hz, 1.3 Hz, 1H), 4.83 ppm (d, *J*=5.9 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 165.3, 133.8, 132.5, 131.8, 131.4, 131.1, 130.0, 126.5, 118.7, 66.1 ppm; **IR** (NaCl): ν = 3079 (m), 2946 (m), 2880 (w), 1731 (vs), 1593 (m), 1437 (m), 1296 (s), 1250 (vs), 1120 (m), 1050 (s), 936 (w), 748 (m), 649 cm^{-1} (w); **MS** (ion trap, EI, 70 eV): m/z (%) = 196 [M^+] (10), 141 (67), 140 (100), 139 (60), 111 (3), 41 (6); **CHN** Anal. calcd. for $C_{10}H_9ClO_2$: C, 61.08%; H, 4.61%; found: C, 61.07%; H, 4.74%.

Synthesis of allyl 3–hydroxybenzoate (4.1.8–3g)

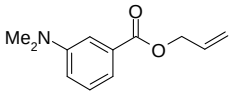
[CAS: 83281–53–2]



Using method A, compound **4.1.8–3g** was prepared from 3–hydroxy benzoic acid (**4.1.8–1g**) (1.38 g, 10.0 mmol) yielding **4.1.8–3g** as a colourless solid (0.89 g, 4.99 mmol, 50%).

m.p.: 49–50 °C. **^{1}H–NMR** (400 MHz, $CDCl_3$): δ = 7.68 – 7.59 (m, 2H), 7.33 (t, *J*=7.8 Hz, 1H), 7.09 (dd, *J*=8.2 Hz, 1.9 Hz, 1H), 6.68 (s, 1H), 6.10 (ddt, *J*=17.1 Hz, 10.6 Hz, 5.7 Hz, 1H), 5.42 (dd, *J*=17.1 Hz, 1.3 Hz, 1H), 5.34 – 5.27 (m, 1H), 4.84 ppm (d, *J*=5.8 Hz, 2H); **^{13}C–NMR** (151 MHz, $CDCl_3$): δ = 166.7, 156.0, 131.8, 131.2, 129.7, 121.8, 120.5, 118.5, 116.4, 65.9 ppm; **IR** (KBr): ν = 3415 (m), 3081 (w), 2945 (w), 1694 (vs), 1601 (m), 14563 (s), 1374 (m), 1284 (m), 1218 (m), 1111 (m), 975 (m), 917 (w), 887 (m), 802 cm^{-1} (w); **MS** (ion trap, EI, 70 eV): m/z (%) = 178 [M^+] (8), 121 (100), 93 (22), 65 (23), 63 (10), 53 (3), 41 (6); **CHN** Anal. calcd. for $C_{10}H_{10}O_3$: C, 67.41%; H, 5.66%; found: C, 67.07%; H, 5.88%.

Synthesis of allyl 3–(dimethylamino)benzoate (4.1.8–3h)



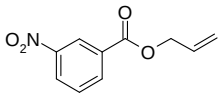
Using method B, compound **4.1.8–3h** was prepared from 3–(dimethylamino)benzoic acid (**4.1.8–1h**) (1.82 g, 11.0 mmol) and allyl alcohol (0.59 g, 10.0 mmol) yielding **4.1.8–3h** as a colourless liquid (1.41 g, 6.85 mmol, 69%).

^{1}H–NMR (200 MHz, $CDCl_3$): δ = 7.41 – 7.62 (m, 3H), 7.07 (d, *J*=8.2 Hz, 1H), 6.21 (ddt, *J*=16.1 Hz, 10.6 Hz, 5.2 Hz, 1H), 5.58 (dd, *J*=17.1 Hz, 1.5 Hz, 1H), 5.45 (dd, *J*=10.4 Hz, 1.2 Hz, 1H), 4.99 (d, *J*=5.7 Hz, 2H), 3.11 ppm (s, 6H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 166.8, 150.3, 132.3, 130.6, 128.9, 117.8, 117.4, 116.7, 113.1, 65.3, 40.4 ppm (2C); **IR** (NaCl): ν = 3421 (w), 3079 (w), 2939 (w), 2881 (w), 1717 (vs), 1603 (m), 1577 (m), 1497 (m), 1437 (m), 1361 (m), 1258 (vs), 1232 (m), 1112 (m), 1082 (w), 998 (m), 934 (w), 864 (w), 752 (m), 684 cm^{-1} (w); **MS** (ion trap, EI, 70 eV): m/z (%) = 205 [M^+] (100), 164 (26), 148 (22), 120 (67), 104 (11), 77 (8),

42 (7); **CHN** Anal. calcd. for $C_{12}H_{15}NO_2$: C, 70.22%; H, 7.37%; N, 6.82%; found: C, 70.24%; H, 7.15%; N, 6.62%.

Synthesis of allyl 3–nitrobenzoate (4.1.8–3i)

[CAS: 779–80–6]

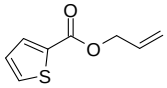


Using method A, compound **4.1.8–3i** was prepared from 3–nitro benzoic acid (**4.1.8–1i**) (1.67 g, 10.0 mmol) yielding **4.1.8–3i** as colourless oil (1.71 g, 8.23 mmol, 82%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.89 (t, *J*=1.9 Hz, 1H), 8.47 – 8.36 (m, 2H), 7.67 (t, *J*=8.0 Hz, 1H), 6.04 (ddt, *J*=16.0 Hz, 11.2 Hz, 5.5 Hz, 1H), 5.45 (dq, *J*=17.2 Hz, 1.4 Hz, 1H), 5.35 (dq, *J*=10.4 Hz, 1.2 Hz, 1H), 4.89 ppm (dt, *J*=5.9 Hz, 1.3 Hz, 2H); **^{13}C–NMR** (151 MHz, $CDCl_3$): δ = 164.1, 148.2, 135.3, 131.9, 131.5, 129.6, 127.4, 124.6, 119.2, 66.4 ppm; **IR** (NaCl): ν = 3091 (m), 2875 (m), 1731 (vs), 1617 (m), 1533 (vs), 1479 (m), 1441 (m), 1351 (vs), 1296 (vs), 1284 (s), 1262 (vs), 1134 (s), 1084 (w), 1070 (m), 976 (m), 924 (m), 820 (w), 774 (w), 718 cm^{-1} (s); MS (ion trap, EI, 70 eV): m/z (%) = 207 [M^+] (1), 150 (100), 134 (3), 104 (20), 92 (6), 76 (12), 50 (9); **CHN** Anal. calcd. for $C_{10}H_9NO_4$: C, 57.97%; H, 4.38%; N, 6.76%; found: C, 57.95%; H, 4.35%; N, 6.66%.

Synthesis of allyl thiophene–2–carboxylate (4.1.8–3j)

[CAS: 431948–67–3]



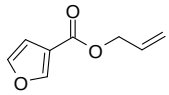
Using method B, compound **4.1.8–3j** was prepared from thiophene–2–carboxylic acid (**4.1.8–1j**) (1.41 g, 11.0 mmol) and allyl alcohol (0.59 g, 10.0 mmol) yielding **4.1.8–3j** as a colourless liquid (1.28 g, 7.62 mmol, 76%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J*=3.5 Hz, 1H), 7.57 (d, *J*=5.0 Hz, 1H), 7.11 (t, *J*=4.4 Hz, 1H), 6.09 (ddt, *J*=17.2 Hz, 10.8 Hz, 5.3 Hz, 1H), 5.38 (m, 1H), 5.29 (d, *J*=10.6 Hz, 1H), 4.81 ppm (d, *J*=5.5 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 161.8, 133.6, 133.5, 132.4,

132.0, 127.7, 118.3, 65.6 ppm; **IR** (NaCl): ν = 3404 (w), 3095 (m), 2945 (w), 1713 (vs), 1649 (w), 1525 (m), 1417 (s), 1365 (m), 1276 (s), 1258 (s), 1226 (m), 1092 (s), 1076 (m), 1038 (w), 996 (w), 936 (w), 860 (w), 750 (m), 720 cm^{-1} (m); **MS** (ion trap, EI, 70 eV): m/z (%) = 168 [M^+] (6), 123 (3), 111 (100), 83 (2), 57 (2), 41 (4), **CHNS** Anal. calcd. for $C_8H_8O_2S$: C, 57.12%; H, 4.79%; S, 19.06%; found: C, 57.24%; H, 4.90%; S, 19.14%.

Synthesis of allyl furan–3–carboxylate (4.1.8–3k)

[CAS: 743420–67–9]

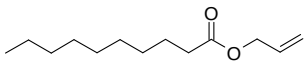


Using method A, compound **4.1.8–3k** was prepared from furan–3–carboxylic acid (**4.1.8–1k**) (1.12 g, 10.0 mmol) yielding **4.1.8–3k** as a colourless oil (1.07 g, 7.03 mmol, 70%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1H), 7.42 (s, 1H), 6.75 (s, 1H), 5.98 (ddt, *J*=16.8 Hz, 11.0 Hz, 5.7 Hz, 1H), 5.38 (d, *J*=17.2 Hz, 1H), 5.29 (d, *J*=10.2 Hz, 1H), 4.75 ppm (d, *J*=5.9 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 162.6, 147.7, 143.7, 132.1, 119.2, 118.2, 109.7, 65.0 ppm; **IR** (NaCl): ν = 3152 (m), 3134 (m), 2949 (w), 2883 (w), 1725 (vs), 1649 (w), 1577 (m), 1507 (m), 1399 (w), 1308 (vs), 1164 (vs), 1078 (m), 1010 (w), 986 (m), 936 (w), 874 (m), 830 (w), 762 (m), 742 (w), 604 cm^{-1} (w); MS (ion trap, EI, 70 eV): m/z (%) = 152 [M^+] (6), 124 (3), 106 (3), 95 (100), 67 (5), 41 (5); **HRMS–EI** (TOF): m/z [M^+] calcd for $C_8H_8O_3$, 152.0473; found, 152.0464.

Synthesis of allyl decanoate (4.1.8–3m)

[CAS: 57856–81–2]



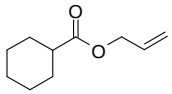
Using method A, compound **4.1.8–3m** was prepared from decanoic acid (**4.1.8–1m**) (1.76 g, 10.0 mmol) yielding **4.1.8–3m** as a colourless oil (1.94 g, 9.14 mmol, 91%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 5.95 (ddt, *J*=16.6 Hz, 10.8 Hz, 5.8 Hz, 1H), 5.29 (d, *J*=17.1 Hz, 1H), 5.21 (d, *J*=10.6 Hz, 1H), 4.55 (d, *J*=5.8 Hz, 2H), 2.31 (t, *J*=7.6 Hz, 2H), 1.66 – 1.56 (m,

2H), 1.32 – 1.21 (m, 12H), 0.85 ppm (t, *J*=6.7 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 173.5, 132.3, 118.0, 64.9, 34.2, 31.8, 29.4, 29.2 (2C), 29.1, 24.9, 22.6, 14.1 ppm; **IR** (NaCl): ν = 2955 (s), 2927 (vs), 2855 (s), 1741 (s), 1649 (w), 1459 (w), 1419 (w), 1377 (w), 1274 (w), 1244 (w), 1166 (m), 1113 (w), 990 (w), 930 (w), 722 cm^{-1} (w); **MS** (ion trap, EI, 70 eV): m/z (%) = 213 [M^+] (89), 171 (46), 155 (100), 153 (95), 113 (45), 95 (70), 81 (77); **HRMS–EI** (TOF): m/z [M^+] calcd for $C_{13}H_{24}O_2$, 212.1776; found, 212.1767.

Synthesis of allyl cyclohexanecarboxylate (4.1.8–3n)

[CAS: 16491–63–7]

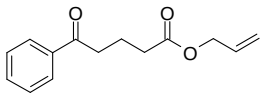


Using method B, compound **4.1.8–3n** was prepared from cyclohexanecarboxylic acid (**4.1.8–1n**) (1.41 g, 11.0 mmol) and allyl alcohol (**4.1.8–2a**) (0.59 g, 10.0 mmol) yielding **4.1.8–3n** as a colourless liquid (1.59 g, 7.42 mmol, 94%).

^{1}H–NMR (600 MHz, $CDCl_3$): δ = 5.90 (dt, *J*=22.6 Hz, 10.6 Hz, 5.6 Hz, 1H), 5.31 (ddt, *J*=16.0 Hz, 10.6 Hz, 5.6 Hz, 1H), 5.20 (dd, *J*=10.5 Hz, 1.3 Hz, 1H), 4.55 (t, *J*=1.4 Hz, 2H), 2.31 (tt, *J*=11.4 Hz, 3.6 Hz, 1H), 1.93 – 1.88 (m, 2H), 1.76 – 1.71 (m, 2H), 1.65 – 1.60 (m, 1H), 1.47 – 1.40 (m, 2H), 1.28 – 1.21 ppm (m, 3H); **^{13}C–NMR** (151 MHz, $CDCl_3$): δ = 175.7, 132.4, 117.8, 64.7, 43.2, 29.0 (3C), 25.7, 25.4 ppm; **IR** (NaCl): ν = 3087 (w), 2933 (s), 2857 (m), 1735 (vs), 1649 (w), 1451 (w), 1377 (w), 1312 (w), 1274 (w), 1246 (m), 1170 (m), 1132 (m), 1040 (w), 984 (w), 930 cm^{-1} (w); MS (ion trap, EI, 70 eV): m/z (%) = 168 [M^+] (4), 111 (10), 83 (100), 81 (43), 67 (10), 55 (75), 41 (17); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{10}H_{16}O_2$, 168.1150; found, 168.1149.

Synthesis of allyl 5–oxo–5–phenylpentanoate (4.1.8–3o)

[CAS: 1384266–60–7]

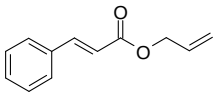


Using method B, compound **4.1.8–3o** was prepared from 5–oxo–5–phenylpentanoic acid (**4.1.8–1o**) (2.11 g, 11.0 mmol) and allyl alcohol (**4.1.8–2a**) (0.59 g, 10.0 mmol) yielding **4.1.8–3o** as a colourless liquid (2.26 g, 9.74 mmol, 97%).

^{1}H–NMR (200 MHz, $CDCl_3$): δ = 8.01 – 7.91 (m, 2H), 7.61 – 7.52 (m, 1H), 7.51 – 7.41 (m, 2H), 5.92 (ddt, *J*=17.2 Hz, 10.4 Hz, 5.7 Hz, 1H), 5.32 (dq, *J*=17.2 Hz, 1.6 Hz, 1H), 5.24 (dq, *J*=10.4 Hz, 1.3 Hz, 1H), 4.60 (dt, *J*=5.7 Hz, 1.4 Hz, 2H), 3.07 (t, *J*=7.2 Hz, 2H), 2.55 – 2.44 (m, 2H), 2.10 ppm (quin, *J*=7.2 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 199.2, 172.8, 136.7, 133.0, 132.1, 128.5 (2C), 127.9 (2C), 118.2, 65.0, 37.3, 33.2, 19.3 ppm; **IR** (NaCl): ν = 3083 (m), 2943 (s), 1735 (vs), 1685 (vs), 1597 (m), 1447 (m), 1375 (m), 1276 (m), 1204 (m), 1180 (m), 1150 (m), 992 (m), 932 (w), 748 cm^{-1} (w); **MS** (ion trap, EI, 70 eV): m/z (%) = 232 [M^+] (1), 175 (7), 147 (13), 120 (12), 105 (100), 77 (40), 51 (12); **CHN** Anal. calcd. for $C_{14}H_{16}O_3$: C, 72.39%; H, 6.94%; found: C, 72.17%; H, 6.96%.

Synthesis of allyl cinnamate (4.1.8–3p)

[CAS: 1866–31–5]



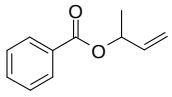
Using method B, compound **4.1.8–3p** was prepared from cinnamic acid (**4.1.8–1p**) (1.63 g, 11.0 mmol) and allyl alcohol (**4.1.8–2a**) (0.59 g, 10.0 mmol) yielding **4.1.8–3p** as a colourless liquid (0.81 g, 4.32 mmol, 43%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J*=16.0 Hz, 1H), 7.52 (d, *J*=6.5 Hz, 2H), 7.41 – 7.35 (m, 3H), 6.46 (d, *J*=16.0 Hz, 1H), 6.04 (ddt, *J*=16.0 Hz, 10.6 Hz, 5.5 Hz, 1H), 5.37 (d, *J*=17.2 Hz, 1H), 5.27 (d, *J*=10.6 Hz, 1H), 4.71 ppm (d, *J*=5.9 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 166.5, 145.0, 134.3, 132.2, 130.3, 128.8 (2C), 128.0 (2C), 118.2, 117.8, 65.1 ppm;

IR (NaCl): ν = 3061 (m), 2942 (m), 2882 (w), 1713 (vs), 1635 (s), 1577 (w), 1495 (w), 1449 (m), 1310 (s), 1280 (m), 1254 (m), 1202 (m), 1168 (s), 990 (m), 934 (w), 864 (w), 768 (m), 712 cm^{-1} (w); **MS** (ion trap, EI, 70 eV): m/z (%) = 188 [M^+] (3), 143 (9), 131 (100), 104 (34), 103 (73), 77 (39), 51 (17); **CHN** Anal. calcd. for $C_{12}H_{12}O_2$: C, 76.57%; H, 6.43%; found: C, 76.37%; H, 6.34%.

Synthesis of but–3–en–2–yl benzoate (4.1.8–3q)

[CAS: 65001–62–9]

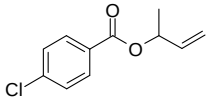


Using method B, compound **4.1.8–3q** was prepared from benzoic acid (**4.1.8–1a**) (1.34 g, 11.0 mmol) and but–3–en–2–ol (**4.1.8–2b**) (0.72 g, 10.0 mmol) yielding **4.1.8–3q** as a colourless liquid (1.33 g, 75.2 mmol, 75%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.10 – 8.03 (m, 2H), 7.61 – 7.52 (m, 1H), 7.48 – 7.39 (m, 2H), 5.98 (ddd, *J*=17.3 Hz, 10.5 Hz, 5.8 Hz, 1H), 5.67 – 5.57 (m, 1H), 5.35 (dt, *J*=17.3 Hz, 1.3 Hz, 1H), 5.20 (dt, *J*=10.5 Hz, 1.3 Hz, 1H), 1.46 ppm (d, *J*=6.6 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 165.8, 137.7, 132.8, 130.6, 129.6 (2 C), 128.3 (2 C), 115.8, 71.5, 20.1 ppm; **IR** (NaCl): ν = 3068 (w), 2981 (m), 2931 (m), 1717 (vs), 1601 (w), 1451 (m), 1314 (m), 1272 (vs), 1176 (w), 1114 (m), 1070 (w), 1048 (w), 1026 (w), 932 (w), 712 cm^{-1} (m); **MS** (ion trap, EI, 70 eV): m/z (%) = 176 [M^+] (1), 147 (3), 123 (11), 105 (100), 104 (3), 77 (8), 55 (8), 51 (5); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{11}H_{12}O_2$, 176.0837; found, 176.0833.

Synthesis of but–3–en–2–yl 4–chlorobenzoate (4.1.8–3r)

[CAS: 1384266–61–8]

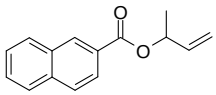


Using method C, compound **4.1.8–3r** was prepared from 4–chlorobenzoyl chloride (**4.1.8–1'q**) (1.75 g, 10.0 mmol) and but–3–en–2–ol (**4.1.8–2b**) (0.90 g, 12.5 mmol) yielding **4.1.8–3r** as a colourless liquid (1.33 g, 6.30 mmol, 63%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.05 – 7.95 (m, 2H), 7.46 – 7.37 (m, 2H), 5.96 (ddd, *J*=17.2 Hz, 10.5 Hz, 5.9 Hz, 1H), 5.65 – 5.54 (m, 1H), 5.34 (dt, *J*=17.3 Hz, 1.2 Hz, 1H), 5.20 (dt, *J*=10.5 Hz, 1.2 Hz, 1H), 1.45 ppm (d, *J*=6.4 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 164.9, 139.3, 137.5, 131.0 (2 C), 129.0, 128.6 (2 C), 116.1, 71.9, 20.0 ppm; **IR** (NaCl): ν = 3090 (w), 2981 (m), 2933 (m), 1719 (vs), 1593 (vs), 1488 (s), 1402 (s), 1334 (s), 1270 (vs), 1172 (s), 1116 (vs), 1104 (vs), 1092 (vs), 1016 (s), 930 (m), 850 (s), 760 cm^{-1} (vs); **MS** (ion trap, EI, 70 eV): m/z (%) = 210 [M^+] (1), 157 (6), 141 (34), 139 (100), 111 (11), 75 (5), 55 (9); **CHN** Anal. calcd. for $C_{11}H_{11}ClO_2$: C, 62.72%; H, 5.26%; found: C, 62.62%; H, 5.34%.

Synthesis of but–3–en–2–yl 2–naphtoate (4.1.8–3s)

[CAS: 1384266–62–9]

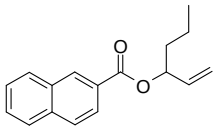


Using method C, compound **4.1.8–3s** was prepared from 2–naphthoyl chloride (**4.1.8–1'l**) (1.91 g, 10.0 mmol) and but–3–en–2–ol (**4.1.8–2b**) (0.90 g, 12.5 mmol) yielding **4.1.8–3s** as a colourless liquid (1.62 g, 7.16 mmol, 72%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.64 (s, 1H), 8.08 (d, *J*=8.6 Hz, 1H), 7.96 (d, *J*=7.8 Hz, 1H), 7.88 (d, *J*=8.6 Hz, 2H), 7.54 – 7.62 (m, 2H), 6.02 (ddd, *J*=17.0, 10.8, 5.9 Hz, 1H), 5.67 (q, *J*=6.7 Hz, 1H), 5.37 (d, *J*=17.2 Hz, 1H), 5.22 (d, *J*=10.2 Hz, 1H), 1.51 ppm (d, *J*=6.3 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 165.9, 137.8, 135.5, 132.5, 131.0, 129.3, 128.2, 128.1, 127.8, 127.7, 126.6, 125.3, 115.9, 71.7, 20.1 ppm; **IR** (NaCl): ν = 3060 (w), 2979 (m), 2931 (m), 1715 (vs), 1466 (m), 1354 (m), 1280 (vs), 1228 (vs), 1196 (vs), 1130 (s), 1092 (s), 956 (s), 916 (m), 778 (s), 762 cm^{-1} (s); **MS** (ion trap, EI, 70 eV): m/z (%) = 226 [M^+] (8), 181 (5), 173 (5), 156 (100), 155 (27), 126 (4), 55 (2); **CHN** Anal. calcd. for $C_{15}H_{14}O_2$: C, 79.62%; H, 6.24%; found: C, 79.62%; H, 6.44%.

Synthesis of hex–1–en–3–yl benzoate (4.1.8–3t)

[CAS: 52513–08–3]

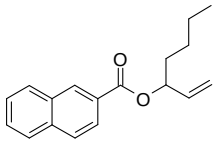


Using method B, compound **4.1.8–3t** was prepared from benzoic acid (**4.1.8–1a**) (1.34 g, 11.0 mmol) and hex–1–en–3–ol (**4.1.8–2c**) (1.00 g, 10.0 mmol) yielding **4.1.8–3t** as a colourless liquid (1.96 g, 9.60 mmol, 96%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J*=7.8 Hz, 2H), 7.54 (t, *J*=7.2 Hz, 1H), 7.43 (t, *J*=7.6 Hz, 2H), 5.89 (ddd, *J*=17.1 Hz, 10.7 Hz, 6.3 Hz, 1H), 5.51 (q, *J*=6.5 Hz, 1H), 5.32 (d, *J*=17.2 Hz, 1H), 5.19 (d, *J*=10.6 Hz, 1H), 1.80 – 1.68 (m, 2H), 1.49 – 1.38 (m, 2H), 0.95 ppm (t, *J*=7.4 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 165.8, 136.6, 132.8, 130.6, 129.5 (2 C), 128.3 (2 C), 116.5, 75.1, 36.4, 18.4, 13.9 ppm; **IR** (NaCl): ν = 3069 (w), 2959 (s), 2935 (s), 2873 (m), 1719 (vs), 1647 (w), 1601 (w), 1451 (m), 1314 (m), 1272 (vs), 1176 (w), 1110 (m), 1070 (m), 1026 (w), 932 (w), 712 cm^{-1} (m); **MS** (ion trap, EI, 70 eV): m/z (%) = 204 [M^+] (1), 105 (100), 83 (17), 77 (16), 67 (7), 55 (5), 51 (7); **CHN** Anal. calcd. for $C_{13}H_{16}O_2$: C, 76.44%; H, 7.90%; found: C, 76.29%; H, 7.76%.

Synthesis of hept–1–en–3–yl benzoate (4.1.8–3u)

[CAS: 1384266–63–0]



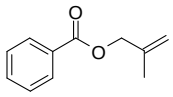
Using method C, compound **4.1.8–3u** was prepared from benzoyl chloride (**4.1.8–1'a**) (1.41 g, 10.0 mmol) and hept–1–en–3–ol (**4.1.8–2d**) (1.43 g, 12.5 mmol) yielding **4.1.8–3u** as a colourless liquid (1.70 g, 7.75 mmol, 78%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J*=7.0 Hz, 2H), 7.56 (t, *J*=7.4 Hz, 1H), 7.45 (t, *J*=7.6 Hz, 2H), 5.92 (ddd, *J*=17.0, 10.4, 6.3 Hz, 1H), 5.52 (q, *J*=6.3 Hz, 1H), 5.34 (d, *J*=17.2 Hz, 1H), 5.22 (d, *J*=10.6 Hz, 1H), 1.68 – 1.89 (m, 2H), 1.31 – 1.48 (m, 4H), 0.93 ppm (t, *J*=6.8 Hz,

3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 165.7, 136.6, 132.7, 130.5, 129.5 (2 C), 128.2 (2 C), 116.4, 75.2, 34.0, 27.2, 22.4, 13.9 ppm; **IR** (NaCl): ν = 3087 (w), 3069 (w), 2955 (s), 2933 (s), 2861 (m), 1719 (vs), 1452 (s), 1314 (s), 1270 (vs), 1112 (vs), 1070 (s), 968 (s), 934 (s), 712 (vs), 688 cm^{-1} (s); **MS** (ion trap, EI, 70 eV): m/z (%) = 218 [M^+] (1), 175 (1), 105 (100), 97 (33), 96 (6), 77 (6), 55 (4), 41 (1); **CHN** Anal. calcd. for $C_{14}H_{18}O_2$: C, 77.03%; H, 8.31%; found: C, 77.35%; H, 8.50%.

Synthesis of 2–methylallyl benzoate (4.1.8–3v)

[CAS: 829–53–8]

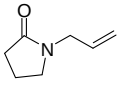


Using method B, compound **4.1.8–3v** was prepared from benzoic acid (**4.1.8–1a**) (1.34 g, 11.0 mmol) and 2–methylprop–2–en–1–ol (**4.1.8–2e**) (0.74 g, 10.0 mmol) yielding **4.1.8–3v** as a colourless liquid (1.65 g, 9.35 mmol, 94%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J= 7.2 Hz, 2H), 7.58 (t, J=7.4 Hz, 1H), 7.46 (t, J=7.6 Hz, 2H), 5.09 (s, 1H), 5.00 (s, 1H), 4.76 (s, 2H), 1.85 ppm (s, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 166.2, 140.0, 132.9, 130.2, 129.6 (2 C), 128.4 (2 C), 112.9, 68.1, 19.6 ppm; **MS** (ion trap, EI, 70 eV): m/z (%) = 177 [M^+] (1) 161 (1), 105 (100), 77 (26), 55 (3), 51 (12), 41 (1); **IR** (NaCl): ν = 3318 (w), 2975 (w), 2943 (w), 2879 (w), 1723 (vs), 1601 (w), 1451 (m), 1316 (m), 1270 (vs), 1176 (w), 1114 (s), 1070 (m), 1028 (m), 906 (w), 710 cm^{-1} (s); The analytical data matched those reported in the literature for 2–methylallyl benzoate (**4.1.8–3v**).[294,295]

Synthesis of 1–allylpyrrolidin–2–one (4.1.8–7)

[CAS: 2687–97–0]



Allyl bromide (1.81 g, 15.0 mmol, 1.39 mL) was added dropwise to a stirred suspension of 2–pyrrolidinone (0.85 g, 10.0 mmol, 0.77 mL) and KOH powder (0.99 g, 15.0 mmol) in DMF (9 mL). The mixture was stirred at 45 °C for additional 72 h, diluted with water (40 mL) and

extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water (40 mL), a saturated solution of sodium bicarbonate (20 mL), dried over $MgSO_4$ and the volatile compounds were removed *in vacuo* (100 mbar, 40 °C) to afford a slightly yellow crude product, that was further purified by column chromatography (SiO_2, hexane/ ethyl acetate) to yield **4.1.8–7** as a colourless oil (0.62 g, 4.95 mmol, 50%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 5.72 (ddt, *J*=17.4 Hz, 9.9 Hz, 6.1 Hz, 1H), 5.22 – 5.12 (m, 2H), 3.88 (d, *J*=5.9 Hz, 2H), 3.34 (t, *J*=7.0 Hz, 2H), 2.40 (t, *J*=8.2 Hz, 2H), 2.01 ppm (qu, *J*= 7.6 Hz, 2H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 174.6, 132.4, 117.7, 46.7, 45.1, 30.9, 17.7 ppm; **IR** (NaCl): ν = 3520 (w), 2979 (m), 2949 (m), 2915 (m), 2895 (m), 1681 (vs), 1495 (m), 1463 (m), 1441 (s), 1417 (s), 1268 (s), 1202 (w), 994 (w), 926 (m), 764 (w), 692 cm^{-1} (w); **MS** (ion trap, EI, 70 eV): m/z (%) = 125 [M^+] (91), 110 (40), 82 (42), 70 (100), 69 (28), 68 (42), 41 (48); **HRMS–EI** (TOF) (*m/z*): [M^+] calcd. for $C_7H_{11}NO$, 168.1150; found, 168.1149.

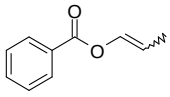
6.8.3. Synthesis of the enol esters

General procedure for the synthesis of enol esters

Toluene (1.50 mL), the allylic ester **4.1.8–3** (1.00 mmol) and the stock solution of di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (**4.1.8–17**) (0.5 mL, 2.50 μmol) were added via syringe to a 20 mL vessel. When not otherwise stated, the resulting mixture was stirred at 50 °C for 16 h. Once the reaction time was completed, the crude mixture was diluted with H_2O (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the volatiles were removed *in vacuo* (50 mbar, 40 °C) to afford the corresponding enol ester **4.1.8–4**, which was further purified by column chromatography (SiO_2, *n*–pentane/diethyl ether).

Synthesis of prop–1–enyl benzoate (4.1.8–4a)

[CAS: (*E*)–Isomer = 1309584–66–4; (*Z*)–Isomer = 555154–63–7]

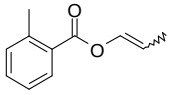


Compound **4.1.8–4a** was prepared from allyl benzoate (**4.1.8–3a**) (162 mg, 1.00 mmol) yielding (*E*)– and (*Z*)–prop–1–enyl benzoate (**4.1.8–4a**) as colourless liquid (146 mg, 90% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z/E* 2:1): δ = 8.12 – 8.00 (m, 2 H^Z + 2 H^E), 7.59 – 7.51 (m, 1 H^Z + 1 H^E), 7.48 – 7.37 (m, 2 H^Z + 2 H^E), 7.26 – 7.18 (m, 1 H^Z + 1 H^E), 5.60 – 5.52 (m, 1 H^E), 5.05 – 4.98 (m, 1 H^Z), 1.76 (dd, *J*=6.8 Hz, 1.8 Hz, 3 H^Z), 1.67 ppm (dd, *J*=7.0 Hz, 1.6 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 163.6, 135.0, 133.4, 129.9 (2C), 129.4, 128.5 (2C), 109.2, 10.0 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 163.8, 136.1, 133.3, 129.8 (2C), 129.3, 128.4 (2C), 110.4, 12.4 ppm; **IR** (NaCl): ν = 2921 (m), 1731 (vs), 1674 (w), 1601 (w), 1452 (m), 1389 (w), 1266 (vs), 1118 (s), 1070 (w), 1026 (w), 928 (w), 706 cm^{-1} (m); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 162 [M^+] (1), 106 (8), 105 (100), 77 (15), 51 (7), 41 (1); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 162 [M^+] (1), 106 (8), 105 (100), 77 (28), 51 (11), 41 (1); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{10}H_{10}O_2$, 162.0681; found, 162.0686. **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{10}H_{10}O_2$, 162.0681; found, 162.0682.

Synthesis of prop–1–enyl 2–methylbenzoate (4.1.8–4b)

[CAS: (*E*)–Isomer = 1384266–23–2; (*Z*)–Isomer = 1384266–24–3]

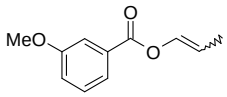


Compound **4.1.8–4b** was prepared from allyl 2–methylbenzoate (**4.1.8–3b**) (176 mg, 1.00 mmol) yielding (*E*)– and (*Z*)–1–enyl 2–methylbenzoate (**4.1.8–4b**) as colourless liquid (173 mg, 98% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 2:1): δ = 9.97 – 7.91 (m, 1 H^Z), 7.88 (dd, *J*=8.0 Hz, 1.4 Hz, 1 H^E), 7.37 – 7.29 (m, 1 H^Z + 1 H^E), 7.23 – 7.12 (m, 3 H^Z + 3 H^E), 5.48 (dq, *J*=13.3 Hz, 7.4 Hz, 1 H^E), 4.95 (dq, *J*=6.7 Hz, 1 H^Z), 2.56 (s, 3 H^Z), 2.53 (s, 3 H^E), 1.69 (dd, *J*=7.0 Hz, 2.0 Hz, 3 H^Z), 1.62 ppm (dd, *J*=7.0 Hz, 1.6 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 163.9, 140.6, 134.7, 132.1, 131.5, 130.6, 128.2, 125.5, 108.5, 21.6, 9.8 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 164.2, 140.5, 135.8, 132.0, 131.4, 130.4, 128.2, 125.4, 109.8, 21.4, 12.1 ppm; **IR** (NaCl): ν = 3067 (w), 3029 (w), 2969 (m), 2925 (m), 2861 (w), 1730 (vs), 1674 (m), 1601 (w), 1457 (m), 1384 (w), 1289 (m), 1243 (vs), 1141 (m), 1081 (s), 929 (m), 732 (s), 693 (w), 667 cm^{-1} (w); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 175 (1), 120 (9), 119 (100), 91 (41), 77 (1), 65 (14), 50 (2), 41 (1); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 175 (1), 120 (10), 119 (100), 91 (34), 77 (1), 65 (13), 41 (1); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{11}H_{12}O_2$, 176.0837; found, 176.0833; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{11}H_{12}O_2$, 176.0837; found, 176.0856.

Synthesis of prop–1–enyl 3–methoxybenzoate (4.1.8–4c)

[CAS: (*E*)–Isomer = 1384266–25–4; (*Z*)–Isomer = 1384266–26–5]



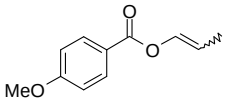
Compound **4.1.8–4c** was prepared from allyl 3–methoxybenzoate (**4.1.8–3c**) (192 mg, 1.00 mmol) yielding (*E*)– and (*Z*)–prop–1–enyl 3–methoxybenzoate (**4.1.8–3c**) as colourless liquid (172 mg, 90% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 2:1): δ = 7.65 – 7.56 (m, 1 H^Z + 1 H^E), 7.53 (dd, *J*=2.4 Hz, 1.4 Hz, 1 H^Z), 7.50 (dd, *J*=2.5 Hz, 1.5 Hz, 1 H^E), 7.32 – 7.24 (m, 1 H^E + 1 H^Z), 7.19 – 7.14 (m, 1 H^Z + 1 H^E), 7.07 – 7.00 (m, 1 H^Z + 1 H^E), 5.52 (dq, *J*=13.6 Hz, 7.3 Hz, 1 H^E), 4.97 (dq, *J*=6.7 Hz, 1 H^Z), 3.80 – 3.72 (m, 3 H^Z + 3 H^E), 1.71 (dd, *J*=6.8 Hz, 1.8 Hz, 3 H^Z), 1.62 ppm (dd, *J*=7.1 Hz, 1.5 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 163.4, 159.6, 135.0, 130.7, 129.48, 122.2, 119.7, 114.4, 109.2, 55.4, 10.0 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 163.7, 159.6, 136.1, 130.5, 129.4, 122.2, 119.9, 114.2, 110.4, 55.4, 12.4 ppm; **IR** (NaCl): ν = 3080 (w), 2943 (s), 2921 (m), 1731 (vs), 1675 (m), 1601 (m), 1585 (m), 1487 (s), 1453 (m),

1431 (m), 1276 (vs), 1224 (s), 1182 (m), 1116 (s), 1046 (m), 994 (w), 929 (w), 908 (w), 876 (w), 802 (w), 750 (m), 736 (w), 682 cm^{-1} (w); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 192 [M^+] (1), 135 (100), 107 (20), 92 (8), 77 (13), 63 (7), 51 (2); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 192 [M^+] (1), 135 (100), 107 (22), 92 (9), 77 (16), 63 (7), 51 (2); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{11}H_{12}O_3$, 192.0786; found, 192.0785; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{11}H_{12}O_3$, 192.0786; found:192.0791.

Synthesis of prop–1–enyl 4–methoxybenzoate (4.1.8–4d)

[CAS: (*E*)–Isomer = 1384266–27–6; (*Z*)–Isomer = 1384266–28–7]

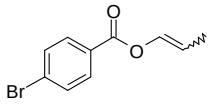


Compound **4.1.8–4d** was prepared from allyl 4–methoxybenzoate (**4.1.8–3d**) (192 mg, 1.00 mmol) yielding (*E*)– and (*Z*)–prop–1–enyl 4–methoxybenzoate (**4.1.8–4d**) as colourless liquid (175 mg, 91% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 2:1): δ = 8.11 – 8.02 (m, 2 H^Z + 2 H^E), 7.32 – 7.23 (m, 1 H^Z + 1 H^E), 6.98 – 6.92 (m, 2 H^Z + 2 H^E), 5.58 (dd, *J*=12.3 Hz, 7.0 Hz, 1 H^E), 5.08 – 4.99 (m, 1 H^Z), 3.88 (s, 3 H^Z), 3.87 (s, 3 H^E), 1.82 – 1.78 (m, 3 H^Z), 1.71 ppm (dd, *J*=7.0 Hz, 1.8 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 163.7, 163.2, 135.0, 131.9 (2C), 121.7, 113.7 (2C), 108.6, 55.3, 9.9 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 163.6, 163.5, 136.2, 131.9 (2C), 121.5, 113.7 (2C), 109.7, 55.3, 12.3 ppm; **IR** (NaCl): ν = 2937 (m), 1717 (vs), 1605 (s), 1510 (s), 1461 (w), 1442 (w), 1316 (m), 1256 (vs), 1165 (vs), 1098 (vs), 1026 (s), 928 (m), 844 (s), 764 cm^{-1} (m); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 192 [M^+] (1), 135 (100), 107 (10), 92 (8), 77 (14), 63 (6), 50 (3); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 192 [M^+] (1), 135 (100), 107 (11), 92 (9), 77 (18), 63 (6), 50 (3); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{11}H_{12}O_3$, 192.0786; found, 192.0782; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{11}H_{12}O_3$, 192.0786; found:192.0790.

Synthesis of prop–1–enyl 4–bromobenzoate (4.1.8–4e)

[CAS: (*E*)–Isomer = 1384266–29–8; (*Z*)–Isomer = 1384266–30–1]

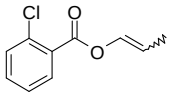


Compound **4.1.8–4e** was prepared from allyl 4–bromobenzoate (**4.1.8–3e**) (241 mg, 1.00 mmol) yielding (*E*)– and (*Z*)–prop–1–enyl 4–bromobenzoate (**4.1.8–4e**) as colourless liquid (175 mg, 73% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 2:1): δ = 8.01 – 7.88 (m, 2 H^Z + 2 H^E), 7.65 – 7.53 (m, 2 H^Z + 2 H^E), 7.26 – 7.19 (m, 1 H^Z + 1 H^E), 5.60 (dq, *J*=14.1 Hz, 7.6 Hz, 1 H^E), 5.07 (dq, *J*=6.7 Hz, 1 H^Z), 1.78 (dd, *J*=6.9 Hz, 1.6 Hz, 3 H^Z), 1.70 ppm (dd, *J*=7.1 Hz, 1.5 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 162.8, 134.9, 131.9 (2C), 131.3 (2C), 128.6, 128.3, 109.6, 10.1 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 163.1, 136.0, 131.8 (2C), 131.3 (2C), 128.5, 128.2, 110.8, 12.4 ppm; **IR** (NaCl): ν = 3080 (w), 2920 (m), 2860 (w), 1731 (vs), 1674 (m), 1591 (s), 1482 (m), 1397 (m), 1266 (vs), 1173 (m), 1118 (s), 1103 (m), 1012 (m), 928 (w), 845 (w), 751 (m), 737 (w), 680 cm^{-1} (w); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 243 [M^+] (1), 241 [M^+] (1), 185 (100), 183 (91), 157 (7), 155 (7), 76 (8) 50 (7); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 243 [M^+] (1), 241 [M^+] (1), 185 (100), 183 (94), 157 (20), 155 (20), 76 (13) 50 (14); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{10}H_9BrO_2$, 239.9786; found, 239.9765; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{10}H_9BrO_2$, 239.9786; found, 239.9785.

Synthesis of prop–1–enyl 2–chlorobenzoate (4.1.8–4f)

[CAS: (*E*)–Isomer = 1384266–31–2; (*Z*)–Isomer = 1384266–32–]



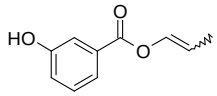
Compound **4.1.8–4f** was prepared from allyl 2–chlorobenzoate (**4.1.8–3f**) (197 mg, 1.00 mmol), and the stock solution of di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I)

(1.00 mL, 5.00 µmol) in toluene (1 mL), yielding (*E*)– and (*Z*)–prop–1–enyl 2–chlorobenzoate (**4.1.8–4f**) as colourless liquid (178 mg, 91% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 2:1): δ = 8.00 – 7.94 (m, 1 H^Z), 7.93 – 7.87 (m, 1 H^E), 7.54 – 7.42 (m, 2 H^Z + 2 H^E), 7.40 – 7.25 (m, 2 H^Z + 2 H^E), 5.62 (dq, *J*=12.3 Hz, 7.0 Hz, 1 H^E), 5.15 – 5.06 (m, 1 H^Z), 1.79 (dd, *J*=6.8 Hz, 1.8 Hz, 3 H^Z), 1.72 ppm (dd, *J*=7.0 Hz, 1.8 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 162.4, 134.9, 134.3, 133.0, 131.9, 131.3, 129.0, 126.6, 109.8, 10.1 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 162.6, 136.0, 134.2, 132.9, 131.6, 131.2, 129.0, 126.5, 111.0, 12.3 ppm; **IR** (NaCl): ν = 3079 (m), 2922 (m), 2862 (w), 1742 (vs), 1675 (m), 1592 (m), 1437 (m), 1388 (w), 1286 (m), 1247 (vs), 1123 (s), 1052 (m), 928 (m), 745 (s), 651 cm^{-1} (w); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 197 [M^+] (1), 141 (34), 139 (100), 113 (8), 111 (25), 75 (12), 50 (7); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 197 [M^+] (1), 141 (34), 139 (100), 113 (8), 111 (27), 75 (13), 50 (7); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{10}H_9ClO_2$, 196.0291; found, 196.0284; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{10}H_9ClO_2$, 196.0291; found, 196.0309.

Synthesis of prop–1–enyl 3–hydroxybenzoate (4.1.8–4g)

[CAS: (*E*)–Isomer = 1384266–33–4; (*Z*)–Isomer = 1384266–34–5]



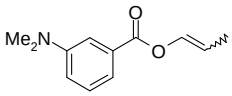
Compound **4.1.8–4g** was prepared from allyl 3–hydroxybenzoate (**4.1.8–4g**) (184 mg, 1.00 mmol) and di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (19.4 mg, 25.0 µmol) in toluene (2 mL), yielding (*E*)– and (*Z*)–prop–1–enyl 3–hydroxybenzoate (**4.1.8–2g**) as colourless liquid (175 mg, 98% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 2:1): δ = 7.73 – 7.62 (m, 2 H^Z + 2 H^E), 7.35 (q, *J*=7.7 Hz, 1 H^Z + 1 H^E), 7.29 – 7.22 (m, 1 H^Z + 1 H^E), 7.15 – 7.09 (m, 1 H^Z + 1 H^E), 6.29 (br. s, 1 H^Z + 1 H^E), 5.61 (dq, *J*=12.5 Hz, 7.0 Hz, 1 H^E), 5.14 – 5.04 (m, 1 H^Z), 1.79 (dd, *J*=6.9 Hz, 1.9 Hz, 3 H^Z), 1.71 ppm (dd, *J*=7.0 Hz, 1.8 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 164.1, 156.0, 134.8, 130.4, 129.8, 122.1, 121.0, 116.6, 109.9, 10.0 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 164.4, 156.0, 135.9, 130.3, 129.8, 122.1, 120.9, 116.6, 111.1, 12.3 ppm; **IR**

(NaCl): ν = 3389 (m), 2976 (m), 2921 (w), 1731 (vs), 1710 (vs), 1601 (s), 1590 (s), 1453 (s), 1290 (vs), 1236 (vs), 1218 (vs), 1116 (s), 999 (m), 927 (m), 751 (s), 733 cm^{-1} (m); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 178 [M^+] (1), 122 (8), 121 (100), 93 (31), 65 (22), 53 (2), 40 (2); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 178 [M^+] (1), 122 (8), 121 (100), 93 (32), 65 (20), 53 (2), 40 (1); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{10}H_{10}O_3$, 178.0630; found, 178.0627; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{10}H_{10}O_3$, 178.0630; found, 178.0624.

Synthesis of prop–1–enyl 3–(dimethylamino)benzoate (4.1.8–4h)

[CAS: (*E*)–Isomer = 1384266–35–6; (*Z*)–Isomer = 1384266–36–7]

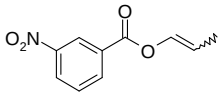


Compound **4.1.8–4h** was prepared from allyl 3–(dimethylamino)benzoate (**4.1.8–3h**) (205 mg, 1.00 mmol) and di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (19.4 mg, 25.0 µmol) in toluene (2 mL) yielding (*E*)– and (*Z*)–prop–1–enyl 3–(dimethylamino)benzoate (**4.1.8–4h**) as pale yellow liquid (187 mg, 91% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 2:1): δ = 7.49 – 7.39 (m, 2 H^Z + 2 H^E), 7.34 – 7.23 (m, 2 H^Z + 2 H^E), 6.97 – 6.88 (m, 1 H^Z + 1 H^E), 5.59 (dq, *J*=13.8 Hz, 6.8 Hz, 1 H^E), 5.04 (dq, *J*=6.7 Hz, 1 H^Z), 3.00 – 2.98 (m, 6 H^Z + 6 H^E), 1.79 (dd, *J*=6.9 Hz, 1.6 Hz, 3 H^Z), 1.71 ppm (dd, *J*=6.9 Hz, 1.6 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 164.2, 150.4, 135.1, 130.0, 129.1, 117.7, 117.2, 113.4, 108.9, 40.5 (2C), 10.0 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 164.5, 150.5, 136.3, 129.9, 129.0, 117.7, 117.2, 113.3, 110.1, 40.5 (2C), 12.4 ppm; **IR** (NaCl): ν = 3077 (w), 2919 (m), 2884 (w), 2807 (w), 1727 (vs), 1603 (s), 1498 (m), 1437 (m), 1359 (s), 1252 (vs), 1118 (s), 1008 (m), 994 (m), 930 (m), 862 (w), 748 cm^{-1} (s); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 205 [M^+] (25), 149 (11), 148 (100), 120 (36), 104 (9), 77 (8), 42 (13); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 205 [M^+] (24), 149 (10), 148 (100), 120 (40), 104 (11), 77 (11), 42 (14); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{12}H_{15}NO_2$, 205.1103; found, 205.1102; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{12}H_{15}NO_2$, 205.1103; found, 205.1101.

Synthesis of prop–1–enyl 3–nitrobenzoate (4.1.8–4i)

[CAS: (*E*)–Isomer = 1384266–37–8; (*Z*)–Isomer = 1384266–38–9]

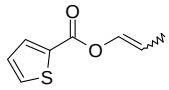


Compound **4.1.8–4i** was prepared from allyl 3–nitrobenzoate (**4.1.8–3i**) (207 mg, 1.00 mmol) and di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (19.4 mg, 25.0 µmol) in toluene (2 mL) yielding (*E*)– and (*Z*)–prop–1–enyl 3–nitrobenzoate (**4.1.8–4i**) as colourless solid (181 mg, 87% yield, *E*/*Z* 1:1).

m.p.: 36–37 °C. **^{1}H–NMR** (400 MHz, $CDCl_3$, *Z/E* 1:1): δ = 8.92 (dt, *J*=8.8 Hz, 1.8 Hz, 1 H^Z + 1 H^E), 8.52 – 8.36 (m, 2 H^Z + 2 H^E), 7.75 – 7.65 (m, 1 H^Z + 1 H^E), 7.34 – 7.23 (m, 1 H^Z + 1 H^E), 5.70 (dq, *J*=12.3 Hz, 7.0 Hz, 1 H^E), 1.84 (dd, *J*=6.9 Hz, 1.9 Hz, 1 H^Z), 1.84 (dd, *J*=6.9 Hz, 1.9 Hz, 3 H^Z), 1.74 ppm (dd, *J*=7.0 Hz, 1.8 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 161.5, 148.3, 135.5, 134.7, 131.2, 129.7, 127.8, 124.8, 110.4, 10.1 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 161.7, 148.3, 135.8, 135.4, 131.1, 129.8, 127.7, 124.8, 111.7, 12.4 ppm; **IR** (KBr): ν = 3087 (w), 2927 (w), 2865 (w), 2164 (w), 1732 (s), 1677 (w), 1616 (w), 1531 (s), 1439 (w), 1387 (w), 1346 (s), 1302 (m), 1283 (s), 1258 (vs), 1236 (s), 1140 (vs), 1118 (s), 1096 (m), 1049 (m), 987 (m), 919 (s), 843 (w), 835 (w), 816 (w), 768 (w), 710 cm^{-1} (vs); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 207 [M^+] (1), 151 (9), 150 (100), 104 (31), 92 (5), 76 (23), 50 (13); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 207 [M^+] (1), 151 (9), 150 (100), 104 (32), 92 (6), 76 (25), 50 (13); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{10}H_9NO_4$, 207.0532; found, 207.0509; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{10}H_9NO_4$, 207.0532; found, 207.0542.

Synthesis of prop–1–enyl thiophene–2–carboxylate (4.1.8–4j)

[CAS: (*E*)–Isomer = 1384266–39–0; (*Z*)–Isomer = 1384266–40–3]

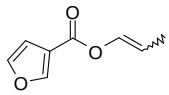


Compound **4.1.8–4j** was prepared from allyl thiophene–2–carboxylate (**4.1.8–3j**) (168 mg, 1.00 mmol) and di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (19.4 mg, 25.0 µmol) in toluene (2 mL) yielding (*E*)– and (*Z*)–prop–1–enyl thiophene–2–carboxylate (**4.1.8–4j**) as colourless liquid (94.0 mg, 56% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 2:1): δ = 7.90 (dd, *J*=3.9 Hz, 1.2 Hz, 1 H^Z + 1 H^E), 7.64 – 7.59 (m, 1 H^Z + 1 H^E), 7.26 – 7.09 (m, 2 H^Z + 2 H^E), 5.59 (dq, *J*=14.1 Hz, 7.0 Hz, 1 H^E), 5.05 (dq, *J*=6.7 Hz, 1 H^Z), 1.78 (dd, *J*=6.8 Hz, 1.8 Hz, 3 H^Z), 1.71 ppm (dd, *J*=7.0 Hz, 1.6 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 159.2, 134.7, 134.1, 133.2, 132.8, 127.9, 109.3, 10.0 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 159.4, 135.8, 134.1, 133.1, 132.7, 127.9, 110.5, 12.4 ppm; **IR** (NaCl): ν = 3103 (w), 2922 (w), 2862 (w), 1723 (vs), 1523 (m), 1417 (s), 1361 (m), 1270 (vs), 1256 (vs), 1116 (s), 1098 (s), 928 (w), 862 (w), 730 cm^{-1} (m); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 168 [M^+] (1), 111 (100), 83 (5), 57 (3), 45 (3); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 168 [M^+] (1), 111 (100), 83 (5), 57 (3), 45 (3); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_8H_8O_2S$, 168.0245; found,168.0235; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_8H_8O_2S$, 168.0245; found,168.0232.

Synthesis of prop–1–enyl furan–3–carboxylate (4.1.8–4k)

[CAS: (*E*)–Isomer = 1384266–41–4; (*Z*)–Isomer = 1384266–42–5]

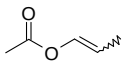


Compound **4.1.8–4k** was prepared from allyl furan–3–carboxylate (**4.1.8–3k**) (152 mg, 1.00 mmol) yielding (*E*)– and (*Z*)–prop–1–enyl furan–3–carboxylate (**4.1.8–4k**) as colourless liquid (115 mg, 76% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 2:1): δ = 8.12 (s, 1 H^Z), 8.09 (s, 1 H^E), 7.47 (t, *J*=1.8 Hz, 1 H^Z), 7.45 (t, *J*=1.6 Hz, 1 H^E), 7.23 – 7.17 (m, 1 H^Z + 1 H^E), 6.83 – 6.78 (m, 1 H^Z + 1 H^E), 5.54 (dq, *J*=14.1 Hz, 1 H^E), 5.03 (dq, *J*=6.7 Hz, 1 H^Z), 1.75 (dd, *J*=6.7 Hz, 1.8 Hz, 3 H^Z), 1.70 ppm (dd, *J*=7.0 Hz, 1.8 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 160.0, 148.3, 144.0, 135.6, 134.5, 118.7, 109.8, 9.9 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 160.3, 148.3, 143.9, 135.6, 134.5, 118.6, 110.2, 12.4 ppm; **IR** (NaCl): ν = 2957 (w), 2923 (m), 2858 (w), 1735 (s), 1575 (m), 1507 (m), 1304 (s), 1266 (s), 1162 (vs), 1080 (m), 1012 (w), 930 (m), 828 (m), 804 (m), 758 (m), 736 (m), 710 (m), 604 cm^{-1} (w); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 152 [M^+] (4), 124 (1), 95 (100), 67 (6), 53 (1), 41 (1); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 152 [M^+] (4), 124 (1), 95 (100), 67 (6), 53 (1), 41 (1); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_8H_8O_3$, 152.0473; found 152.0460; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_8H_8O_3$, 152.0473; found 152.0463.

Synthesis of prop–1–enyl acetate (4.1.8–4l)

[CAS: (*E*)–Isomer = 1528–10–5; (*Z*)–Isomer = 3102–47–4]

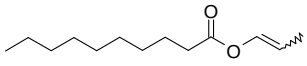


Allyl acetate (**4.1.8–3l**) (101 mg, 1.00 mmol) and di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (3.9 mg, 0.50 µmol) were stirred in toluene–d_8 (2 mL) for 16 h at 50 °C yielding prop–1–enyl acetate (**4.1.8–4l**) as a mixture (97% yield, *E*/*Z* 1:2). The yield and selectivity were determined via NMR with anisole (52.1 mg, 0.48 mmol) as internal standard.

^{1}H–NMR (400 MHz, toluene–d_8, *Z*/*E* 2:1): δ = 6.74 (d, *J*=7.8 Hz, 1 H^Z + 1 H^E), 5.24 (dq, *J*=14.0, 7.0 Hz, 1 H^E), 4.61 (dq, *J*=6.8 Hz, 1 H^Z), 1.58 – 1.70 (m, 3 H^Z + 3 H^E), 1.52 (dd, *J*=6.8, 1.8 Hz, 3 H^Z), 1.33 ppm (dd, *J*=7.0, 1.8 Hz, 3 H^E). The analytical data matched those reported in the literature for prop–1–enyl acetate (**4.1.8–4l**).[296]

Synthesis of prop–1–enyl decanoate (4.1.8–4m)

[CAS: (*E*)–Isomer = 1384266–43–6; (*Z*)–Isomer = 1384266–44–7]

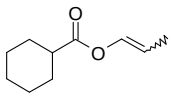


Compound **4.1.8–4m** was prepared from allyl decanoate (**4.1.8–3m**) (212 mg, 1.00 mmol) yielding (*E*)– and (*Z*)–prop–1–enyl decanoate (**4.1.8–4m**) as colourless liquid (189 mg, 89% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z/E* 2:1): δ = 7.11 – 6.98 (m, 1 H^Z + 1 H^E), 5.41 (dq, *J*=12.3 Hz, 6.8 Hz, 1 H^E), 4.92 (dq, *J*=6.8 Hz, 1 H^Z), 2.41 (t, *J*=7.6 Hz, 2 H^Z), 2.35 (t, *J*=7.4 Hz, 2 H^E), 1.73 – 1.58 (m, 5 H^Z + 5 H^E), 1.40 – 1.20 (m, 12 H^Z + 12 H^E), 0.88 ppm (t, *J*=6.7 Hz, 3 H^Z + 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 171.0, 134.9, 108.4, 34.1, 31.9, 29.4, 29.2 (2C), 29.1, 24.8, 22.7, 14.1, 9.8 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 171.1, 136.0, 109.6, 34.0, 31.9, 29.4, 29.2 (2C), 29.1, 24.7, 22.7, 14.1, 12.3 ppm; **IR** (NaCl): ν = 2925 (s), 2855 (m), 1754 (vs), 1675 (w), 1458 (w), 1237 (w), 1154 (s), 1123 (m), 1026 (w), 930 (w), 738 cm^{-1} (w); MS (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 212 [M^+] (2), 155 (100), 95 (94), 81 (81), 71 (45), 57 (46), 43 (65); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 212 [M^+] (1), 155 (100), 95 (95), 81 (82), 71 (43), 57 (44), 43 (62); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{13}H_{24}O_2$, 212.1776; found, 212.1759; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{13}H_{24}O_2$, 212.1776; found, 212.1773.

Synthesis of prop–1–enyl cyclohexanecarboxylate (4.1.8–4n)

[CAS: (*E*)–Isomer = 1384266–45–8; (*Z*)–Isomer = 1384266–46–9]



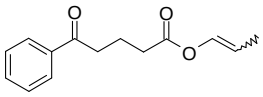
Compound **4.1.8–4n** was prepared from allyl cyclohexanecarboxylate (**4.1.8–3n**) (168 mg, 1.00 mmol) yielding (*E*)– and (*Z*)–prop–1–enyl cyclohexane–carboxylate (**4.1.8–4n**) as colourless liquid (135 mg, 80% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z/E* 2:1): δ = 7.09 – 7.04 (m, 1 H^E), 7.04 – 6.99 (m, 1 H^Z), 5.41 (dq, *J*=13.7 Hz, 7.0 Hz, 1 H^E), 4.92 (dq, *J*=6.7 Hz, 1 H^Z), 2.46 – 2.29 (m, 1 H^Z + 1 H^E), 2.01 –

1.89 (m, 2 H^Z + 2 H^E), 1.83 – 1.72 (m, 2 H^Z + 2 H^E), 1.70 – 1.61 (m, 4 H^Z + 4 H^E), 1.56 – 1.40 (m, 2 H^Z + 2 H^E), 1.35 – 1.22 ppm (m, 3 H^Z + 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 173.1, 135.0, 108.4, 43.0, 28.9 (2C), 25.7, 25.4 (2C), 9.8 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 173.3, 136.1, 109.4, 42.9, 28.8 (2C), 25.7, 25.3 (2C), 12.3 ppm; **IR** (NaCl): ν = 2935 (vs), 2857 (s), 1747 (vs), 1673 (m), 1451 (m), 1375 (w), 1314 (m), 1244 (s), 1162 (vs), 1134 (s), 1042 (m), 930 (w), 734 cm^{-1} (w); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 168 [M^+] (1), 111 (18), 110 (9), 83 (100), 67 (7), 55 (62), 41 (7); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 168 [M^+] (1), 111 (9), 110 (13), 83 (100), 67 (9), 55 (64), 41 (7); **HRMS–EI** (TOF) (m/z): [M^+, (*Z*)–isomer] calcd. for $C_{10}H_{16}O_2$, 168.1150; found 168.1152; **HRMS–EI** (TOF) (m/z): [M^+, (*E*)–isomer] calcd. for $C_{10}H_{16}O_2$, 168.1150; found 168.1158.

Synthesis of prop–1–enyl 5–oxo–5–phenylpentanoate (4.1.8–4o)

[CAS: (*E*)–Isomer = 1384266–47–0; (*Z*)–Isomer = 1384266–48–1]



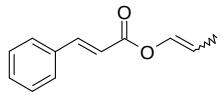
Compound **4.1.8–4o** was prepared from allyl 5–oxo–5–phenylpentanoate (**4.1.8–3o**) (232 mg, 1.00 mmol) yielding (*E*)– and (*Z*)–prop–1–enyl 5–oxo–5–phenylpentanoate (**4.1.8–4o**) as colourless solid (204 mg, 88% yield, *E/Z* 1:2).

m.p.: 33–34 °C. **^{1}H–NMR** (400 MHz, $CDCl_3$, *Z/E* 2:1): δ = 8.02 – 7.91 (m, 2 H^Z + 2 H^E), 7.61 – 7.51 (m, 1 H^Z + 1 H^E), 7.51 – 7.41 (m, 2 H^Z + 2 H^E), 7.11 – 7.00 (m, 1 H^Z + 1 H^E), 5.42 (dq, *J*=14.1 Hz, 7.0 Hz, 1 H^E), 4.94 (dq, *J*=6.8 Hz, 1 H^Z), 3.13 – 3.04 (m, 2 H^Z + 2 H^E), 2.61 – 2.54 (m, 2 H^Z), 2.54 – 2.47 (m, 2 H^E), 2.18 – 2.06 (m, 2 H^Z + 2 H^E), 1.67 – 1.62 ppm (m, 3 H^Z + 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 199.2, 170.4, 136.7, 134.7, 133.1, 128.6 (2C), 128.0 (2C), 108.7, 37.3, 33.0, 19.1, 9.8 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 199.2, 170.5, 136.7, 135.8, 133.1, 128.6 (2C), 128.0 (2C), 109.9, 37.2, 33.0, 19.2, 12.3 ppm; **IR** (KBr): ν = 3067 (m), 2943 (m), 2921 (w), 1747 (vs), 1675 (vs), 1597 (m), 1579 (m), 1448 (m), 1417 (w), 1381 (m), 1281 (m), 1172 (s), 1152 (s), 1000 (m), 932 (m), 734 (s), 690 (s), 660 (w), 608 (w), 576 cm^{-1} (w); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 232 [M^+] (1), 175 (69), 147 (87), 105 (100), 77 (38), 51 (14), 42 (4); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z

(%) = 232 [M^+] (1), 175 (65), 147 (81), 105 (100), 77 (42), 51 (15), 42 (5); **CHN** Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39%; H, 6.94%; found: C, 72.11%; H, 6.84%.

Synthesis of prop–1–enyl cinnamate (4.1.8–4p)

[CAS: (*E*)–Isomer = 1384266–49–2; (*Z*)–Isomer = 1384266–49–2]

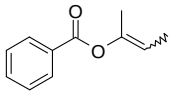


Compound **4.1.8–4p** was prepared from allyl cinnamate (**4.1.8–3p**) (188 mg, 1.00 mmol) yielding (*E*)– and (*Z*)–prop–1–enyl cinnamate (**4.1.8–4p**) as colourless liquid (180 mg, 96% yield, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, Z/*E* 2:1): δ = 7.85 – 7.74 (m, 1 H^Z + 1 H^E), 7.61 – 7.54 (m, 2 H^Z + 2 H^E), 7.45 – 7.38 (m, 3 H^Z + 3 H^E), 7.26 – 7.16 (m, 1 H^Z + 1 H^E), 6.52 (d, *J*=16.0 Hz, 1 H^Z), 6.46 (d, *J*=15.6 Hz, 1 H^E), 5.54 (dq, *J*=13.7 Hz, 6.7 Hz, 1 H^E), 5.01 (dq, *J*=6.7 Hz, 1 H^Z), 1.77 (d, *J*=7.0 Hz, 3 H^Z), 1.70 ppm (d, *J*=7.0 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 164.0, 146.1, 134.9, 134.2, 130.6, 128.9 (2C), 128.2 (2C), 117.1, 108.8, 10.0 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 164.1, 146.0, 136.0, 134.2, 130.6, 128.9 (2C), 128.2 (2C), 117.0, 110.0, 12.4 ppm; **IR** (NaCl): ν = 3064 (m), 3029 (w), 2919 (m), 1722 (vs), 1635 (vs), 1449 (m), 1389 (w), 1328 (w), 1310 (m), 1240 (s), 1202 (m), 1159 (vs), 1022 (w), 980 (m), 928 (w), 861 (w), 765 (m), 708 (w), 682 cm^{-1} (w); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 188 [M^+] (1), 131 (100), 103 (35), 102 (6), 77 (11), 63 (1), 51 (5); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 188 [M^+] (1), 131 (100), 103 (38), 102 (7), 77 (14), 63 (1), 51 (6). **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{12}H_{12}O_2$, 188.0837; found, 188.0834; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{12}H_{12}O_2$, 188.0837; found, 188.0844.

Synthesis of but–2–en–2–yl benzoate (4.1.8–4q)

[CAS: (*E*)–Isomer = 56544–12–8; (*Z*)–Isomer = 56544–13–9]

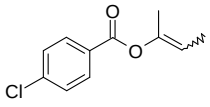


Compound **4.1.8–4q** was prepared from but–3–en–2–yl benzoate (**4.1.8–3q**) (176 mg, 1.00 mmol) and the stock solution of di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (1 mL, 5.00 μmol) in toluene (1 mL) yielding (*E*)– and (*Z*)–but–2–en–2–yl benzoate (**4.1.8–4q**) as colourless liquid (146 mg, 83% yield, *E*/*Z* 1:3).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z/E* 3:1): δ = 8.14 (d, *J*=7.4 Hz, 2 H^Z), 8.09 (d, *J*=7.4 Hz, 2 H^E), 7.64 – 7.56 (m, 1 H^Z + 1 H^E), 7.52 – 7.44 (m, 2 H^Z + 2 H^E), 5.32 (q, *J*= 7.0 Hz, 1 H^E), 5.18 (q, *J*=6.7 Hz, 1 H^Z), 2.00 (s, 3 H^Z + 3 H^E), 1.71 (d, *J*=7.4 Hz, 3 H^E), 1.55 ppm (dd, *J*=6.8 Hz, 1.0 Hz, 3 H^Z); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 164.3, 145.7, 133.2, 129.9 (2C), 129.8, 128.4 (2C), 111.6, 19.6, 10.7 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 165.3, 146.0, 133.1, 129.9 (2C), 129.8, 128.4 (2C), 112.1, 14.9, 11.8 ppm; **IR** (NaCl): ν = 2970 (w), 2923 (m), 2864 (w), 1726 (vs), 1601 (m), 1451 (m), 1376 (m), 1259 (s), 1173 (s), 1160 (s), 1106 (s), 1083 (m), 1066 (m), 1025 (m), 940 (w), 880 (w), 792 cm^{-1} (w); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 176 [M^+] (1), 105 (100), 77 (45), 51 (15), 42 (1); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 176 [M^+] (1), 105 (100), 77 (42), 51 (14), 42 (2); **HRMS–EI** (TOF): m/z [M+, (*Z*)–isomer] calcd. for $C_{11}H_{12}O_2$, 176.0837; found, 176.0828; **HRMS–EI** (TOF): m/z [M+, (*E*)–isomer] calcd. for $C_{11}H_{12}O_2$, 176.0837; found, 176.0837.

Synthesis of but–2–en–2–yl 4–chlorobenzoate (4.1.8–4r)

[CAS: (*E*)–Isomer = 1384266–51–6; (*Z*)–Isomer = 1384266–52–7]



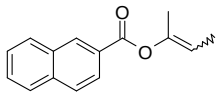
Compound **4.1.8–4r** was prepared from but–3–en–2–yl 4–chlorobenzoate (**4.1.8–3r**) (211 mg, 1.00 mmol) and the stock solution of di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I)

(1 mL, 5.00 µmol) in toluene (1 mL) yielding (*E*)– and (*Z*)– of but–2–en–2–yl 4–chlorobenzoate (**4.1.8–4r**) as colourless liquid (183 mg, 87%, *E*/*Z* 1:3).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 3:1): δ = 8.08 – 8.04 (m, 2 H^Z), 8.02 (dd, *J*=9.0 Hz, 2.3 Hz, 2 H^E), 7.48 – 7.42 (m, 2 H^Z + 2 H^E), 5.33 – 5.26 (m, 1 H^E), 5.21 – 5.14 (m, 1 H^Z), 2.01 – 1.95 (m, 3 H^Z + 3 H^E), 1.70 (dq, *J*=7.0 Hz, 1.2 Hz, 3 H^E), 1.53 ppm (dq, *J*=6.8 Hz, 1.5 Hz, 3 H^Z); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 163.5, 145.6, 139.8, 131.3 (2C), 128.8 (2C), 128.3, 111.8, 19.5, 10.7 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 164.5, 145.9, 139.6, 131.3 (2C), 128.8 (2C), 128.6, 112.4, 15.0, 11.9 ppm; **IR** (NaCl): ν = 3051 (w), 2983 (w), 1922 (m), 2863 (w), 1731 (vs), 1593 (s), 1488 (m), 1262 (vs), 1182 (s), 1170 (s), 1114 (s), 1104 (vs), 1090 (vs), 1014 (s), 850 (m), 756 cm^{-1} (s); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 210 [M^+] (1), 141 (34), 139 (100), 113 (9), 111 (27), 75 (12), 50 (7); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 210 [M^+] (1), 141 (34), 139 (100), 113 (8), 111 (25), 75 (9), 50 (5); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{11}H_{11}ClO_2$, 210.0448; found, 210.0444; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{11}H_{11}ClO_2$, 210.0448; found, 210.0449.

Synthesis of but–2–en–2–yl 2–naphtoate (4.1.8–4s)

[CAS: (*E*)–Isomer = 1384266–53–8; (*Z*)–Isomer = 1384266–54–9]



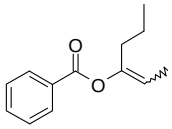
Compound **4.1.8–4s** was prepared from but–3–en–2–yl 2–naphtoate (**4.1.8–3s**) (226 mg, 1.00 mmol) and the stock solution of di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (1 mL, 5.00 µmol) in toluene (1 mL) yielding (*E*)– and (*Z*)– but–2–en–2–yl 2–naphtoate (**4.1.8–4s**) as a mixture (215 mg, 95%, *E*/*Z* 1:3).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 1:1): δ = 8.71 (d, *J*=0.8 Hz, 1 H^Z), 8.66 (d, *J*=0.8 Hz, 1 H^E), 8.13 (dd, *J*=16.2 Hz, 1.8 Hz, 1 H^E), 8.11 (dd, *J*=16.2 Hz, 1.8 Hz, 1 H^Z), 8.01 – 7.96 (m, 1 H^Z + 1 H^E), 7.95 – 7.88 (m, 2 H^Z + 2 H^E), 7.66 – 7.54 (m, 2 H^Z + 2 H^E), 5.36 (dq, *J*=7.1 Hz, 1.1 Hz, 1 H^E), 5.26 – 5.19 (m, 1 H^Z), 2.06 – 2.02 (m, 3 H^Z + 3 H^E), 1.74 (dq, *J*=7.0 Hz, 1.2 Hz, 3 H^E), 1.59 ppm (dq, *J*=6.8 Hz, 1.5 Hz, 3 H^Z); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 164.5, 145.8, 135.7, 132.5, 131.5, 129.4, 128.4, 128.2, 127.8, 127.0, 126.7, 125.4, 111.7, 19.6, 10.8 ppm;

^{13}C–NMR (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 165.5, 146.1, 135.6, 132.5, 131.4, 129.4, 128.3, 128.2, 127.8, 127.3, 126.7, 125.4, 112.2, 15.0, 11.9 ppm; **IR** (NaCl): ν = 3059 (w), 2982 (w), 2919 (m), 1727 (vs), 1468 (m), 1446 (m), 1354 (m), 1276 (vs), 1194 (vs), 1178 (vs), 1128 (s), 1100 (s), 1076 (s), 958 (m), 776 (s), 762 cm^{-1} (s); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 226 [M^+] (1), 155 (100), 127 (35), 101 (3), 87 (1), 77 (5), 50 (2); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 226 [M^+] (1), 155 (100), 127 (33), 101 (3), 87 (1), 77 (4), 50 (3); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{15}H_{14}O_2$, 226.0994; found, 226.0988; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{15}H_{14}O_2$, 226.0994; found, 226.0990.

Synthesis of hex–2–en–3–yl benzoate (4.1.8–4t)

[CAS: (*E*)–Isomer = 1384266–55–0; (*Z*)–Isomer = 1384266–56–1]



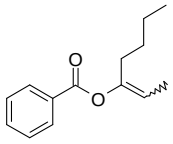
Compound **4.1.8–4t** was prepared from hex–1–en–3–yl benzoate (**4.1.8–3t**) (204 mg, 1.00 mmol) and the stock solution of di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (1 mL, 5.00 µmol) in toluene (1 mL) at 25 °C yielding (*E*)– and (*Z*)–hex–2–en–3–yl benzoate (**4.1.8–4t**) as colourless liquid (178 mg, 87% yield, *Z*/*E* 5:1 + other isomers).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 5:1 + other isomer): δ = 8.18 – 8.06 (m, 2 H^Z + 2 H^E), 7.64 – 7.56 (m, 1 H^Z + 1 H^E), 7.53 – 7.44 (m, 2 H^Z + 2 H^E), 5.33 (q, *J*=7.0 Hz, 1 H^E), 5.19 (q, *J*=6.7 Hz, 1 H^Z), 2.37 (t, *J*=7.4 Hz, 3 H^E), 2.28 (t, *J*=7.4 Hz, 3 H^Z), 1.59 – 1.49 (m, 4 H^Z + 4 H^E), 1.01 – 0.91 ppm (m, 3 H^Z + 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 164.3, 149.2, 133.2, 130.2, 129.9 (2C), 128.4 (2C), 110.9, 35.6, 20.0, 13.6, 10.7 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 165.4, 149.3, 133.1, 129.9, 129.8 (2C), 128.4 (2C), 112.6, 30.6, 20.1, 13.6, 11.8 ppm; **IR** (NaCl): ν = 2961 (s), 2933 (m), 2871 (m), 1733 (vs), 1601 (w), 1451 (m), 1262 (s), 1174 (m), 1114 (m), 1090 (m), 1068 (m), 1026 (w), 971 (w), 790 (w), 708 cm^{-1} (m); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 204 [M^+] (1), 147 (2), 105 (100), 77 (17), 55 (3), 51 (6), 41 (1); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 204 [M^+] (1), 147 (2), 105 (100), 77 (28), 55 (1), 51 (9), 41 (2); **HRMS–EI** (TOF) (m/z): [M^+, (*Z*)–isomer] calcd. for $C_{13}H_{16}O_2$,

204.1150; found, 204.1154; **HRMS–EI** (TOF) (m/z): [M^+, (*E*)–isomer] calcd. for $C_{13}H_{16}O_2$, 204.1150; found, 204.1160.

Synthesis of hept–2–en–3–yl benzoate (4.1.8–4u)

[CAS: (*E*)–Isomer = 1384266–57–2; (*Z*)–Isomer = 1384266–58–3]

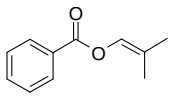


Compound **4.1.8–4u** was prepared from hept–1–en–3–yl benzoate (**4.1.8–3u**) (218 mg, 1.00 mmol) at 25 °C yielding (*E*)– and (*Z*)–hept–2–en–3–yl benzoate (**4.1.8–4u**) as colourless liquid (193 mg, 88%, *E*/*Z* 1:5 + other isomers).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 5:1 + other isomers): δ = 8.18 – 8.11 (m, 2 H^Z), 8.11 – 8.08 (m, 2 H^E), 7.63 – 7.56 (m, 1 H^Z + 1 H^E), 7.52 – 7.44 (m, 2 H^Z + 2 H^E), 5.34 – 5.27 (m, 1 H^E), 5.19 (qt, *J*=6.8 Hz, 1.0 Hz, 1 H^Z), 2.40 (t, *J*=7.4 Hz, 2 H^E), 2.34 – 2.26 (m, 2 H^Z), 1.59 – 1.52 (m, 3 H^Z + 3 H^E), 1.52 – 1.43 (m, 4 H^Z + 4 H^E), 1.37 (dq), 1.11 (t, *J*=7.4 Hz, 3 H^E), 0.91 ppm (t, *J*=7.3 Hz, 3 H^Z); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 164.23, 149.40, 133.12, 129.87 (2C), 129.81, 128.39 (2C), 110.63, 33.22, 28.76, 22.12, 13.80, 10.67 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 164.40, 149.56, 133.10, 129.85 (2C), 129.79, 128.34 (2C), 112.26, 33.22, 28.86, 22.19, 13.70, 11.27 ppm; **IR** (NaCl): ν = 3061 (w), 2957 (s), 2931 (m), 2862 (m), 1731 (vs), 1452 (m), 1262 (vs), 1173 (s), 1092 (vs), 1068 (vs), 1025 (m), 708 cm^{-1} (vs); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 218 [M^+] (1), 161 (2), 105 (100), 77 (9), 55 (3), 51 (3), 41 (1); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 218 [M^+] (1), 161 (2), 105 (100), 77 (25), 55 (1), 51 (7), 41 (1); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_{14}H_{18}O_2$, 218.1307; found, 218.1310; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_{14}H_{18}O_2$, 218.1307; found 218.1305.

Synthesis of 2–methylprop–1–enyl benzoate (4.1.8–4v)

[CAS: 86123–18–4]

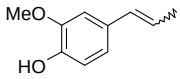


Compound **4.1.8–4v** was prepared from 2–methylallyl benzoate (**4.1.8–3v**) (176 mg, 1.00 mmol) and di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (7.77 mg, 0.01 mmol) in toluene (2 mL) yielding 2–methylprop–1–enyl benzoate (**4.1.8–4v**) as a colourless liquid (151 mg, 86%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.15 – 8.09 (m, 2H), 7.63 – 7.56 (m, 1H), 7.51 – 7.44 (m, 2H), 7.12 (spt, *J*=1.4 Hz, 1H), 1.83 (d, *J*=1.2 Hz, 3H), 1.74 ppm (d, *J*=1.2 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 163.7, 133.2, 129.9, 129.7 (2C), 129.6, 128.4 (2C), 118.9, 19.7, 15.8 ppm; **IR** (NaCl): ν = 3093 (w), 2969 (w), 2917 (w), 2859 (w), 1727 (vs), 1601 (w), 1451 (m), 1336 (w), 1270 (vs), 1130 (vs), 1068 (w), 1028 (w), 814 (w), 708 cm^{-1} (s); **MS** (Ion trap, EI, 70 eV): m/z (%) = 176 [M^+] (1), 106 (8), 105 (100), 77 (13), 51 (7), 41 (1); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{11}H_{12}O_2$, 176.0837; found, 176.0835.

Synthesis of 2–methoxy–4–(prop–1–enyl)phenol [(E)–Isoeugenol] (4.1.8–6)

[CAS: (*E*)–Isomer = 5932–68–3; (*Z*)–Isomer = 5912–86–7]



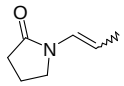
Eugenol (**4.1.8–5**) (164 mg, 1.00 mmol) and a stock solution of di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (0.05 mL, 0.25 µmol) were stirred in toluene (1.95 mL) for 2 h at 50 °C yielding **4.1.8–6** as a colourless liquid (133 mg, 81%, *E*/*Z* >20:1, GC yield: 96%, *E*/*Z* >20:1).

^{1}H–NMR (400 MHz, $CDCl_3$, (*E*)–Isomer): δ = 6.89 – 6.84 (m, 3H), 6.34 (dd, *J*=15.7 Hz, 1.7 Hz, 1H), 6.14 – 6.07 (m, 1H), 5.61 (s, 1H), 3.92 – 3.89 (m, 3H), 1.88 ppm (dd, *J*=6.7 Hz, 1.8 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 146.5, 144.7, 130.7, 130.6, 123.4, 119.2, 114.3, 107.8, 55.8, 18.3 ppm; **IR** (NaCl): ν = 3503 (w), 3016 (w), 2937 (w), 2913 (w), 2849 (w), 1739 (w), 1596 (w), 1509 (vs), 1464 (w), 1450 (w), 1425 (m), 1366 (w), 1261 (s), 1230 (s), 1203 (s), 1153 (s), 1120 (m), 1031 (m), 960 (m), 855 (m), 784 cm^{-1} (m); **MS** (Ion trap, EI, 70 eV): m/z

(%) = 164 [M^+] (100), 149 (42), 131 (27), 121 (25), 103 (39), 91 (30), 77 (33); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{10}H_{12}O_2$, 164.0837; found, 164.0841.

Synthesis of 1–(prop–1–enyl)pyrrolidin–2–one (4.1.8–8)

[CAS: (*E*)–Isomer = 140165–83–9; (*Z*)–Isomer = 1384131–91–2]

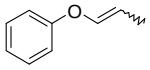


1–allylpyrrolidin–2–one (**4.1.8–7**) (125 mg, 1.00 mmol) and a stock solution of di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (0.3 mL, 1.50 µmol) were stirred in toluene (1.7 mL) for 4 h at 50 °C yielding **4.1.8–8** as a colourless liquid (118 mg, 94%, *E*/*Z* >20:1, GC yield: 92%, *E*/*Z* >20:1).

^{1}H–NMR (400 MHz, $CDCl_3$, (*E*)–Isomer): δ = 6.87 – 6.77 (m, 1H), 4.90 (dq, *J*=14.1 Hz, 6.8 Hz, 1H), 3.44 (t, *J*=7.2 Hz, 2H), 2.42 (t, *J*=8.0 Hz, 2H), 2.04 (quin, *J*=7.6 Hz, 2H), 1.68 ppm (dd, *J*=6.7 Hz, 1.6 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 172.5, 124.2, 106.7, 45.1, 31.1, 17.3, 15.0 ppm; **IR** (NaCl): ν = 3056 (w), 2969 (m), 2921 (m), 2885 (m), 1697 (vs), 1669 (vs), 1488 (s), 1462 (s), 1410 (vs), 1298 (vs), 1250 (vs), 1049 (s), 952 (vs), 787 cm^{-1} (w); **MS** (Ion trap, EI, 70 eV): m/z (%) = 125 [M^+] (97), 110 (23), 96 (13), 82 (33), 70 (100), 54 (9), 41 (27); **HRMS–EI** (TOF): m/z [M^+] calcd for $C_7H_{11}NO$, 125.0841; found, 125.0838.

Synthesis of (prop–1–enyloxy)benzene (4.1.8–10).

[CAS: (*E*)–Isomer = 4696–24–6; (*Z*)–Isomer = 4696–23–5]



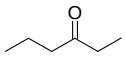
Allyloxybenzene (**4.1.8–9**) (134 mg, 1.00 mmol) and di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (3.89 mg, 5.00 µmol) were stirred in diethyl ether (2 mL) for 2 h at 50 °C yielding (*E*)– and (*Z*)–(prop–1–enyloxy)benzene (**4.1.8–10**) as colourless liquid (125 mg, 93% yield, *E*/*Z* 1:2, GC yield: 94%, *E*/*Z* 1:2).

^{1}H–NMR (400 MHz, $CDCl_3$, *Z*/*E* 2:1): δ = 7.40 – 7.35 (m, 2 H^Z + 2 H^E), 7.13 – 7.03 (m, 3 H^Z + 3 H^E), 6.49 (dq, *J*=12.0 Hz, 1.6 Hz, 1 H^E), 6.45 (dq, *J*=6.1 Hz, 1.6 Hz, 1 H^Z), 5.46 (dq, *J*=12.0

Hz, 6.9 Hz, 1 H^E), 4.95 (dq, *J*=6.9 Hz, 1 H^Z), 1.81 (dd, *J*=6.9 Hz, 1.8 Hz, 3 H^Z), 1.74 ppm (dd, *J*=6.9, 1.8 Hz, 3 H^E); **^{13}C–NMR** (101 MHz, $CDCl_3$, (*Z*)–Isomer): δ = 157.5, 140.8, 129.5 (2C), 122.3, 116.1 (2C), 107.4, 9.3 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$, (*E*)–Isomer): δ = 157.4, 141.9, 129.5 (2C), 122.3, 116.2 (2C), 108.2, 12.2 ppm; **IR** (NaCl): ν = 3041 (s), 2921 (s), 1671 (m), 1595 (vs), 1491 (vs), 1395 (w), 1254 (vs), 1228 (s), 1166 (w), 1122 (w), 1030 (m), 928 (w), 754 (m), 692 cm^{-1} (w); **MS** (Ion trap, EI, 70 eV, (*Z*)–isomer): m/z (%) = 134 [M^+] (100), 119 (26), 105 (26), 91 (15), 77 (8), 66 (9), 51 (11); **MS** (Ion trap, EI, 70 eV, (*E*)–isomer): m/z (%) = 134 [M^+] (100), 119 (20), 105 (26), 91 (9), 77 (5), 66 (6), 51 (6); **HRMS–EI** (TOF): m/z [M^+, (*Z*)–isomer] calcd. for $C_9H_{10}O$, 134.0732; found, 134.0731; **HRMS–EI** (TOF): m/z [M^+, (*E*)–isomer] calcd. for $C_9H_{10}O$, 134.0732; found 134.0731.

Synthesis of 3–Hexanone (4.1.8–12)

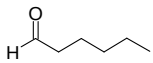
[CAS: 589–38–8]



1–Hexen–3–ol (**4.1.8–11**) (100 mg, 1.00 mmol) and a stock solution of di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) in diethyl ether (0.05 mL, 0.25 µmol) were stirred in diethyl ether (1.95 mL) for 30 min at 50 °C. The solution was measured by GC using *n*–dodecane as internal standard (80% of 3–hexanone (**4.1.8–12**)).

Synthesis of Hexanal (4.1.8–14)

[CAS: 66–25–1]

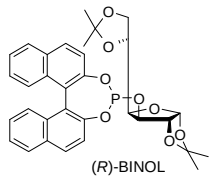


5–Hexen–1–ol (**4.1.8–13**) (100 mg, 1.00 mmol) and di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (11.7 mg, 15 µmol) were stirred in THF (2 mL) for 16 h at 50 °C. The solution was measured by GC using *n*–dodecane as internal standard (94% of hexanal (**4.1.8–14**)).

Preparative scale synthesis of prop–1–enyl benzoate (4.1.8–4a)

A 50 mL vessel was charged with di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (27.2 mg, 35.0 µmol) and toluene (20 mL) as well as allyl benzoate (**4.1.8–3a**) (1.76 g, 10.0 mmol) were added via syringe. The mixture was stirred at 50 °C for 16 h, cooled to room temperature, diluted with diethyl ether (40 mL), filtered through a pad of celite (5 g) and the solvent was removed *in vacuo* (50 mbar, 40 °C). The crude product was purified by column chromatography (SiO_2, diethyl ether/*n*–pentane gradient) to give (*E*)– and (*Z*)–prop–1–enyl benzoate (**4.1.8–4a**) as colourless liquid (1.65 g, 94% yield, *E*/*Z* 1:2). The analytical data matched those reported above.

6.8.4. Synthesis of the chiral phosphite ligand



Under nitrogen atmosphere, a 50 mL round bottom flask was charged with (R)–(+)–1,1'–Bi–2–naphthol (2.00 g, 7.00 mmol), freshly distilled phosphorus trichloride (6.00 mL, 9.42 g 68.6 mmol) and 50 µl DMF. The suspension was heated up to reflux (90 °C) for 24 h until the solid was dissolved completely. After cooling to room temperature, the phosphorus trichloride was removed by trap–to–trap distillation. The residue was diluted with dry and degassed diethyl ether (10 mL) and the solution was filtered. The solvent was removed *in vacuo*. Then again diethyl ether (5–10 mL) was added and removed *in vacuo*, yielding the crude chlorophosphite **4.1.8–16'** (2.4 g, 6.84 mmol, 98%) as a colourless foam. **^{31}P–NMR** (162 MHz, $CDCl_3$): δ = 178.2 ppm.

The chlorophosphite **4.1.8–16'** was used without further purification in the next step. Under nitrogen atmosphere, chlorophosphite **4.1.8–16'** (929 mg, 2.65 mmol) was dissolved in dry and degassed toluene (20 mL) and the solution was cooled to –40 °C. Afterwards, a solution of diacetone–D–glucose (704 mg, 2.65 mmol) and triethylamine (553 µL, 402 mg, 3.98 mmol) in dry and degassed toluene (20 mL) was added slowly within 15–30 min. After complete addition, the reaction mixture was warmed up to room temperature and stirred another 16 h at that

temperature. The solvent was removed over trap−to−trap distillation and the residue was purified by column chromatography (SiO_2, dichloromethane), yielding the corresponding phosphite ligand **4.1.8–16** (444 mg, 0.77 mmol, 29%) as colourless solid. The analytical data matched those reported in the literature.[297]

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 7.91 – 8.01 (m, 4H), 7.42 – 7.51 (m, 4H), 7.34 – 7.40 (m, 2H), 7.17 – 7.32 (m, 2H), 5.86 (d, J=3.9 Hz, 1H), 4.75 – 4.80 (m, 1H), 4.70 (d, J=3.9 Hz, 1H), 4.31 (m, 1H), 4.07 – 4.14 (m, 2H), 3.96 (dd, J=8.6, 5.5 Hz, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.46 (s, 3H), 1.33 ppm (s, 3H); **^{31}P–NMR** (162 MHz, $CDCl_3$): δ = 145.3 ppm; **IR** (ATR): ν = 3430 (w), 2986 (w), 2937 (w), 1619 (m), 1594 (m), 1510 (m), 1594 (m), 1510 (m), 1464 (m), 1375 (m), 1216 (s), 1071 (m), 1015 (m), 947 (m), 816 (s), 748 cm^{-1} (s).

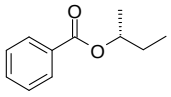
6.8.5. Asymmetric hydrogenations

6.8.5.1. General procedure for the enantioselective hydrogenation of enol esters

All hydrogenations were performed according to Reetz and Gooßen *et al.*[297] using stock solutions of the chiral ligand **4.1.8–16** (2.00 μmol/mL), the rhodium precursor $[Rh(cod)_2]BF_4$ (2.00 μmol/mL) and the corresponding enol esters **4.1.8–4** (0.10 mmol/mL) in CH_2Cl_2. The ligand **16** (0.50 mL, 1.00 μmol) was added to the solution of $[Rh(cod)_2]BF_4$ (0.25 mL, 0.50 μmol). The corresponding enol ester **4.1.8–4** (1.00 mL, 0.10 mmol) and additional CH_2Cl_2 (2 mL) were added to the bright yellow solution and the vial was placed in an autoclave. The autoclave was purged with argon, pressurized with hydrogen (60 bar) and the reaction mixture was stirred for 20 h at 30 °C. After cooling to room temperature, the mixture was filtered through silica gel and concentrated to receive the corresponding hydrogenated ester as colourless liquid.

Synthesis of (R)–sec–butyl benzoate (4.1.8–15q)

[CAS: 5519–33–5]

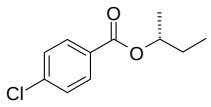


Compound **4.1.8–15q** was prepared from a mixture of (*E*)– and (*Z*)–but–2–en–2–yl benzoate (**4.1.8–4q**) (17.6 mg, 0.1 mmol, E/Z 1:3) yielding (R)–2–butyl benzoate (**4.1.8–15q**) (15.0 mg, 84%, 96%ee) as colourless liquid.

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J*=7.4 Hz, 2H), 7.56 (t, *J*=7.2 Hz, 1H), 7.45 (t, *J*=7.6 Hz, 2H), 5.17 – 5.04 (m, 1H), 1.86 – 1.59 (m, 2H), 1.35 (d, *J*=6.3 Hz, 3H), 0.99 ppm (t, *J*=7.4 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 166.2, 132.6, 130.9, 129.5 (2 C), 128.2 (2 C), 72.8, 28.9, 19.5, 9.7 ppm; **IR** (NaCl): ν = 3061 (w), 2973 (m), 2935 (w), 2879 (w), 1715 (vs), 1641 (m), 1452 (m), 1392 (w), 1276 (vs), 1176 (w), 1108 (m), 1026 (m), 968 (w), 888 (w), 862 (w), 712 cm^{-1} (s); **MS** (Ion trap, EI, 70 eV): m/z (%) = 178 [M^+] (1), 123 (45), 105 (100), 77 (34), 56 (6), 51 (15), 41 (5); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{11}H_{14}O_2$, 178.0994; found, 178.0986; **$[\alpha]_D^{25}$** = –40.9 (c = 0.675, $CHCl_3$) (Lit. [*S*–isomer], +39.7 (c = 0.12, $CHCl_3$, ee 98%)).[298]

Synthesis of (R)–sec–butyl 4–chlorobenzoate (4.1.8–15r)

[CAS: 1384266–64–1]



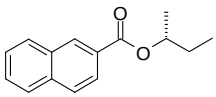
Compound **4.1.8–15r** was prepared from a mixture of (*E*)– and (*Z*)– of but–2–en–2–yl 4–chlorobenzoate (**4.1.8–4r**) (21.1 mg, 0.10 mmol, *E*/*Z* 1:3) yielding (R)–*sec*–butyl 4–chloro–benzoate (**4.1.8–15r**) (19.8 mg, 93%, 94%ee) as colourless liquid.

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J=8.6 Hz, 2H), 7.41 (d, J=8.4 Hz, 2H), 5.09 (qt, J=6.3 Hz, 1H), 1.60 – 1.82 (m, 2H), 1.34 (d, J=6.2 Hz, 3H), 0.97 ppm (t, J=7.4 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 165.3, 139.1, 130.9 (2 C), 129.3, 128.6 (2 C), 73.2, 28.9, 19.5, 9.7 ppm; **IR** (NaCl): ν = 2971 (m), 2931 (m), 1719 (vs), 1593 (s), 1488 (s), 1462 (m), 1456

(m), 1402 (s), 1306 (s), 1274 (vs), 1104 (vs), 1092 (vs), 1016 (s), 850 (s), 760 cm^{-1} (vs); **MS** (Ion trap, EI, 70 eV): m/z (%) = 212 [M^+] (1), 159 (15), 157 (45), 141 (36), 139 (100), 111 (25), 75 (12); **HRMS–EI** (TOF) (m/z): [M^+] calcd. for $C_{11}H_{13}ClO_2$, 212.0604; found, 212.0605; $\mathbf{[\alpha]_D^{25}}$ = –37.1 (c = 1.155, $CHCl_3$).

Synthesis of (R)–sec–butyl 2–naphthoate (4.1.8–15s)

[CAS: 1384266–65–2]

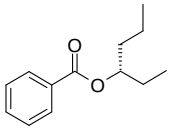


Compound **4.1.8–15s** was prepared from a mixture of (*E*)– and (*Z*)– but–2–en–2–yl 2–naphtoate (**4.1.8–4s**) (22.6 mg, 0.1 mmol, *E*/*Z* 1:3) yielding (R)–*sec*–butyl 2–naphthoate (**4.1.8–15s**) (20.1 mg, 88%, 98%ee) as colourless liquid.

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.63 – 8.60 (m, 1H), 8.09 (dd, *J*=8.7 Hz, 1.7 Hz, 1H), 7.97 (d, *J*=8.0 Hz, 1H), 7.89 (d, *J*=8.6 Hz, 2H), 7.63 – 7.52 (m, 2H), 5.23 – 5.14 (m, 1H), 1.89 – 1.67 (m, 2H), 1.40 (d, *J*=6.2 Hz, 3H), 1.03 ppm (t, *J*=7.4 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 166.4, 135.4, 132.5, 130.8, 129.3, 128.2, 128.1, 128.0, 127.7, 126.5, 125.3, 73.0, 29.0, 19.6, 9.8 ppm; **IR** (NaCl): ν = 3060 (w), 2971 (m), 2933 (m), 1713 (vs), 1464 (m), 1454 (m), 1354 (m), 1284 (vs), 1228 (vs), 1198 (vs), 1128 (s), 1092 (s), 967 (w), 955(w), 866 (m), 780 (s), 762 cm^{-1} (s); **MS** (Ion trap, EI, 70 eV): m/z (%) = 228 [M^+] (55), 172 (64), 155 (100), 127 (34), 77 (5), 41 (2); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{15}H_{16}O_2$, 228.1150; found, 228.1154.

Synthesis of (R)–3–hexyl benzoate (4.1.8–15t)

[CAS: 1384266–66–3]

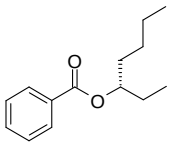


Compound **4.1.8–15t** was prepared from a mixture of (*E*)– and (*Z*)– hex–2–en–3–yl benzoate (**4.1.8–4t**) (20.4 mg, 0.10 mmol, *E*/*Z* 1:5 + other isomers) yielding (R)–3–hexyl benzoate (**4.1.8–15t**) (19.6 mg, 95%, 82%ee) as colourless liquid.

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.09 – 8.04 (m, 2H), 7.59 – 7.53 (m, 1H), 7.48 – 7.41 (m, 2H), 5.15 – 5.06 (m, 1H), 1.76 – 1.60 (m, 4H), 1.47 – 1.34 (m, 2H), 0.99 – 0.91 ppm (m, 6H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 166.4, 132.7 (2 C), 130.8, 129.5, 128.3 (2 C), 75.9, 35.9, 27.1, 18.6, 14.0, 9.6 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 206 [M^+] (1), 123 (35), 105 (100), 77 (27), 56 (5), 51 (7), 41 (4); **IR** (NaCl): ν = 2963 (m), 2935 (m), 2875 (m), 1715 (vs), 1462 (w), 1452 (m), 1314 (m), 1276 (vs), 1108 (s), 1070 (m), 932 (m), 910 (s), 734 (s), 711 cm^{-1} (vs); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{13}H_{18}O_2$, 206.1307; found, 206.1303.

Synthesis of (R)–3–heptyl benzoate (4.1.8–15u)

[CAS: 1384266–67–4]



Compound **4.1.8–15u** was prepared from a mixture of (*E*)– and (*Z*)– hept–2–en–3–yl benzoate (**4.1.8–4u**) (21.8 mg, 0.1 mmol, *E*/*Z* 1:5 + other isomers) yielding (R)–3–heptyl benzoate (**4.1.8–15u**) (19.2 mg, 87%, 77%ee) as colourless liquid.

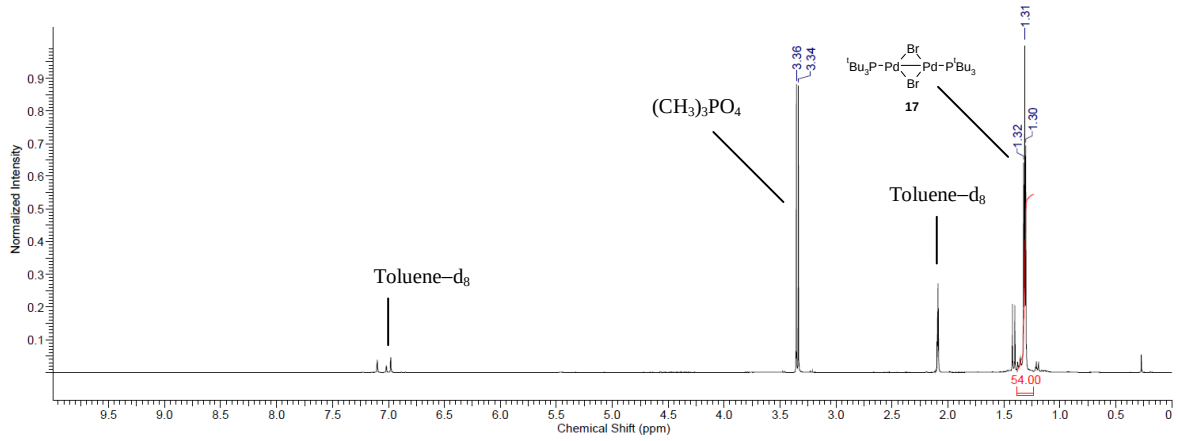
^{1}H–NMR (400 MHz, $CDCl_3$): δ = 8.10 – 8.04 (m, 2H), 7.56 (tt, *J*=7.4 Hz, 1.4 Hz, 1H), 7.48 – 7.42 (m, 2H), 5.09 (tt, *J*=6.0 Hz, 1H), 1.75 – 1.63 (m, 4H), 1.41 – 1.30 (m, 4H), 0.96 (t, *J*=7.5 Hz, 3H), 0.91 ppm (t, *J*=7.2 Hz, 3H); **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 166.4, 132.6, 130.8, 129.5 (2 C), 128.3 (2 C), 76.1, 33.4, 27.5, 27.1, 22.6, 14.0, 9.6 ppm; **MS** (Ion trap, EI, 70 eV): m/z (%) = 163 (1), 123 (33), 105 (100), 77 (14), 70 (5), 56 (5), 51 (6), 41 (4); **IR** (NaCl): ν = 3061 (w), 2959 (s), 2931 (s), 2872 (m), 2860 (m), 1717 (vs), 1452 (s), 1314 (s), 1274 (vs), 1175 (m), 1108 (vs), 1070 (m), 1026 (m), 946 (w), 710 cm^{-1} (vs); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{14}H_{20}O_2$, 220.1463; found, 220.1451.

6.8.6. Mechanistic studies

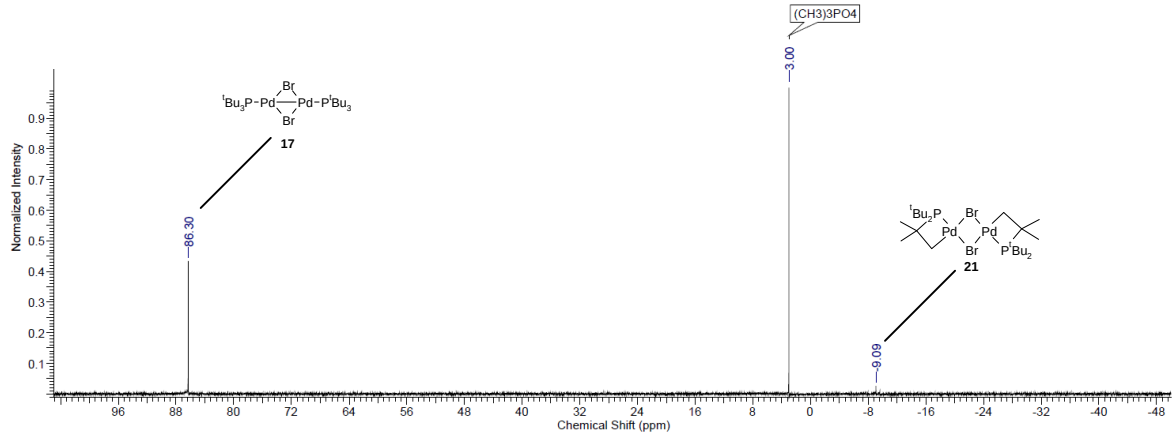
6.8.6.1. In situ NMR studies

Under an argon atmosphere, a NMR tube was charged with di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (**4.1.8–17**) (10.0 mg, 12.0 µmol), allyl benzoate (**4.1.8–3a**) (162 mg, 1.00 mmol), toluene–d_8 (0.4 mL) and trimethylphosphate (1.5 µl, 12.0 µmol) as internal standard. The dark green solution was left in an ultrasonic bath for 1 min and the NMR spectra were measured at 25 °C.

^{1}H–NMR (600 MHz, toluene–d_8)

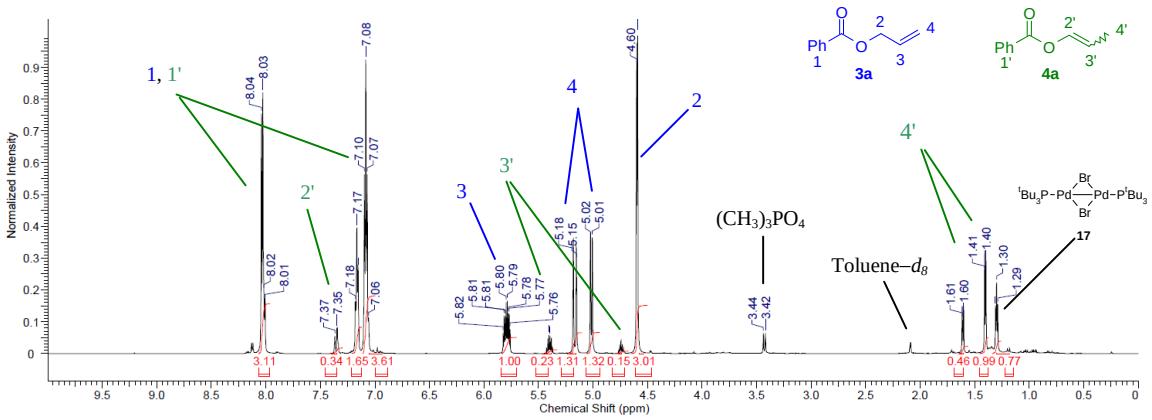


^{31}P–NMR (243 MHz, toluene–d_8)

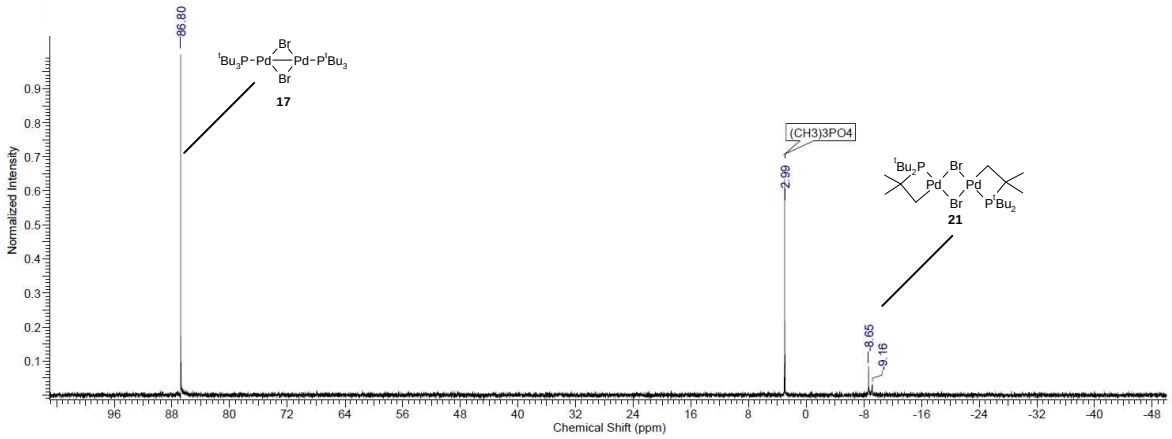


Reaction solution after 15 min:

^{1}H–NMR (600 MHz, toluene–d_8)

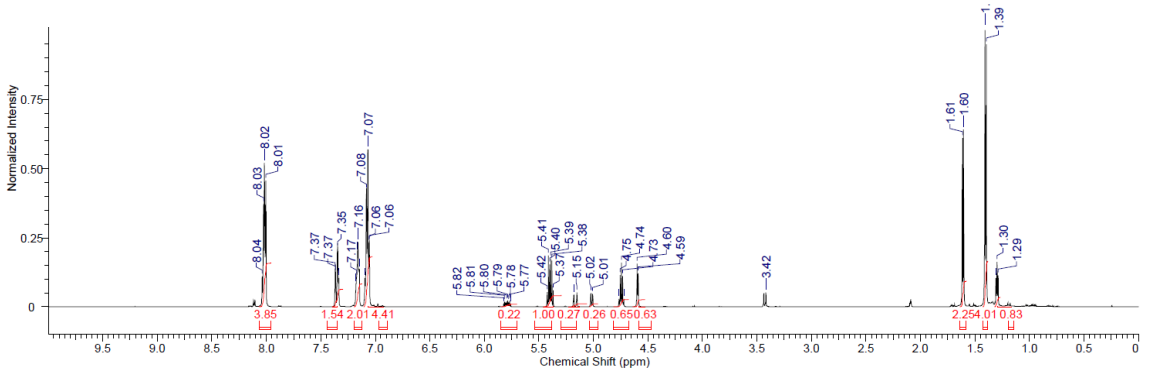


^{31}P–NMR (243 MHz, toluene–d_8)

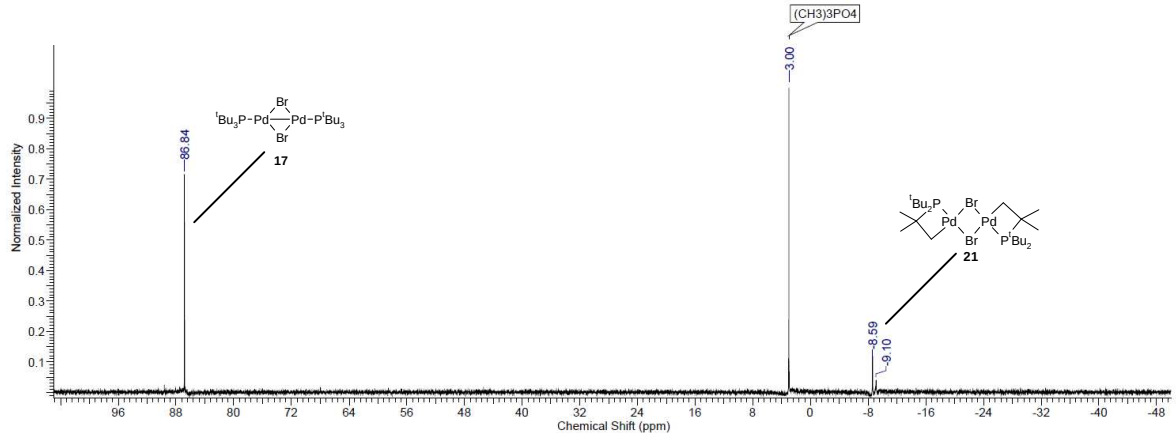


Reaction solution after 45 min:

^{1}H–NMR (600 MHz, toluene–d_8)

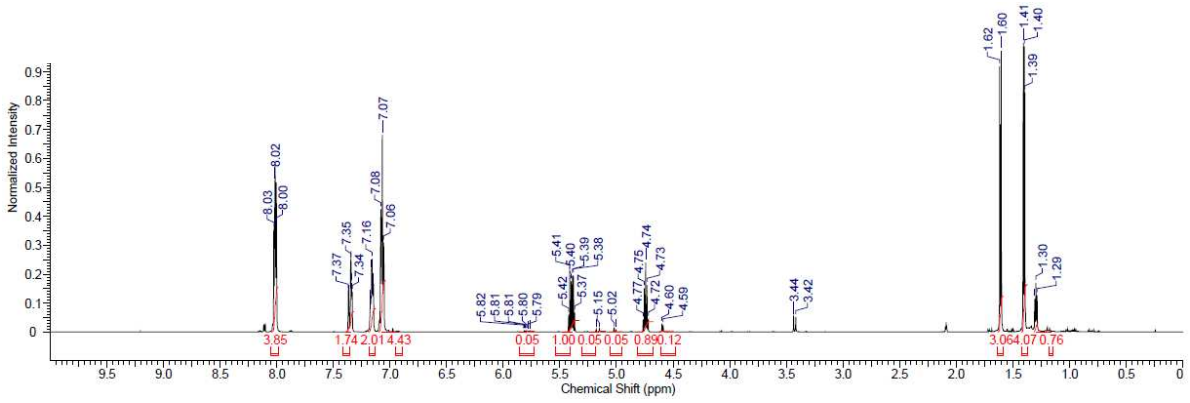


^{31}P–NMR (243 MHz, toluene–d_8)

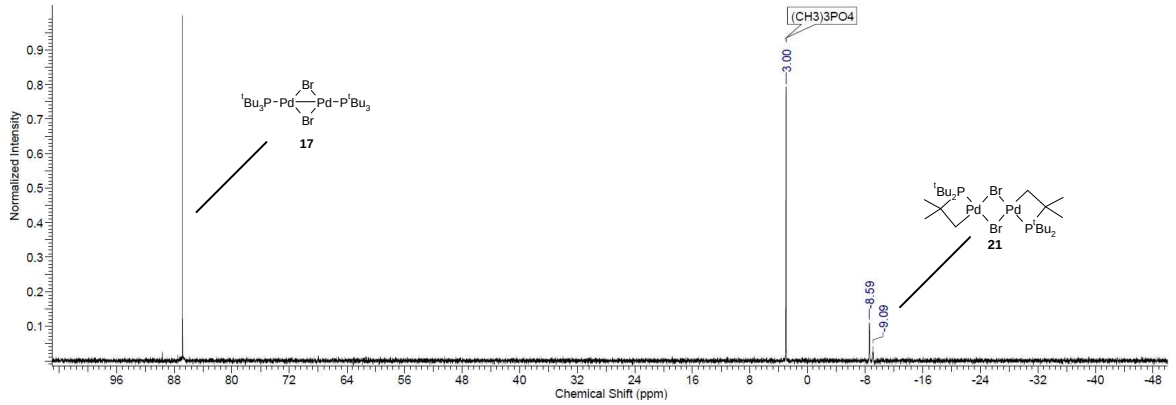


Reaction solution after 75 min:

^{1}H–NMR (600 MHz, toluene–d_8)

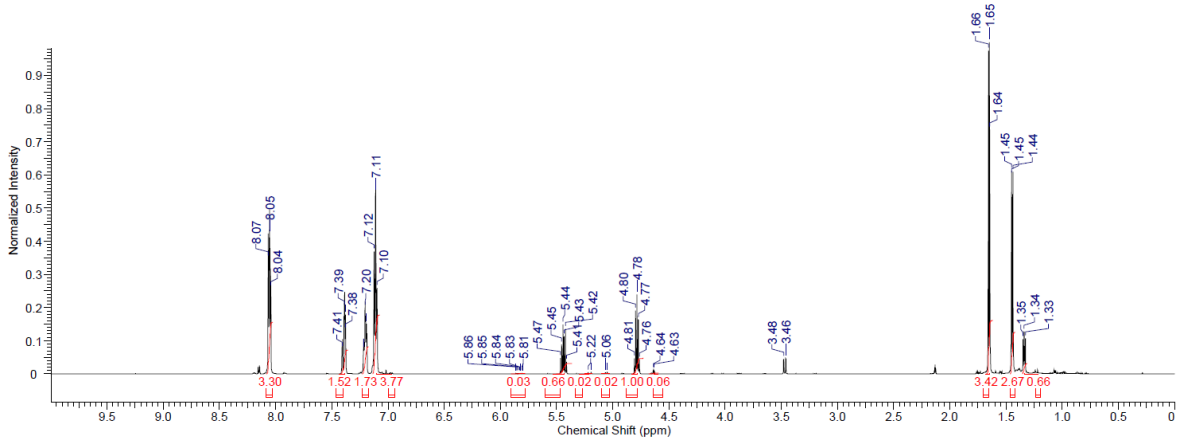


^{31}P–NMR (243 MHz, toluene–d_8)

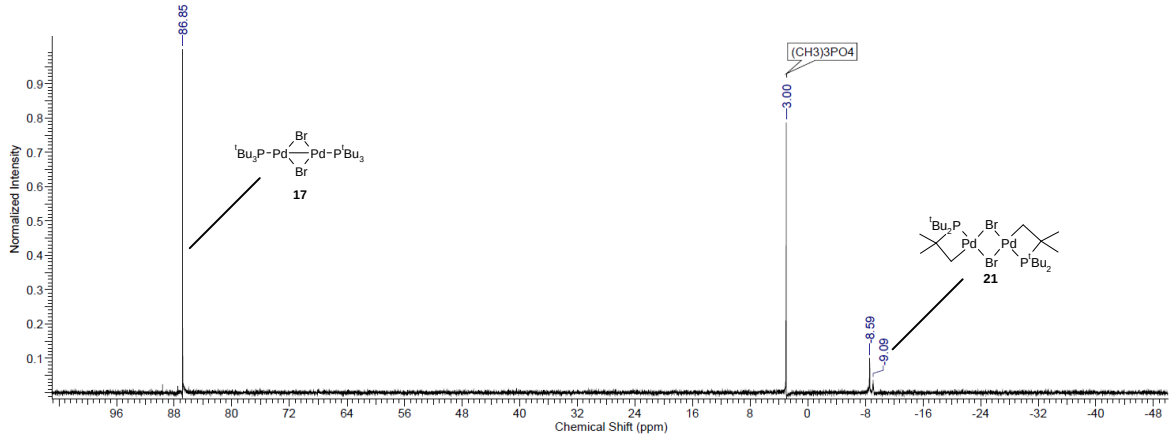


Reaction solution after 2.5 h:

^{1}H–NMR (600 MHz, toluene–d_8)

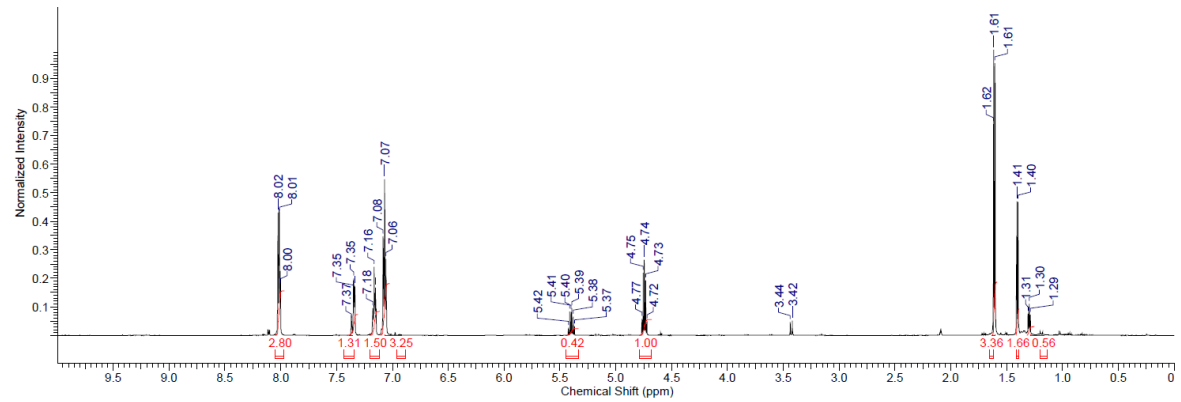


^{31}P–NMR (243 MHz, toluene–d_8)

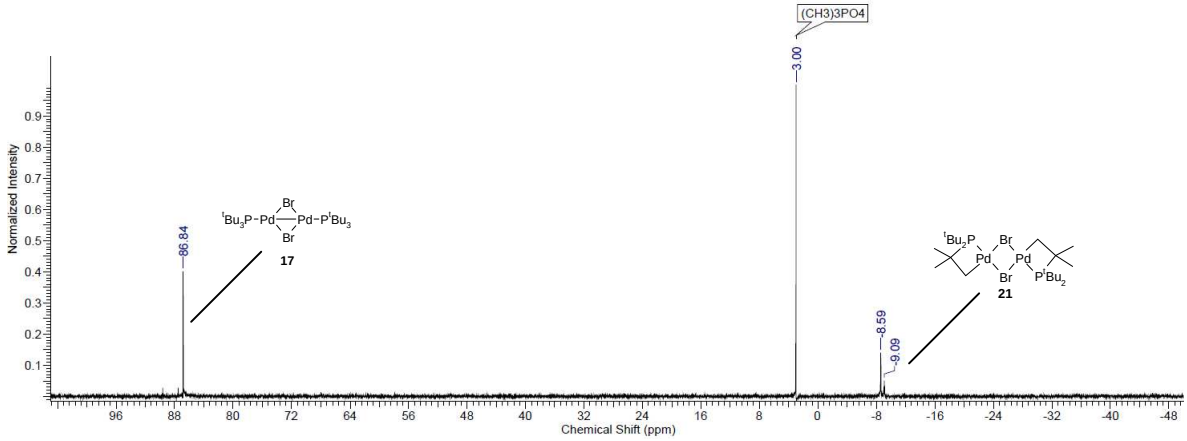


Reaction solution after 6 h:

^{1}H–NMR (600 MHz, toluene–d_8)



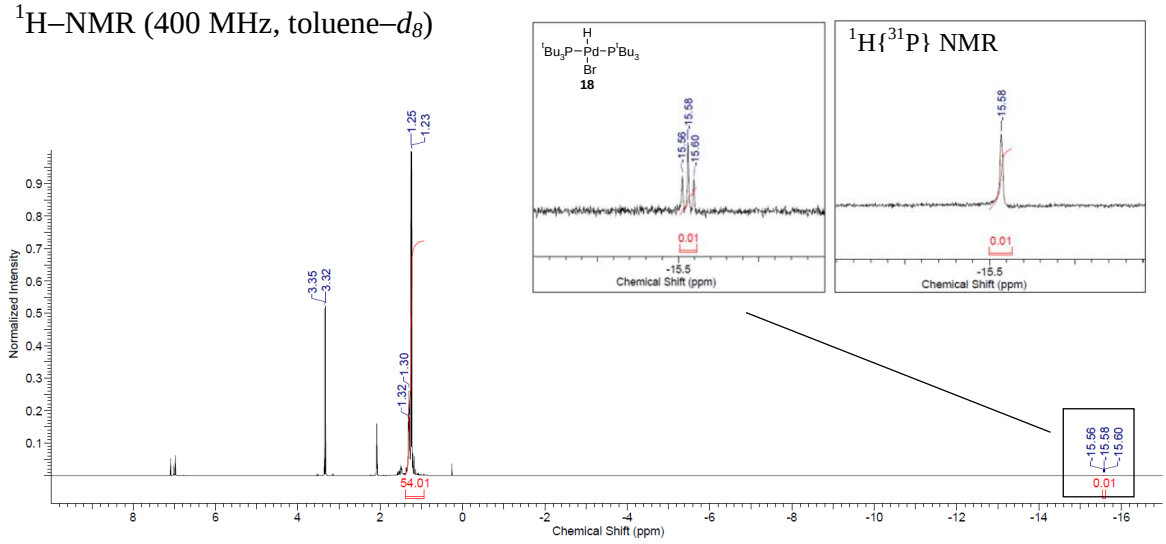
^{31}P–NMR (243 MHz, toluene–d_8)



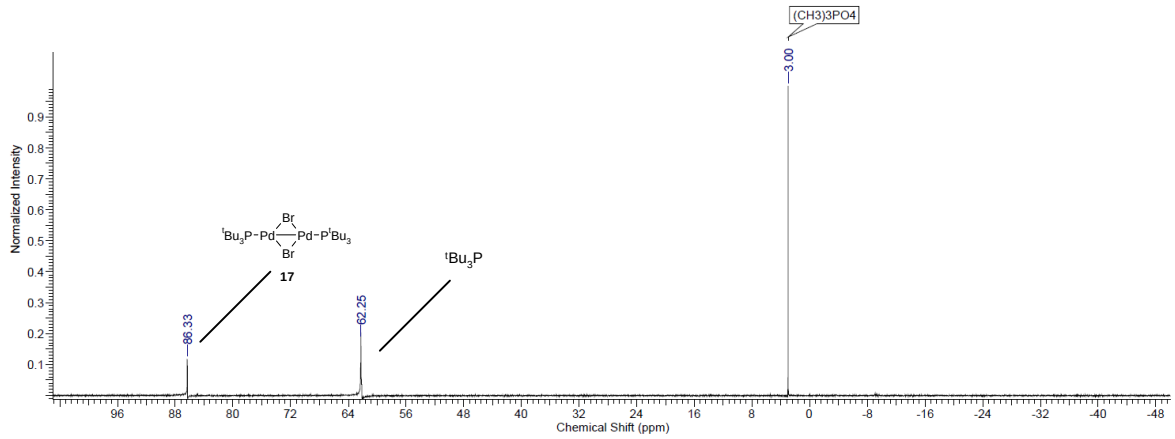
Formation of the Pd–hydride species 18 by addition of $^{t}Bu_3P$ to the Pd(I)–dimer 4.1.8–17:

Under an argon atmosphere, a NMR tube was charged with di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (**4.1.8–17**) (10.0 mg, 12.0 µmol), tri–*t*–butylphosphine (12 µl, 10.0 mg, 0.05 mmol), toluene–d_8 (0.4 mL) and trimethylphosphate (1.5 µl, 12.0 µmol) as internal standard. The dark green solution was left in an ultrasonic bath for 1 min and the NMR spectra were measured after 2 h at 25°C.

^{1}H–NMR (400 MHz, toluene–d_8)



^{31}P–NMR (162 MHz, toluene–d_8)

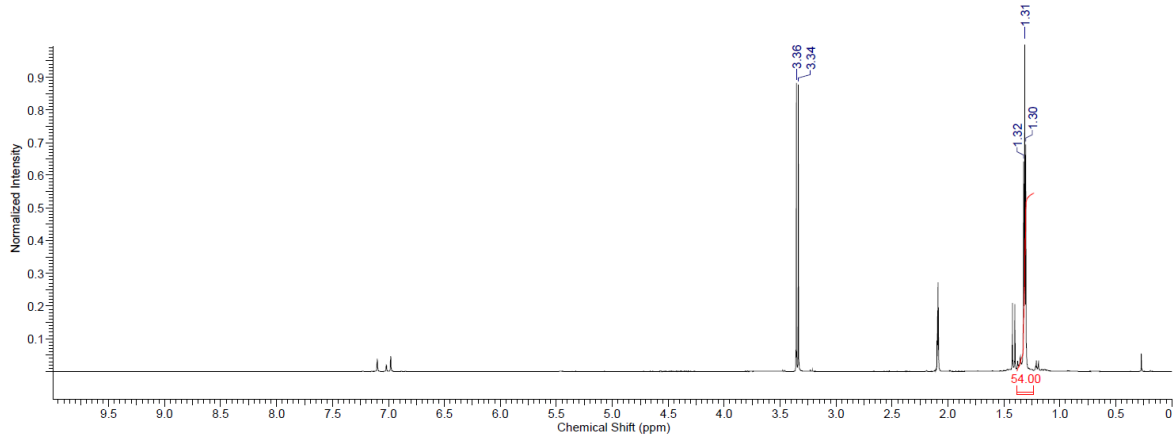


Formation of the Pd–cycle 21 from the Pd(I)–dimer 4.1.8–17:

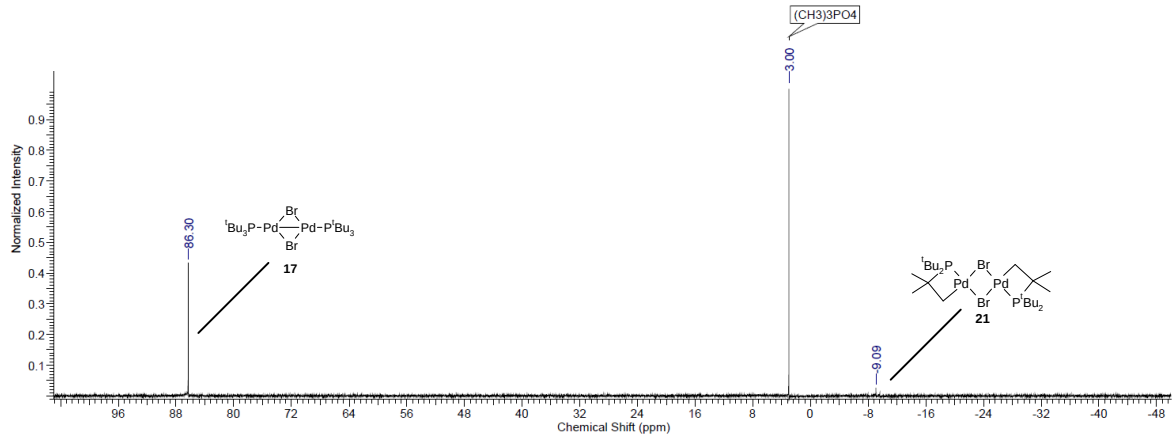
Under an argon atmosphere, a NMR tube was charged with di–μ–bromobis(tri–*tert*butylphosphine)dipalladium(I) (**4.1.8–17**) (10.0 mg, 12.0 µmol) in toluene–d_8 (0.5 mL) and trimethylphosphate (1.5 µl, 12.0 µmol) as internal standard. The dark green solution was left in an ultrasonic bath for 1 min and the NMR spectra were measured after 15 min at 25°C. During 7 days at room temperature, the solution changed slowly from dark green to yellow with a black precipitate. NMR spectra were measured again after 7 days.

After 15 min:

^{1}H–NMR (600 MHz, toluene–d_8)

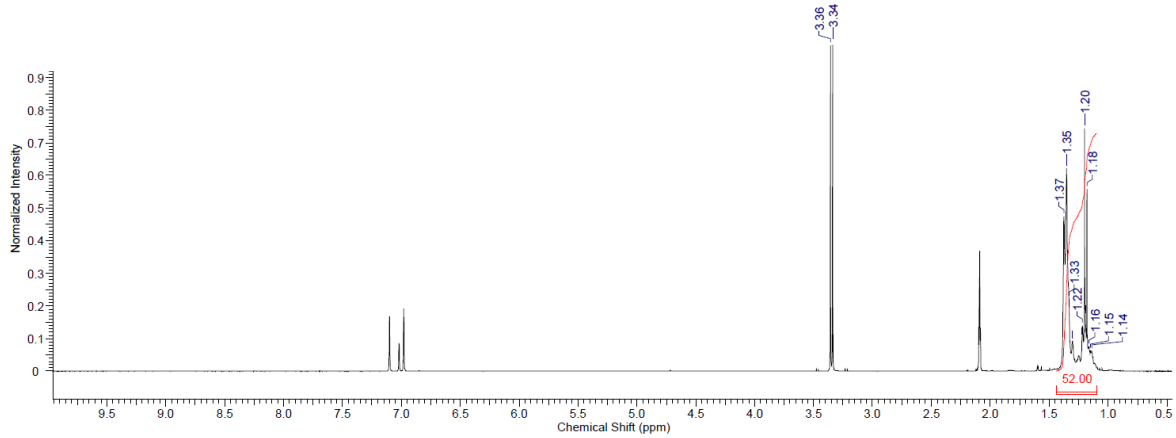


^{31}P–NMR (243 MHz, toluene–d_8)

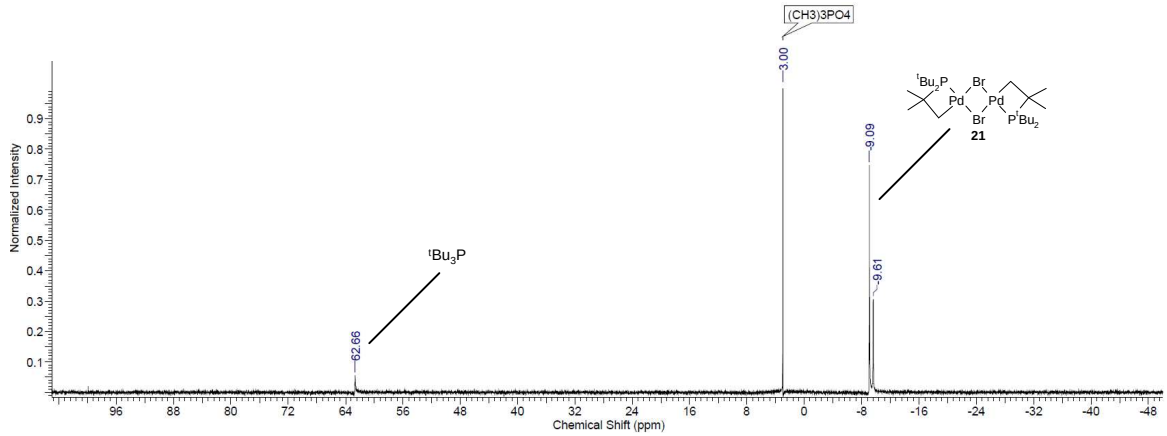


After 7 days:

^{1}H–NMR (400 MHz, toluene–d_8)



^{31}P–NMR (162 MHz, toluene–d_8)



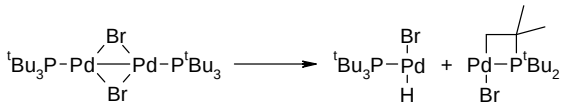
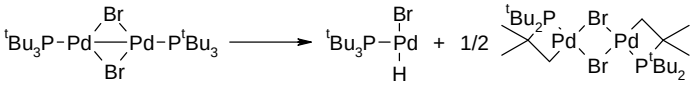
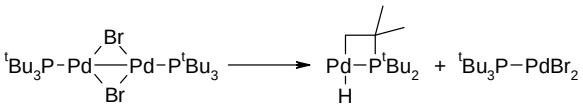
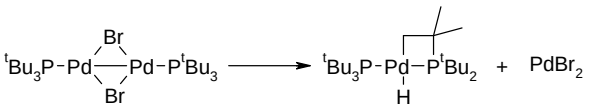
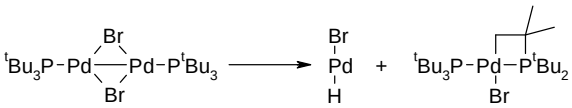
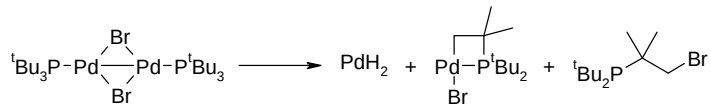
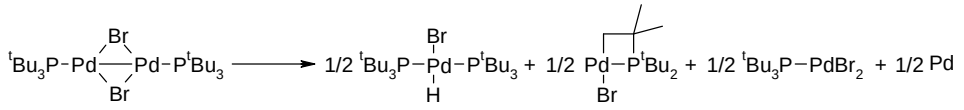
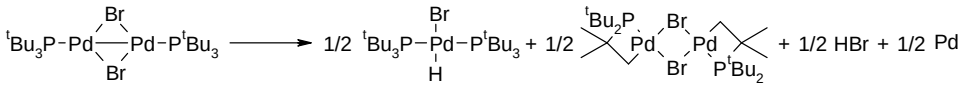
6.8.6.2. Quantum chemical calculations

All calculations were performed with the Gaussian 09[299] program package and the B3LYP density functional.[300–302] The atoms H, C, Br and P were described by the 6–31G(d) basis,[303] while the Stuttgart RSC 1997 ECP pseudopotential was used to represent Pd.[304] All geometries were fully optimized. Harmonic force constants were calculated for the optimized geometries to characterize the stationary points as minima. Thermal corrections from the frequency calculations were scaled with Wong's scaling factor (f = 0.9804) for B3LYP/6–31G(d).[305] Additional single point energy calculation were performed on all structures employing the 6–311+G(2d,p) basis[306] for the atoms H, C, Br and P. All ball and stick models were rendered with GaussView 5.[307] Total energies (hartree) from B3LYP/6–311+G(2d,p) single point energy calculations, unscaled thermal corrections (hartree) from B3LYP/6–31G(d) frequency calculations at 298.15 K and page numbers for the optimized coordinates:

Structure	**Total energy**	E_{298}	U_{298}	H_{298}	G_{298}
$[Pd(\mu\text{–}Br)(P^tBu_3)]_2$ (**4.1.8–17**)	–7034.43207729	0.749785	0.795301	0.796245	0.673294
$Pd(H)(Br)(P^tBu_3)_2$ (**4.1.8–18**)	–4332.86843616	0.757315	0.798411	0.799355	0.689714
$Pd(H)(Br)(P^tBu_3)$ (**4.1.8–19**)	–3517.79697051	0.381341	0.403782	0.404726	0.331892
$Pd(Br)(P^tBu_2(C(CH_3)_2CH_2))$ (**4.1.8–20**)	–3516.58376759	0.362050	0.383413	0.384357	0.313285
$[Pd(\mu\text{–}Br)(P^tBu_2(C(CH_3)_2CH_2))]_2$ (**4.1.8–21**)	–7033.21630315	0.724382	0.769125	0.770069	0.647018
$Pd(H)(P^tBu_2(C(CH_3)_2CH_2))$ (**4.1.8–22**)	–942.96134861200	0.367909	0.387469	0.388413	0.323293
$Pd(Br)_2(P^tBu_3)$ (**4.1.8–23**)	–6091.37078319000	0.376391	0.400067	0.401011	0.324586
$Pd(H)(P^tBu_2(C(CH_3)_2CH_2))(P^tBu_3)$ (**4.1.8–24**)	–1758.04083621000	0.741416	0.780156	0.781100	0.676987
$PdBr_2$ (**4.1.8–25**)	–5276.22142443000	0.001224	0.005905	0.006849	–0.025140
Pd(H)(Br) (**4.1.8–26**)	–2702.63184157000	0.009088	0.012408	0.013352	–0.012302
$Pd(Br)(P^tBu_2(C(CH_3)_2CH_2))(P^tBu_3)$(**4.1.8–27**)	–4331.64976879000	0.736801	0.777206	0.778150	0.669691
PdH_2 (**4.1.8–28**)	–129.01178247200	0.010431	0.013308	0.014252	–0.005530
$C(CH_3)_2CH_2Br$ (**4.1.8–29**)	–3388.58601023000	0.362534	0.381607	0.382551	0.317906
P^tBu_3 (**4.1.8–30**)	–815.046504713	0.371565	0.389381	0.390325	0.331192
H_2 (**4.1.8–31**)	–1.17956995577	0.010141	0.012501	0.013446	–0.001347
HBr (**4.1.8–32**)	–2574.74891680	0.005893	0.008254	0.009198	–0.013345
Pd (**4.1.8–33**)	–127.886371702	0.000000	0.001416	0.002360	–0.016592

E_{298} unscaled zero–point vibrational energy correction at 298.15 K
U_{298} unscaled thermal correction to energy at 298.15 K
H_{298} unscaled thermal correction to enthalpy at 298.15 K
G_{298} unscaled thermal correction to Gibbs free enthalpy at 298.15 K

Standard Gibbs free energies of reaction ($\Delta_R G^{\Theta}$ / kcal mol^{-1}) for the formation of various Pd–hydride species from the Pd^{I} dimer complex [Pd(μ–Br)(P^{t}Bu$_3$)]$_2$ (**4.1.8–17**):

Formation of Pd–hydride species	$\Delta_R G^{\theta}$
 **4.1.8-17** **4.1.8-19** **4.1.8-20**	14.9
 **4.1.8-17** **4.1.8-19** **4.1.8-21**	5.9
 **4.1.8-17** **4.1.8-22** **4.1.8-23**	47.1
 **4.1.8-17** **4.1.8-24** **4.1.8-25**	93.4
 **4.1.8-17** **4.1.8-26** **4.1.8-27**	84.6
 **4.1.8-17** **4.1.8-28** **4.1.8-20** **4.1.8-29**	127.9
 **4.1.8-17** **4.1.8-18** **4.1.8-20** **4.1.8-23** **4.1.8-33**	37.6
 **4.1.8-17** **4.1.8-18** **4.1.8-21** **4.1.8-32** **4.1.8-33**	33.0

6.9. Sandmeyer Trifluoromethylation of Arenediazonium Tetrafluoroborates

6.9.1. General Methods

The diazonium salts were prepared from the corresponding anilines following the procedures below and were directly used. All other starting materials were commercially available. All the anilines and solvents were purified by distillation or sublimation prior to use. The others chemicals were used without further purification.

6.9.2. Synthesis of arenediazonium tetrafluoroborates

Procedure A

In an Erlenmeyer flask, the aniline (10 mmol) was dissolved in an aqueous solution of HBF_4 (50%, 5 mL, 40 mmol) and a saturated solution of sodium nitrite (760 mg, 11 mmol) was added dropwise at 0°C. The excess of oxidant was removed by the addition of urea. Then, the precipitated diazonium salt was filtered off and dissolved in the less amount of acetone. Diethyl ether was added to the clear solution, causing the precipitation of the arenediazonium tetrafluoroborate that was filtered off and washed with diethyl ether (3 × 10 mL). The arenediazonium tetrafluoroborate was dried *in vacuo* (10^{-3} mbar) for 10 minutes and was then directly used without further purification.

Procedure B

In a 50 mL round–bottom flask, the aniline (10 mmol) was dissolved in a mixture of absolute ethanol (3 mL) and an aqueous solution of HBF_4 (50%, 2.5 mL, 20 mmol) and *tert*–butyl nitrite (2.7 mL, 20 mmol) was added dropwise to the solution at 0°C. The reaction was stirred at room temperature for 1h and diethyl ether (20 mL) was added to precipitate the arenediazonium tetrafluoroborate that was filtered off and washed with diethyl ether (3 × 10 mL). The arenediazonium tetrafluoroborate was dried *in vacuo* (10^{-3} mbar) for 10 minutes and was then directly used without further purification.

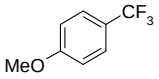
6.9.3. Synthesis of benzotrifluorides

Standard procedure for the synthesis of benzotrifluorides from the corresponding arenediazonium salts

An oven–dried 20 mL crimp cap vessel with Teflon–coated stirrer bar was charged with copper thiocyanate (73.5 mg, 0.60 mmol) and cesium carbonate (489 mg, 1.50 mmol) and was brought under an atmosphere of dry nitrogen. Acetonitrile (2 mL) and trifluoromethyltrimethylsilane (240 µL, 1.50 mmol) were added via syringe under nitrogen. The resulting suspension was stirred at room temperature for 10 minutes and a solution of the arenediazonium tetrafluoroborate (1 mmol) in acetonitrile (2 mL) was added dropwise via syringe. The reaction mixture was stirred at ambient temperature for 16 h. The resulting mixture was filtered through a short pad of celite (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (3 × 10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40°C). The residue was further purified by flash chromatography (SiO_2, pentane/diethyl ether gradient), yielding the corresponding benzotrifluorides.

Synthesis of 1–methoxy–4–(trifluoromethyl)benzene (4.2.2–2)

[CAS: 402–52–8]



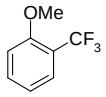
Compound **4.2.2–2** was prepared following the standard procedure, starting from 4–methoxybenzenediazonium tetrafluoroborate [CAS: 459–64–3] (444 mg, 2.00 mmol) prepared by **procedure A**. After purification, **4.2.2–2** was isolated as colourless liquid (286 mg, 1.62 mmol, 81%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ= 7.56 (d, ^3J(H,H)=8.5 Hz, 2H), 6.97 (d, ^3J(H,H)=8.5 Hz, 2H), 3.86 ppm (s, 3H; CH_3); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -61.5 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 162.0, 126.9 (q, ^3J(C,F)=3.6 Hz, 2C), 124.5 (q, ^1J(C,F)=270.6 Hz, 1C), 122.8 (q, ^2J(C,F)=32.7 Hz, 1C), 113.9 (2C), 55.4 ppm; **MS** (Ion trap, EI): m/z (%) = 176

[M^+](68), 157 (100), 146 (75), 145 (77), 113 (89), 83 (43), 63 (67); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_8H_7F_3O$, 176.0449; found, 176.0448.

Synthesis of 1–methoxy–2–(trifluoromethyl)benzene (4.2.2–3)

[CAS: 395–48–2]

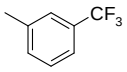


Compound **4.2.2–3** was prepared following the standard procedure, starting from 2–methoxybenzenediazonium tetrafluoroborate [CAS: 492–95–5] (111 mg, 0.50 mmol) prepared by **procedure B**. After the reaction, trifluoroethanol as internal standard (36 µL, 0.5 mmol) was added to the reaction mixture and the trifluoromethylated product **4.2.2–3** was formed in 57% yield as determined by ^{19}F–NMR spectroscopic analysis and confirmed by GC–MS analytics.

^{19}F–NMR (376 MHz, DMSO–d_6): δ = -62.9 ppm; **MS** (Ion trap, EI): m/z (%) = 176 [M^+] (9), 175 (100), 156 (8), 132 (8), 126 (8), 113 (9), 112 (10).

Synthesis of 1–methyl–3–(trifluoromethyl)benzene (4.2.2–4)

[CAS: 401–79–6]

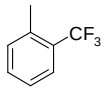


Compound **4.2.2–4** was prepared following the standard procedure, starting from 3–methylbenzenediazonium tetrafluoroborate [CAS: 1422–76–0] (103 mg, 0.50 mmol) prepared by **procedure A**. After the reaction, trifluoroethanol as internal standard (36 µL, 0.5 mmol) was added to the reaction mixture and the trifluoromethylated product **4.2.2–4** was formed in 98% yield as determined by ^{19}F–NMR spectroscopic analysis and confirmed by GC–MS analytics.

^{19}F–NMR (376 MHz, DMSO–d_6): δ = -63.1 ppm; **MS** (Ion trap, EI): m/z (%) = 160 [M^+] (7), 159 (100), 140 (14), 108 (10), 91 (8), 68 (8), 64 (10).

Synthesis of 1–methyl–2–(trifluoromethyl)benzene (4.2.2–5)

[CAS: 5140–17–6]

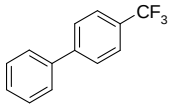


Compound **4.2.2–5** was prepared following the standard procedure, starting from 2–methylbenzenediazonium tetrafluoroborate [CAS: 2093–46–1] (103 mg, 0.50 mmol) prepared by **procedure A**. After the reaction, trifluoroethanol as internal standard (36 µL, 0.5 mmol) was added to the reaction mixture and the trifluoromethylated product **4.2.2–5** was formed in 75% yield as determined by ^{19}F–NMR spectroscopic analysis and confirmed by GC–MS analytics.

^{19}F–NMR (376 MHz, DMSO–d_6): δ = -62.1 ppm; **MS** (Ion trap, EI): m/z (%) = 160 [M^+] (8), 159 (100), 140 (13), 139 (10), 108 (9), 91 (12), 64 (8).

Synthesis of 4–(trifluoromethyl)biphenyl (4.2.2–6)

[CAS: 398–36–7]

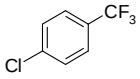


Compound **4.2.2–6** was prepared following the standard procedure, starting from [1,1'–biphenyl]–4–diazonium tetrafluoroborate (268 mg, 1.00 mmol) prepared by **procedure B**. After purification, **4.2.2–6** was isolated as colourless solid (173 mg, 0.78 mmol, 78%).

m.p. 69–70 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ = 7.80–7.72 (m, 4H), 7.57–7.63 (m, 2H), 7.58–7.51 (m, 2H), 7.51–7.44 ppm (m, 1H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ = -62.3 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 144.7, 139.7, 129.3 (q, ^2J(C,F)=32.7 Hz, 1C), 129.0 (2C), 128.2, 127.4 (2C), 127.3 (2C), 125.7 (q, ^3J(C,F)=3.6 Hz, 2C), 124.4 ppm (q, ^1J(C,F)=272.5 Hz, 1C); **IR** ν = 1614 (w), 1327 (m), 1273 (m), 1112 (vs), 1073 (s), 843 (s), 767 (s), 727 (vs), 689 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 223 [M^+] (14), 222 (100), 203 (5), 153 (9), 152 (11), 69 (5), 50 (6); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{13}H_9F_3$, 222.0656; found, 222.0657.

Synthesis of 1–chloro–4–(trifluoromethyl)benzene (4.2.2–7)

[CAS: 98–56–6]

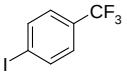


Compound **4.2.2–7** was prepared following the standard procedure, starting from 4–chlorobenzenediazonium tetrafluoroborate [CAS: 673–41–6] (113 mg, 0.50 mmol) prepared by **procedure A**. After the reaction, trifluoroethanol as internal standard (36 µL, 0.5 mmol) was added to the reaction mixture and the trifluoromethylated product **4.2.2–7** was formed in 98% yield as determined by ^{19}F–NMR spectroscopic analysis and confirmed by GC–MS analytics.

^{19}F–NMR (376 MHz, DMSO–d_6): δ = -63.1 ppm; **MS** (Ion trap, EI): m/z (%) = 182 [M^+] (32), 180 [M^+] (100), 161 (33), 145 (41), 130 (23), 75 (23), 50 (20).

Synthesis of 1–iodo–4–(trifluoromethyl)benzene (4.2.2–8)

[CAS: 455–13–0]

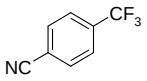


Compound **4.2.2–8** was prepared following the standard procedure, starting from 4–iodobenzenediazonium tetrafluoroborate [CAS: 1514–50–7] (649 mg, 2.00 mmol) prepared by **procedure A**. After chromatography, **4.2.2–8** was obtained as light yellow liquid (373 mg, 1.37 mmol, 69%) which contained traces of diiodobenzene that can be removed by low temperature crystallization from pentane.

^{1}H–NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, ^3J(H,H)=8.1 Hz, 2H), 7.36 ppm (d, ^3J(H,H)=8.1 Hz, 2H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ = -63.0 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 138.0 (2C), 130.2 (q, ^2J(C,F)=33.0 Hz, 1C), 126.8 (q, ^3J(C,F)=3.7 Hz, 2C), 124.0 (q, ^1J(C,F)=272.2 Hz, 1C), 98.6 ppm (q, J(C,F)=2.2 Hz, 1C); **MS** (Ion trap, EI): m/z (%) = 272 [M^+] (7), 271 (100), 252 (3), 145 (2), 144 (7), 143 (3), 75 (3); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_7H_4F_3I$, 271.9310; found, 271.9303.

Synthesis of 4–(trifluoromethyl)benzonitrile (4.2.2–9)

[CAS: 455–18–5]

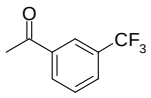


Compound **4.2.2–9** was prepared following the standard procedure, starting from 4–cyanobenzenediazonium tetrafluoroborate [CAS: 2252–32–6] (108 mg, 0.50 mmol) prepared by **procedure B**. After purification, **4.2.2–9** was isolated as colourless solid (58 mg, 0.34 mmol, 68%).

m.p. 38–39 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 7.83 (d, ^{3}J(H,H)=8.3 Hz, 2H), 7.77 ppm (d, ^{3}J(H,H)=8.5 Hz, 2H); **^{19}F–NMR** (376 MHz, DMSO–d_6): δ= -63.9 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 134.6 (q, ^{2}J(C,F)=33.0 Hz, 1C), 132.7 (2C), 126.2 (q, ^{3}J(C,F)=4.4 Hz, 2C), 123.0 (q, ^{1}J(C,F)=272.9 Hz, 1C), 117.4, 116.0 ppm (q, J(C,F)=1.5 Hz, 1C); **MS** (Ion trap, EI): m/z (%) = 171 [M^+] (9), 170 (100), 152 (23), 121 (32), 75 (11), 69 (10), 50 (13); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_8H_4F_3N$, 171.0296; found, 171.0299

Synthesis of 3–(trifluoromethyl)acetophenone (4.2.2–10)

[CAS: 349–76–8]



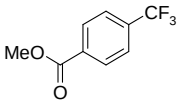
Compound **4.2.2–10** was prepared following the standard procedure, starting from 3–acetylbenzenediazonium tetrafluoroborate[308] (234 mg, 1.00 mmol) prepared by **procedure B**. After purification, **4.2.2–10** was isolated as colourless liquid (126 mg, 0.67 mmol, 67%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ= 8.22 (s, 1H), 8.15 (d, ^{3}J(H,H)=7.8 Hz, 1H), 7.83 (d, ^{3}J(H,H)=7.8 Hz, 1H), 7.63 (t, ^{3}J(H,H)=7.8 Hz, 1H), 2.66 ppm (s, 3H, CH_3); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -62.8 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 196.6, 137.5, 131.4, 131.2 (q, ^{2}J(C,F)=32.7 Hz, 1C), 129.5 (q, ^{3}J(C,F)=3.6 Hz, 1C), 129.3, 125.1 (q, ^{3}J(C,F)=3.6 Hz, 1C), 123.7 (q, ^{1}J(C,F)=272.5 Hz, 1C), 26.6 ppm; **MS** (Ion trap, EI): m/z (%) = 188 [M^+] (9), 173

(33), 169 (24), 145 (100), 75 (21), 50 (22), 43 (38); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_9H_7F_3O$, 188.0449; found, 188.0446.

Synthesis of methyl 4–(trifluoromethyl)benzoate (4.2.2–11)

[CAS: 2967–66–0]

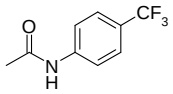


Compound **4.2.2–11** was prepared following the standard procedure, starting from 4–(methoxycarbonyl)benzenediazonium tetrafluoroborate[309] (250 mg, 1.00 mmol) prepared by **procedure A**. After purification, **4.2.2–11** was isolated as colourless liquid (144 mg, 0.71 mmol, 71%) but contained traces of methyl benzoate, which was not easily separable by chromatography on silica gel.

^{1}H–NMR (400 MHz, $CDCl_3$): δ= 8.16 (d, ^3J(H,H)=8.2 Hz, 2H), 7.72 (d, ^3J(H,H)= 8.3 Hz, 2H), 3.97 ppm (s, 3H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -63.1 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 165.9, 134.4 (q, ^2J(C,F)=32.7 Hz, 1C), 133.3, 130.0 (2C), 125.4 (q, ^3J(C,F)=3.6 Hz, 2C), 123.6 (q, ^1J(C,F)=272.5 Hz, 1C), 52.5 ppm; **MS** (Ion trap, EI): m/z (%) = 204 [M^+] (11), 203 (11), 185 (17), 174 (9), 173 (100), 145 (32), 75 (7); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_9H_7F_3O_2$, 204.0398; found, 204.0395.

Synthesis of methyl 4–(trifluoromethyl)acetanilide (4.2.2–12)

[CAS: 349–97–3]



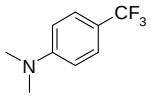
Compound **4.2.2–12** was prepared following the standard procedure, starting from 4–acetamidobenzenediazonium tetrafluoroborate (249 mg, 1.00 mmol) prepared by **procedure B**. After purification, **4.2.2–12** was isolated as colourless solid (81 mg, 0.4 mmol, 40%).

m.p. 150–151 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 7.70 (br. s, 1H; NH), 7.64 (d, ^3J(H,H)=8.5 Hz, 2H), 7.56 (d, ^3J(H,H)=8.7 Hz, 2H), 2.21 ppm (s, 3H; CH_3); **^{19}F–NMR**

(376 MHz, $CDCl_3$): δ= -62.1 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 168.7, 140.9, 126.2 (q, ^3J(C,F)=3.6 Hz, 2C), 125.9, 124.0 (q, ^1J(C,F)=271.6 Hz, 1C), 119.3 (2C), 24.6 ppm; **IR** ν= 3319 (m), 1673 (s), 1602 (m), 1529 (m), 1408 (m), 1317 (s), 1111 (vs), 1068 (s), 833 (s), 677 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 203 [M^+] (9), 202 (62), 183 (9), 160 (100), 110 (15), 44 (10), 43 (33); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_9H_8F_3NO$, 203.0558; found, 203.0557.

Synthesis of N,N–dimethyl–4–(trifluoromethyl)aniline (4.2.2–13)

[CAS: 329–17–9]

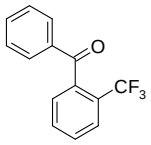


Compound **4.2.2–13** was prepared following the standard procedure, starting from 4–(dimethylamino)benzenediazonium tetrafluoroborate [CAS: 24564–52–1] (470 mg, 2.00 mmol) prepared by **procedure A**. After purification, **4.2.2–13** was isolated as colourless solid (358 mg, 1.89 mmol, 95%).

m.p. 69–70 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 7.51 (d, ^3J(H,H)=9.0 Hz, 2H), 6.74 (d, ^3J(H,H)=9.0 Hz, 2H), 3.04 ppm (s, 6H; CH_3); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -60.7 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 152.3, 126.2 (q, ^3J(C,F)=3.6 Hz, 2C), 125.3 (q, ^1J(C,F)=269.8 Hz, 1C), 117.3 (q, ^2J(C,F)=32.7 Hz, 1C), 111.1 (2C), 32.9 ppm (2C); **IR** ν= 1615 (m), 1535 (w), 1324 (s), 1232 (m), 1195 (m), 1156 (m), 1094 (vs), 1064 (vs), 940 (m), 816 cm^{-1} (vs); **MS** (Ion trap, EI): m/z (%) = 189 [M^+] (43), 188 (100), 172 (11), 170 (7), 145 (8), 119 (8), 118 (10); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_9H_{10}F_3N$, 189.0765; found, 189.0753.

Synthesis of phenyl(2–(trifluoromethyl)phenyl)methanone (4.2.2–14)

[CAS: 727–99–1]

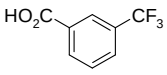


Compound **4.2.2–14** was prepared following the standard procedure, starting from 2–benzoylbenzenediazonium tetrafluoroborate [CAS: 342–62–1] (296 mg, 1.00 mmol) prepared by **procedure B**. After purification, **4.2.2–14** was isolated as colourless solid (184 mg, 0.74 mmol, 74%).

m.p. 60–61 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 7.83–7.76 (m, 3H), 7.67–7.58 (m, 3H), 7.50–7.44 (m, 2H), 7.42–7.38 ppm (m, 1H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -58 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 195.5, 138.3 (q, ^{3}J(C,F)=2.2 Hz, 1C), 136.4 (q, ^{4}J(C,F)=1.5 Hz, 1C), 133.8, 131.4, 130.2 (2 C), 130.0, 129.8, 128.5 (2 C), 128.2 (q, ^{2}J(C,F)=32.3 Hz, 1C), 126.7 (q, ^{3}J(C,F)=4.4 Hz, 1C), 123.6 ppm (q, ^{1}J(C,F)=273.6 Hz, 1C); **MS** (Ion trap, EI): m/z (%) = 250 [M^+] (18), 249 (100), 145 (31), 105 (17), 77 (86), 51 (37), 50 (30); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{14}H_9F_3O$, 250.0605; found, 250.0617.

Synthesis of 3–(trifluoromethyl)benzoic acid (4.2.2–15)

[CAS: 454–92–2]



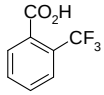
Compound **4.2.2–15** was prepared following the standard procedure, starting from 3–carboxybenzenediazonium tetrafluoroborate[310] (236 mg, 1.00 mmol) prepared by **procedure B**. After purification, **4.2.2–15** was isolated as colourless solid (139 mg, 0.73 mmol, 73%) but contained traces of benzoic acid, which was not easily separable by chromatography on silica gel.

m.p. 102–103 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 10.74 (br. s, 1H), 8.41 (s, 1H), 8.33 (d, ^{3}J(H,H)=7.8 Hz, 1H), 7.90 (d, ^{3}J(H,H)=7.8 Hz, 1H), 7.66 ppm (t, ^{3}J(H,H)=7.8 Hz, 1H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -62.9 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 170.9, 133.4,

131.3 (q, ^{2}J(C,F)=33.0 Hz, 1C), 130.4 (q, ^{3}J(C,F)=3.7 Hz, 1C), 130.1, 129.3, 127.2 (q, ^{3}J(C,F)=3.7 Hz, 1C), 123.5 ppm (q, ^{1}J(C,F)=272.2 Hz, 1C); **IR** ν = 1686 (vs), 1419 (w), 1334 (m), 1266 (vs), 1172 (s), 1120 (vs), 1072 (s), 920 (s), 759 (s), 684 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 190 [M^{+}] (77), 173 (100), 145 (39), 95 (12), 75 (14), 73 (11), 69 (10); **HRMS–EI** (TOF): m/z [M^{+}] calcd. for $C_8H_5F_3O_2$, 190.0242; found, 190.0237.

Synthesis of 2–(trifluoromethyl)benzoic acid (4.2.2–16)

[CAS: 433–97–6]

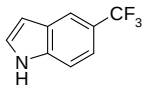


Compound **4.2.2–16** was prepared following the standard procedure, starting from 2–carboxybenzenediazonium tetrafluoroborate [CAS: 14783–89–2] (236 mg, 1.00 mmol) prepared by **procedure B**. After purification, **4.2.2–16** was isolated as colourless solid (166 mg, 0.87 mmol, 87%).

m.p. 106–107 °C; **^{1}H–NMR** (400 MHz, methanol–d_4): δ= 7.84–7.76 (m, 2H), 7.72–7.63 ppm (m, 2H); **^{19}F–NMR** (376 MHz, methanol–d_4): δ= -60.8 ppm; **^{13}C–NMR** (101 MHz, methanol–d_4): δ= 170.2, 133.7 (q, ^{3}J(C,F)=2.7 Hz, 1C), 133.4, 132.4, 131.2, 129.5 (q, ^{2}J(C,F)=32.7 Hz, 1C), 127.8 (q, ^{3}J(C,F)=5.5 Hz, 1C), 125.1 ppm (q, ^{1}J(C,F)=272.5 Hz, 1C); **IR** ν = 1698 (s), 1301 (s), 1284 (vs), 1275 (vs), 1168 (s), 1137 (s), 1125 (vs), 1107 (vs), 1056 (s), 1037 (vs), 764 (vs), 677 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 190 [M^{+}] (39), 151 (50), 145 (100), 95 (41), 75 (56), 50 (57), 45 (47); **HRMS–EI** (TOF): m/z [M^{+}] calcd. for $C_8H_5F_3O_2$, 190.0242; found, 190.0240.

Synthesis of 5–(trifluoromethyl)–1H–indole (4.2.2–17)

[CAS: 100846–24–0]

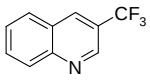


Compound **4.2.2–17** was prepared following the standard procedure, starting from 1H–indole–5–diazonium tetrafluoroborate (231 mg, 1.00 mmol) prepared by **procedure B**. After purification, **4.2.2–17** was isolated as colourless solid (85 mg, 0.46 mmol, 46%).

m.p. 70–71 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 8.35 (br. s, 1h; NH), 7.97 (m, 1H), 7.51–7.42 (m, 2H), 7.33 (m, 1H), 6.67 ppm (m, 1H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -60.3 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 137.1, 127.2, 125.8, 122.6 (q, ^{1}J(C,F)=271.6 Hz, 1C), 122.3 (q, ^{2}J(C,F)=31.8 Hz, 1C), 118.8 (q, ^{3}J(C,F)=3.6 Hz, 1C), 118.5 (q, ^{3}J(C,F)=4.5 Hz, 1C), 111.2, 103.6 ppm; **IR** ν = 3433 (m), 1423 (w), 1332 (s), 1160 (s), 1083 (vs), 1049 (vs), 816 (s), 742 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 185 [M^+] (100), 184 (14), 166 (25), 158 (7), 69 (8), 63 (8), 62 (7); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_9H_6F_3N$, 185.0452; found, 185.0452.

Synthesis of 3–(trifluoromethyl)quinoline (4.2.2–18)

[CAS: 25199–76–2]



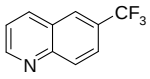
Compound **4.2.2–18** was prepared following the standard procedure, starting from quinoline–3–diazonium tetrafluoroborate[308] (243 mg, 1.00 mmol) prepared by **procedure B**. After purification, **4.2.2–18** was isolated as colourless solid (145 mg, 0.74 mmol, 74%).

m.p. 42–43 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 9.12(d, ^{4}J(H,H)=2.3 Hz, 1H), 8.49–8.46 (m, 1H), 8.21 (d, ^{3}J(H,H)=8.5 Hz, 1H), 7.95 (d, ^{3}J(H,H)=8.0 Hz, 1H), 7.91–7.85 (m, 1H), 7.72–7.66 ppm (m, 1H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -61.8 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 149.4, 146.1 (q, ^{3}J(C,F)=3.3 Hz, 1C), 134.0 (q, ^{3}J(C,F)=2.2 Hz, 1C), 131.8, 129.6, 128.6, 128.0, 126.3, 123.7 (q, ^{1}J(C,F)=272.2 Hz, 1C), 123.6 ppm (q, ^{2}J(C,F)=32.9 Hz, 1C) ; **MS**

(Ion trap, EI): m/z (%) = 198 [M^+] (15), 197 (100), 178 (13), 177 (11), 176 (11), 147 (12), 128 (14); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{10}H_6F_3N$, 197.0452; found, 197.0452.

Synthesis of 6–(trifluoromethyl)quinoline (4.2.2–19)

[CAS: 325–13–3]

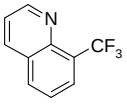


Compound **4.2.2–19** was prepared following the standard procedure, starting from quinoline–6–diazonium tetrafluoroborate[311] (243 mg, 1.00 mmol) prepared by **procedure B**. After purification, **4.2.2–19** was isolated as colourless solid (136 mg, 0.69 mmol, 69%).

^{1}H–NMR (400 MHz, $CDCl_3$): δ= 9.04(d, ^4J(H,H)=2.8 Hz, 1H), 8.30–8.20 (m, 2H), 8.15 (s, 1H), 7.89 (dd, $^{3,4}J$(H,H)=8.9, 1.9 Hz, 1H), 7.52 ppm (dd, $^{3,4}J$(H,H)=8.2, 4.1 Hz, 1H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -62.4 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 152.5, 149.2, 136.8, 130.7, 128.5 (q, ^2J(C,F)=32.7 Hz, 1C), 127.2, 125.8 (q, ^3J(C,F)=4.5 Hz, 1C), 125.1 (q, ^3J(C,F)=2.7 Hz, 1C), 123.9 (q, ^1J(C,F)=272.5 Hz, 1C), 122.3 ppm; **IR** ν = 1466 (w), 1429 (w), 1337 (s), 1144 (s), 1123 (s), 1106 (vs), 1062 (s), 840 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 197 [M^+] (70), 196 (43), 178 (59), 147 (100), 128 (40), 75 (45), 50 (48); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{10}H_6F_3N$, 197.0452; found, 197.0446.

Synthesis of 8–(trifluoromethyl)quinoline (4.2.2–20)

[CAS: 317–57–7]



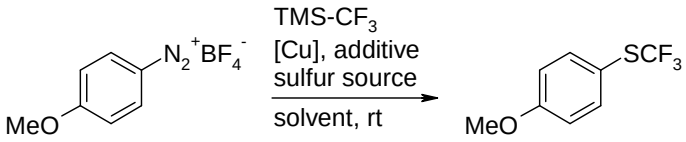
Compound **4.2.2–20** was prepared following the standard procedure, starting from quinoline–8–diazonium tetrafluoroborate (243 mg, 1.00 mmol) prepared by **procedure B**. After purification, **4.2.2–20** was isolated as colourless solid (110 mg, 0.56 mmol, 56%).

m.p. 64–65 °C; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 9.09 (dd, J(H,H)=4.3, 1.8 Hz, 1H), 8.23 (dd, $^{3,4}J$(H,H)=8.4, 1.9 Hz, 1H), 8.09 (d, ^3J(H,H)=7.3 Hz, 1H), 8.03 (d, ^3J(H,H)=8.3 Hz, 1H),

7.61 (t, ^{3}J(H,H)=7.8 Hz, 1H), 7.52 ppm (dd, $^{3,4}J$(H,H)=8.3, 4.3 Hz, 1H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -60.3 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 151.2, 144.7, 136.3, 132.4, 128.7, 128.0 (q, ^{3}J(C,F)=5.5 Hz, 1C), 127.7 (q, ^{2}J(C,F)=29.5 Hz, 1C), 125.2, 124.1 (q, ^{1}J(C,F)=273.4 Hz, 1C), 121.9 ppm; **IR** ν = 1331 (m), 1294 (m), 1205 (m), 1141 (m), 1117 (vs), 1067 (m), 981 (s), 831 (s), 797 (s), 767 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 197 [M^+] (100), 178 (23), 177 (21), 147 (41), 75 (13), 69 (15), 50 (14); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{10}H_6F_3N$, 197.0452; found, 197.0444.

6.10. Sandmeyer Trifluoromethylthiolation of Arenediazonium Salts with Sodium Thiocyanate and Ruppert–Prakash Reagent

6.10.1. Optimization of the reaction conditions



4.2.4-1 **4.2.4-2**

entry	[Cu]	sulfur source	additive	solvent	yield of 4.2.4–2 [%][a]
1[b]	CuSCN	S_8	CsF	MeCN	5
2[b]	"	Lawesson's reagent	"	"	traces
3[b]	"	Na_2S	"	"	0
4	"	NaSCN	"	"	30
5	"	KSCN	"	"	traces
6	"	NH_4SCN	"	"	traces
7	"	NaSCN	Cs_2CO_3	"	98
8	"	"	"	DMF	81
9	"	"	"	acetone	18
10	Cu(0)	"	"	MeCN	1
11	$CuSO_4$	"	"	"	10
12	CuOAc	"	"	"	85
13	CuI	"	"	"	6
14	CuSCN	"	–	"	0
15	"	–	Cs_2CO_3	"	0
16	–	NaSCN	"	"	0
17[c]	CuSCN	"	"	"	34
18[d]	"	"	"	"	98
19[e]	"	"	"	"	67

Reaction conditions: 0.5 mmol [Cu], 2 equiv. additive, 1.5 equiv. sulfur source, 2 mL solvent, RT, dropwise addition of 0.5 mmol **1** in 2 mL of solvent, then 2 equiv. $TMSCF_3$, 12h. [a] Yields were determined by ^{19}F–NMR using 1,3–difluorobenzene as internal standard. [b] $TMSCF_3$ added before **1**. [c] 1 equiv. Cs_2CO_3. [d] 0.5 equiv. CuSCN. [e] 0.1 equiv. CuSCN., Lawesson's reagent = 2,4–bis(4–methoxyphenyl)–1,3,2,4dithiadiphosphetane-2,4–dithione.

6.10.2. General Methods

The diazonium salts were prepared from the corresponding anilines following the procedure below and were directly used. All other starting materials were commercially available. All the anilines and solvents were purified by distillation or sublimation prior to use. The other chemicals were used without further purification.

6.10.3. Synthesis of arenediazonium tetrafluoroborates

In a 50 mL round–bottom flask, the aniline (10 mmol) was dissolved in a mixture of absolute ethanol (3 mL) and an aqueous solution of HBF_4 (50%, 2.5 mL, 20 mmol) and *tert*–butyl nitrite (2.7 mL, 20 mmol) was added dropwise to the solution at 0 °C. The reaction was stirred at room temperature for 1 h and diethyl ether (20 mL) was added to precipitate the arenediazonium tetrafluoroborate that was filtered off and washed with diethyl ether (3 × 10 mL). The arenediazonium tetrafluoroborate was dried *in vacuo* (10^{-3} mbar) for 10 minutes and was then directly used without further purification.

6.10.4. Synthesis of trifluoromethyl thioethers

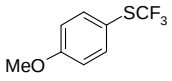
Standard procedure for the synthesis of trifluoromethyl thioethers from the corresponding arenediazonium salts

An oven–dried 20 mL crimp cap vessel with Teflon–coated stirrer bar was charged with copper thiocyanate (61.4 mg, 0.50 mmol), caesium carbonate (652 mg, 2.00 mmol) and sodium thiocyanate (122 mg, 1.50 mmol) and was brought under an atmosphere of dry nitrogen. Acetonitrile (4 mL) was added via syringe and the resulting suspension was stirred at room temperature for 10 minutes. A solution of the arenediazonium tetrafluoroborate (1.00 mmol) in acetonitrile (4 mL) was added dropwise via syringe and the reaction mixture was stirred for another 10 minutes. Trifluoromethyltrimethylsilane (321 µL, 2.00 mmol) was added at once via syringe and the mixture was then stirred at ambient temperature for 16 h. The resulting mixture was filtered through a short pad of celite (5 g) and rinsed with diethyl ether (20 mL). The resulting organic solution was washed with water (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated (700 mbar, 40 °C). The residue was further

purified by flash chromatography (SiO_2, diethyl ether/hexane gradient), yielding the corresponding trifluoromethyl thioethers.

Synthesis of 1–methoxy–4–[(trifluoromethyl)thio]benzene (4.2.4–2)

[CAS: 78914–94–0]

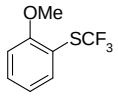


Compound **4.2.4–2** was prepared following the standard procedure, starting from 4–methoxybenzenediazonium tetrafluoroborate [CAS: 459–64–3] (222 mg, 1.00 mmol). After purification, **4.2.4–2** was isolated as colourless liquid (171 mg, 0.82 mmol, 82%).

Rf (SiO_2, hexane:diethyl ether = 4:1): 0.43; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 7.59 (d, ^3J(H,H)=8.8 Hz, 2H), 6.95 (d, ^3J(H,H)=8.8 Hz, 2H), 3.85 ppm (s, 3H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -44.0 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 161.8, 138.3 (2C), 129.6 (q, ^1J(C,F)=308.8 Hz, 1C), 115.0 (2C), 114.8 (q, ^3J(C,F)=1.8 Hz, 1C), 55.4 ppm; **MS** (Ion trap, EI): m/z (%) = 208 [M^+] (10), 207 (100), 138 (75), 123 (10), 95 (14), 69 (9), 68 (25); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_8H_7F_3OS$, 208.0170; found, 208.0172.

Synthesis of 1–methoxy–2–[(trifluoromethyl)thio]benzene (4.2.4–3)

[CAS: 75168–99–9]

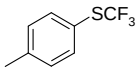


Compound **4.2.4–3** was prepared following the standard procedure, starting from 2–methoxybenzenediazonium tetrafluoroborate [CAS: 492–95–5] (222 mg, 1.00 mmol). After the reaction, 1,3–difluorobenzene as internal standard (100 µL, 1.00 mmol) was added to the reaction mixture and product **4.2.4–3** was formed in 77% yield as determined by ^{19}F–NMR spectroscopic analysis and confirmed by GC–MS analytics.

^{19}F–NMR (376 MHz, DMSO–d_6): δ= -43.3 ppm; **MS** (Ion trap, EI): m/z (%) = 208 [M^+] (11), 207 (100), 138 (13), 111 (31), 109 (8), 95 (8), 68 (13).

Synthesis of 4–[(trifluoromethyl)thio]toluene (4.2.4–4)

[CAS: 352–68–1]

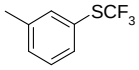


Compound **4.2.4–4** was prepared following the standard procedure, starting from 4–methylbenzenediazonium tetrafluoroborate [CAS: 459–44–9] (206 mg, 1.00 mmol). After the reaction, 1,3–difluorobenzene as internal standard (100 µL, 1.00 mmol) was added to the reaction mixture and product **4.2.4–4** was formed in 98% yield as determined by ^{19}F–NMR spectroscopic analysis and confirmed by GC–MS analytics.

^{19}F–NMR (376 MHz, DMSO–d_6): δ= -44.0 ppm; **MS** (Ion trap, EI): m/z (%) = 191 [M^+] (100), 122 (56), 91 (20), 79 (13), 77 (9), 69 (17), 44 (22).

Synthesis of 3–[(trifluoromethyl)thio]toluene (4.2.4–5)

[CAS: 705–46–4]

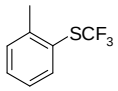


Compound **4.2.4–5** was prepared following the standard procedure, starting from 3–methylbenzenediazonium tetrafluoroborate [CAS: 1422–76–0] (206 mg, 1.00 mmol). After the reaction, 1,3–difluorobenzene as internal standard (100 µL, 1.00 mmol) was added to the reaction mixture and product **4.2.4–5** was formed in 98% yield as determined by ^{19}F–NMR spectroscopic analysis and confirmed by GC–MS analytics.

^{19}F–NMR (376 MHz, DMSO–d_6): δ= -43.6 ppm; **MS** (Ion trap, EI): m/z (%) = 191 [M^+] (100), 122 (34), 91 (28), 79 (10), 77 (9), 69 (15), 44 (27).

Synthesis of 2–[(trifluoromethyl)thio]toluene (4.2.4–6)

[CAS: 1736–75–0]

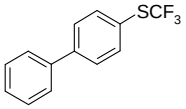


Compound **4.2.4–6** was prepared following the standard procedure, starting from 2–methylbenzenediazonium tetrafluoroborate [CAS: 2093–46–1] (206 mg, 1.00 mmol). After the reaction, 1,3–difluorobenzene as internal standard (100 µL, 1.00 mmol) was added to the reaction mixture and product **4.2.4–6** was formed in 92% yield as determined by ^{19}F–NMR spectroscopic analysis and confirmed by GC–MS analytics.

^{19}F–NMR (376 MHz, DMSO–d_6): δ = -43.3 ppm; **MS** (Ion trap, EI): m/z (%) = 192 [M^+] (9), 191 (100), 122 (55), 91 (8), 77 (8), 68 (14), 44 (39).

Synthesis of 4–[(trifluoromethyl)thio]biphenyl (4.2.4–7)

[CAS: 177551–63–2]

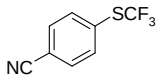


Compound **4.2.4–7** was prepared following the standard procedure, starting from [1,1'–biphenyl]–4–diazonium tetrafluoroborate [CAS: 52053–64–2] (268 mg, 1.00 mmol). After purification, **4.2.4–7** was isolated as colourless solid (187 mg, 0.74 mmol, 74%).

m.p. 41–42 °C; **Rf** (SiO_2, hexane:diethyl ether = 4:1): 0.57; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ = 7.79 (d, ^3J(H,H)=8.3 Hz, 2H), 7.67 (m, 4H), 7.53 (m, 2H), 7.47 ppm (m, 1H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ = -42.6 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 143.8, 139.6, 136.7 (2C), 129.6 (q, ^1J(C,F)=308.8 Hz, 1C), 128.9 (2C), 128.1, 128.1 (2C), 127.2 (2C), 123.0 ppm (q, ^3J(C,F)=1.8 Hz, 1C); **IR** ν = 1477 (w), 1395 (w), 1123 (s), 1105 (vs), 1080 (vs), 836 (m), 759 (vs), 715 (m), 689 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 255 [M^+] (13), 254 (100), 186 (9), 185 (66), 184 (15), 152 (15), 69 (17); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{13}H_9F_3S$, 254.0377; found, 254.0386.

Synthesis of 4–[(trifluoromethyl)thio]benzonitrile (4.2.4–8)

[CAS: 332–26–3]

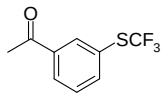


Compound **4.2.4–8** was prepared following the standard procedure, starting from 4–cyanobenzenediazonium tetrafluoroborate [CAS: 2252–32–6] (217 mg, 1.00 mmol). After purification, **4.2.4–8** was isolated as colourless liquid (175 mg, 0.86 mmol, 86%).

m.p. 41–42 °C; **Rf** (SiO_2, hexane:diethyl ether = 4:1): 0.32; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ=7.77 (d, ^3J(H,H)=8.6 Hz, 2H), 7.71 ppm (d, ^3J(H,H)=8.6 Hz, 2H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -41.5 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ=135.9 (2C), 132.9 (2C), 130.5 (q, ^3J(C,F)=1.8 Hz, 1C), 129.0 (q, ^1J(C,F)=308.8 Hz, 1C), 117.6, 114.6 ppm; **IR** ν = 2231 (w), 1488 (w), 1404 (w), 1159 (w), 1116 (vs), 1083 (s), 1019 (m), 834 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 203 [M^+] (15), 184 (15), 135 (9), 134 (100), 106 (12), 90 (23), 69 (43); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_8H_4F_3NS$, 203.0017; found, 203.0019.

Synthesis of 3–[(trifluoromethyl)thio]acetophenone (4.2.4–9)

[CAS: 56773–33–2]



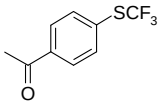
Compound **4.2.4–9** was prepared following the standard procedure, starting from 3–acetylbenzenediazonium tetrafluoroborate [CAS: 59206–56–3] (234 mg, 1.00 mmol). After purification, **4.2.4–9** was isolated as colourless liquid (136 mg, 0.62 mmol, 62%).

Rf (SiO_2, hexane:diethyl ether = 4:1): 0.25; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 8.22 (s, 1H), 8.07 (d, ^3J(H,H)=7.8 Hz, 1H), 7.85 (d, ^3J(H,H)=7.8 Hz, 1H), 7.54 (t, ^3J(H,H)=7.8 Hz, 1H), 2.63 ppm (s, 3H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -42.5 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 196.6, 140.4, 138.2, 136.0, 130.5, 129.8, 129.3 (q, ^1J(C,F)=307.9 Hz, 1C), 125.3 (q, ^3J(C,F)=1.8 Hz, 1C), 26.6 ppm; **MS** (Ion trap, EI): m/z (%) = 220 [M^+] (11), 206 (10), 205 (100), 177 (10),

108 (11), 69 (15), 42 (12); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_9H_7F_3OS$, 220.0170; found, 220.0159.

Synthesis of 4–[(trifluoromethyl)thio]acetophenone (4.2.4–10)

[CAS: 713–67–7]

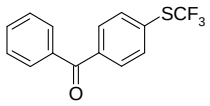


Compound **4.2.4–10** was prepared following the standard procedure, starting from 4–acetylbenzenediazonium tetrafluoroborate [CAS: 350–47–0] (234 mg, 1.00 mmol). After purification, **4.2.4–10** was isolated as colourless liquid (156 mg, 0.71 mmol, 71%).

Rf (SiO_2, hexane:diethyl ether = 4:1): 0.25; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 7.98 (d, ^3J(H,H)=8.2 Hz, 2H), 7.74 (d, ^3J(H,H)=8.3 Hz, 2H), 2.62 ppm (s, 3H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -41.8 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 197.0, 138.4, 135.7 (2C), 129.9 (q, ^3J(C,F)=1.8 Hz, 1C), 129.2 (q, ^1J(C,F)=308.8 Hz, 1C), 129.0 (2C), 26.6 ppm; **MS** (Ion trap, EI): m/z (%) = 220 [M^+] (10), 206 (10), 205 (100), 136 (8), 108 (10), 69 (13), 42 (11); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_9H_7F_3OS$, 220.0170; found, 220.0162.

Synthesis of 4–[(trifluoromethyl)thio]benzophenone (4.2.4–11)

[CAS: 41830–99–3]



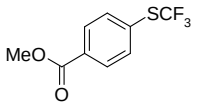
Compound **4.2.4–11** was prepared following the standard procedure, starting from 4–benzoylbenzenediazonium tetrafluoroborate [CAS: 38246–74–1] (296 mg, 1.00 mmol). After purification, **4.2.4–11** was isolated as colourless solid (165 mg, 0.59 mmol, 59%).

m.p. 69–70 °C; **Rf** (SiO_2, hexane:diethyl ether = 4:1): 0.41; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 7.81 (m, 6H), 7.62 (m, 1H), 7.51 ppm (m, 2H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -41.8 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 195.5, 139.4, 136.7, 135.5 (2C), 132.9, 130.6 (2C), 130.0 (2C), 129.3 (q, ^1J(C,F)=308.8 Hz, 1C), 129.0 (q, ^3J(C,F)=1.8 Hz, 1C), 128.4 ppm (2C); **IR**

ν = 1652 (m), 1590 (w), 1280 (w), 1142 (m), 1108 (vs), 1080 (s), 924 (m), 847 (m), 792 (m), 730 (m), 696 (m), 664 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 283 [M^+] (6), 281 (100), 204 (35), 108 (7), 77 (18), 68 (8), 50 (9); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{14}H_9F_3OS$, 282.0326; found, 282.0338.

Synthesis of methyl 4–[(trifluoromethyl)thio]benzoate (4.2.4–12)

[CAS: 88489–60–5]

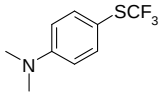


Compound **4.2.4–12** was prepared following the standard procedure, starting from 4–(methoxycarbonyl)benzenediazonium tetrafluoroborate [CAS: 369–48–2] (250 mg, 1.00 mmol). After purification, **4.2.4–12** was isolated as colourless liquid (187 mg, 0.79 mmol, 79%).

Rf (SiO_2, hexane:diethyl ether = 4:1): 0.37; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 8.06 (d, ^3J(H,H)=8.5 Hz, 2H), 7.71 (d, ^3J(H,H)=8.3 Hz, 2H), 3.93 ppm (s, 3H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -41.9 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 166.9, 135.5 (2C), 132.1, 130.4 (2C), 129.8 (q, ^3J(C,F)=1.8 Hz, 1C), 129.3 (q, ^1J(C,F)=308.8 Hz, 1C), 52.4 ppm; **MS** (Ion trap, EI): m/z (%) = 235 [M^+] (91), 206 (9), 205 (100), 176 (7), 108 (11), 69 (18), 63 (7); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_9H_7F_3O_2S$, 236.0119; found, 236.0116.

Synthesis of N,N–dimethyl–4–[(trifluoromethyl)thio]aniline (4.2.4–13)

[CAS: 2677–71–6]



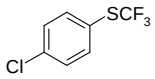
Compound **4.2.4–13** was prepared following the standard procedure, starting from 4–(dimethylamino)benzenediazonium tetrafluoroborate [CAS: 24564–52–1] (235 mg, 1.00 mmol). After purification, **4.2.4–13** was isolated as colourless liquid (183 mg, 0.83 mmol, 83%).

Rf (SiO_2, hexane:diethyl ether = 4:1): 0.40; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 7.51 (d, ^3J(H,H)=8.8 Hz, 2H), 6.70 (d, ^3J(H,H)=8.8 Hz, 2H), 3.03 ppm (s, 6H); **^{19}F–NMR** (376 MHz,

$CDCl_3$): δ= -44.7 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 151.9, 137.9 (2C), 129.8 (q, ^1J(C,F)=308.8 Hz, 1C), 112.3 (2C), 108.2 (q, ^3J(C,F)=1.8 Hz, 1C), 40.0 ppm (2C); **MS** (Ion trap, EI): m/z (%) = 222 [M^+] (14), 221 (100), 220 (7), 152 (57), 151 (8), 108 (7), 69 (8); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_9H_{10}F_3NS$, 221.0486; found, 221.0488.

Synthesis of 1–chloro–4–[(trifluoromethyl)thio]benzene (4.2.4–14)

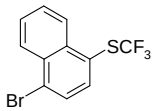
[CAS: 407–16–9]



Compound **4.2.4–14** was prepared following the standard procedure, starting from 4–chlorobenzenediazonium tetrafluoroborate [CAS: 673–41–6] (226 mg, 1.00 mmol). After the reaction, 1,3–difluorobenzene as internal standard (100 µL, 1.00 mmol) was added to the reaction mixture and product **4.2.4–14** was formed in 98% yield as determined by ^{19}F–NMR spectroscopic analysis and confirmed by GC–MS analytics.

^{19}F–NMR (376 MHz, DMSO–d_6): δ= -43.7 ppm; **MS** (Ion trap, EI): m/z (%) = 213 [M^+] (36), 211 (100), 144 (27), 108 (40), 69 (24), 63 (10), 49 (6).

Synthesis of 1–bromo–4–[(trifluoromethyl)thio]naphthalene (4.2.4–15)



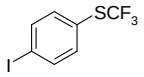
Compound **4.2.4–15** was prepared following the standard procedure, starting from 4–bromonaphthalen–1–yldiazonium tetrafluoroborate [CAS: 341–89–9] (321 mg, 1.00 mmol). After purification, **4.2.4–15** was isolated as colourless liquid (227 mg, 0.74 mmol, 74%).

Rf (SiO_2, hexane:diethyl ether = 4:1): 0.62; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 8.57 (m, 1H), 8.32 (m, 1H), 7.81 (m, 2H), 7.69 ppm (m, 2H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -42.1 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 137.5, 136.1, 132.7, 129.7, 129.2 (q, ^1J(C,F)=309.7 Hz, 1C), 128.4, 128.1, 128.0, 127.9, 126.4, 121.6 ppm (q, ^3J(C,F)=1.8 Hz, 1C); **MS** (Ion trap, EI): m/z (%) = 308 [M^+] (12), 307 (100), 239 (66), 237 (57), 158 (46), 114 (15), 69 (22); **IR** (NaCl): ν =

3073 (w), 1497 (s), 1370 (m), 1158 (s), 1146 (s), 1130 (vs), 1110 (vs), 976 (s), 828 (m), 760 cm^{-1} (s); **HRMS–EI** (TOF) (*m/z*): [M^+] calcd for $C_{11}H_6{}^{79}Br_1F_3{}^{32}S_1$, 305.9320; found, 305.9336.

Synthesis of 1–iodo–4–[(trifluoromethyl)thio]benzene (4.2.4–16)

[CAS: 372–15–6]

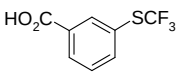


Compound **4.2.4–16** was prepared following the standard procedure, starting from 4–iodobenzenediazonium tetrafluoroborate [CAS: 1514–50–7] (318 mg, 1.00 mmol). After chromatography, **4.2.4–16** was obtained as colourless liquid (238 mg, 0.78 mmol, 78%) which contained traces of iodobenzene.

Rf (SiO_2, hexane:diethyl ether = 4:1): 0.61; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 7.63 (d, ^3J(H,H)=8.5 Hz, 2H), 7.23 ppm (d, ^3J(H,H)=8.3 Hz, 2H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -42.6 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 138.7 (2C), 137.7 (2C), 129.1 (q, ^1J(C,F)=308.8 Hz, 1C), 124.1 (q, ^3J(C,F)=1.8 Hz, 1C), 98.0 ppm; **MS** (Ion trap, EI): m/z (%) = 304 [M^+] (9), 303 (100), 235 (11), 127 (3), 108 (13), 82 (3), 69 (9); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_7H_4F_3IS$, 303.9030; found, 303.9030.

Synthesis of 3–[(trifluoromethyl)thio]benzoic acid (4.2.4–17)

[CAS: 946–65–6]



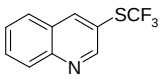
Compound **4.2.4–17** was prepared following the standard procedure, starting from 3–carboxybenzenediazonium tetrafluoroborate [CAS: 20873–47–6] (236 mg, 1.00 mmol). After chromatography, **4.2.4–17** was obtained as colourless solid (52 mg, 0.23 mmol, 23%) which contained 5% of benzoic acid.

m.p. 74–75 °C; **Rf** (SiO_2, hexane:diethyl ether = 4:1): 0.05; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 8.43 (bs, 1H), 8.26 (dt, $^{3,4}J$(H,H)=7.9, 1.4 Hz, 1H), 7.93 (d, ^3J(H,H)=7.8 Hz, 1H), 7.59 ppm

(d, ^{3}J(H,H)=7.8 Hz, 1H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -42.4 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 170.9, 141.4, 137.9, 132.5, 130.8, 129.8, 129.4 (q, ^{1}J(C,F)=308.8 Hz, 1C), 125.4 ppm (q, ^{3}J(C,F)=2.2 Hz, 1C); **IR** ν = 1692 (s), 1426 (w), 1404 (w), 1305 (m), 1291 (m), 1168 (m), 1157 (m), 1102 (vs), 1072 (s), 937 (m), 752 (m), 720 (m), 680 cm^{-1} (m); **MS** (Ion trap, EI): m/z (%) = 222 [M^+] (100), 205 (24), 173 (1), 153 (33), 69 (22), 65 (14), 50 (13); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_8H_5F_3O_2S$, 221.9962; found, 221.9957.

Synthesis of 3–[(trifluoromethyl)thio]quinoline (4.2.4–18)

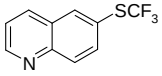
[CAS: 1333415–90–9]



Compound **4.2.4–18** was prepared following the standard procedure, starting from quinoline–3–diazonium tetrafluoroborate [CAS: 398–41–4] (243 mg, 1.00 mmol). After purification, **4.2.4**–**18** was isolated as colourless solid (142 mg, 0.62 mmol, 62%).

Rf (SiO_2, hexane:diethyl ether = 4:1): 0.13; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 9.03 (d, ^{4}J(H,H)=2.3 Hz, 1H), 8.50 (d, ^{4}J(H,H)=2.0 Hz, 1H), 8.15 (m, 1H), 7.82 (m, 2H), 7.62 ppm (m, 1H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -43.3 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 154.5, 148.3, 144.7, 131.6, 129.5, 129.1 (q, ^{1}J(C,F)=308.8 Hz, 1C), 128.0, 127.7, 127.7, 118.2 ppm (q, ^{3}J(C,F)=1.8 Hz, 1C); **MS** (Ion trap, EI): m/z (%) = 229 [M^+] (100), 160 (37), 133 (9), 116 (7), 89 (20), 69 (11), 63 (6); **HRMS–EI** (TOF): m/z [M^+] calcd. for $C_{10}H_6F_3NS$, 229.0173; found, 229.0172.

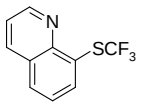
Synthesis of 6–[(trifluoromethyl)thio]quinoline (4.2.4–19)



Compound **4.2.4–19** was prepared following the standard procedure, starting from quinoline–6–diazonium tetrafluoroborate [CAS: 2366–78–1] (243 mg, 1.00 mmol). After purification, **4.2.4**–**19** was isolated as colourless solid (125 mg, 0.55 mmol, 55%).

m.p. 54–55 °C; **Rf** (SiO_2, hexane:diethyl ether = 4:1): 0.08; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 9.02 (br. s, 1H), 8.17 (m, 3H), 7.9 (dd, $^{3,4}J$(H,H)=8.5, 1.8 Hz, 1H), 7.49 ppm (dd, $^{3,4}J$(H,H)=8.0, 4.0 Hz, 1H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -42.3 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 152.2, 148.6, 136.7, 136.2, 135.4, 130.9, 129.5 (q, ^1J(C,F)=308.8 Hz, 1C), 128.3, 122.7 (q, ^3J(C,F)=1.8 Hz, 1C), 122.1 ppm; **IR** (KBr): ν= 1489 (m), 1158 (vs), 1132 (vs), 1116 (vs), 1106 (vs), 1070 (s), 894 (s), 836 (vs), 794 (s), 754 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 230 [M^+] (5), 229 (100), 160 (46), 116 (21), 89 (11), 69 (16), 63 (5); **HRMS–EI** (TOF) (*m/z*): [M^+] calcd for $C_{10}H_6N_1F_3S_1$, 229.0168; found, 229.0165.

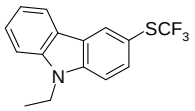
Synthesis of 8–[(trifluoromethyl)thio]quinoline (4.2.4–20)



Compound **4.2.4–20** was prepared following the standard procedure, starting from quinoline–8–diazonium tetrafluoroborate [CAS: 27388–19–8] (243 mg, 1.00 mmol). After purification, **4.2.4–20** was isolated as colourless liquid (72 mg, 0.31 mmol, 31%).

Rf (SiO_2, hexane:diethyl ether = 4:1): 0.15; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ= 9.02 (dd, $^{3,4}J$(H,H)=4.2, 1.7 Hz, 1H), 8.20 (dd, $^{3,4}J$(H,H)=8.3, 1.7 Hz, 1H), 8.08 (d, ^3J(H,H)=7.3 Hz, 1H), 7.88 (m, 1H), 7.63–7.45 ppm (m, 2H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ= -41.1 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ= 150.7, 146.7, 136.5, 134.0, 129.9 (q, ^1J(C,F)=308.8 Hz, 1C), 129.6, 128.8, 126.9 (q, ^3J(C,F)=1.8 Hz, 1C), 126.6, 122.1 ppm; **IR** (NaCl): ν= 1607 (m), 1595 (m), 1491 (s), 1459 (m), 1306 (w), 1108 (vs), 980 (m), 822 (m), 788 (m), 756 cm^{-1} (w); **MS** (Ion trap, EI): m/z (%) = 230 [M^+] (5), 229 (100), 161 (6), 160 (48), 116 (21), 89 (11), 69 (13); **HRMS–EI** (TOF) (*m/z*): [M^+] calcd for $C_{10}H_6N_1F_3S_1$, 229.0166; found, 229.0168.

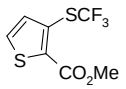
Synthesis of 9–ethyl–3–[(trifluoromethyl)thio]–9H–carbazole (4.2.4–21)



Compound **4.2.4–21** was prepared following the standard procedure, starting from 9–ethyl–9*H*–carbazol–3–diazonium tetrafluoroborate [CAS: 115771–91–0] (309 mg, 1.00 mmol). After purification, **4.2.4–21** was isolated as colourless solid (195 mg, 0.66 mmol, 66%).

m.p. 71–72 °C; **Rf** (SiO_2, hexane:diethyl ether = 4:1): 0.26; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ = 8.45 (d, ^4J(H,H)=1.8 Hz, 1H), 8.15 (d, ^3J(H,H)=7.8 Hz, 1H), 7.78 (dd, $^{3,4}J$(H,H)=8.5, 1.8 Hz, 1H), 7.57 (m, 1H), 7.44 (d, ^3J(H,H)=8.3 Hz, 1H), 7.41 (d, ^3J(H,H)=8.5 Hz, 1H), 7.35 (d, $^{3,4}J$(H,H)=7.5, 0.9 Hz, 1H), 4.32 (q, ^3J(H,H)=7.2 Hz, 2H), 1.45 ppm (t, ^3J(H,H)=7.2 Hz, 3H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ = -43.9 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 141.0, 140.3, 133.7, 130.0 (q, ^1J(C,F)=308.8 Hz, 1C), 129.5, 126.6, 123.8, 122.1, 120.6, 119.7, 112.4 (q, ^3J(C,F)=1.8 Hz, 1C), 109.2, 108.8, 37.6, 13.7 ppm; **IR** (KBr): ν = 2975 (w), 1475 (s), 1449 (s), 1234 (s), 1134 (vs), 1124 (vs), 1108 (vs), 744 (vs), 722 (vs), 604 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 296 [M^+] (6), 295 (100), 281 (5), 280 (31), 227 (7), 226 (47), 69 (14); **HRMS–EI** (TOF) (*m/z*): [M^+] calcd for $C_{15}H_{12}N_1F_332S_1$, 295.0637; found, 295.0636.

Synthesis of methyl 3–[(trifluoromethyl)thio]thiophene–2–carboxylate (4.2.4–22)



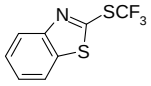
Compound **4.2.4–22** was prepared following the standard procedure, starting from 2–(methoxycarbonyl)thiophene–3–diazonium tetrafluoroborate [CAS: 100421–50–9] (256 mg, 1.00 mmol). After purification, **4.2.4–22** was isolated as colourless liquid (142 mg, 0.59 mmol, 59%).

Rf (SiO_2, hexane:diethyl ether = 4:1): 0.33; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ = 7.60 (d, ^3J(H,H)=5.3 Hz, 1H), 7.25 (dq, ^3J(H,H)=5.3 Hz, ^5J(H,F)=1.4 Hz, 1H), 3.91 ppm (s, 3H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ = -41.4 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 161.7, 131.7, 130.6 (q, ^3J(C,F)=1.8 Hz, 1C), 129.6 (q, ^1J(C,F)=308.8 Hz, 1C), 129.2 (q, ^3J(C,F)=1.8 Hz, 1C),

128.4, 52.5 ppm; **IR** (NaCl): ν = 3105 (m), 2957 (s), 1701 (vs), 1501 (s), 1439 (s), 1407 (s), 1274 (s), 1152 (s), 1136 (s), 1106 cm^{-1} (s); **MS** (Ion trap, EI): m/z (%) = 243 [M^+] (10), 241 (100), 211 (50), 173 (42), 143 (11), 142 (15), 69 (23); **HRMS–EI** (TOF) (*m/z*): [M^+] calcd for $C_7H_5O_2F_332S_2$, 241.9675; found, 241.9678.

Synthesis of 2–[(Trifluoromethyl)thio]benzothiazole (4.2.4–23)

[CAS: 63647–63–2]



Compound **4.2.4–23** was prepared following the standard procedure, starting from 1,3–benzothiazole–2–diazonium tetrafluoroborate [CAS: 29163–72–2] (249 mg, 1.00 mmol). After purification, **4.2.4–23** was isolated as colourless solid (98 mg, 0.42 mmol, 42%).

m.p. 36–37 °C; **Rf** (SiO_2, hexane:diethyl ether = 4:1): 0.40; **^{1}H–NMR** (400 MHz, $CDCl_3$): δ = 8.15 (d, ^3J(H,H)=8.0 Hz, 1H), 7.91 (d, ^3J(H,H)=8.0 Hz, 1H), 7.54 ppm (m, 2H); **^{19}F–NMR** (376 MHz, $CDCl_3$): δ = -40.2 ppm; **^{13}C–NMR** (101 MHz, $CDCl_3$): δ = 153.1, 151.7 (q, ^3J(C,F)=2.7 Hz, 1C), 137.9, 129.7 (q, ^1J(C,F)=310.6 Hz, 1C), 127.0, 126.7, 124.1, 121.3 ppm; **MS** (Ion trap, EI): m/z (%) = 236 [M^+] (19), 235 (27), 166 (100), 122 (16), 108 (24), 69 (42), 63 (12); **HRMS**–**EI** (TOF): m/z [M^+] calcd. for $C_8H_4F_3NS_2$, 234.9737; found, 234.9740.

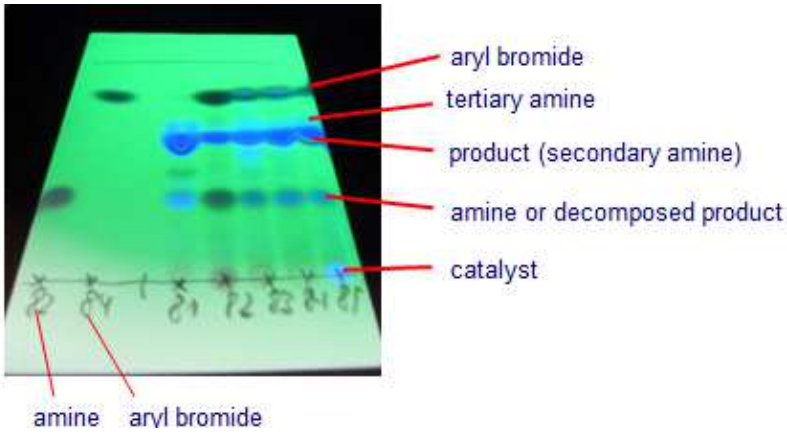
6.11. Pd(dippf)maleimide as highly selective catalyst for the monoarylation of primary amines

6.11.1. General Methods

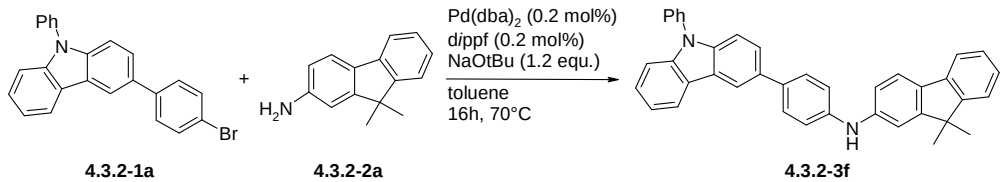
9*H*–fluoren–2–amine (**4.3.2–2e**, CAS: 153–78–6), 2–dibenzofuranamine (**4.3.2–2f**, CAS: 3693–22–9) and 2–dibenzothiophenamine (**4.3.2–2g**, CAS: 7428–91–3) were synthesised following standard procedures.[312,313] All other starting materials were commercially available. The liquid compounds were fractionally distilled prior to use, the solids were used without further purification.

6.11.2. TLC studies

For the TLC studies, small samples of the reaction mixtures were taken, diluted in ethyl acetate, washed with water and deposited on the SiO_2 plate. The compounds were eluted by hexane/ethyl acetate = 4:1.



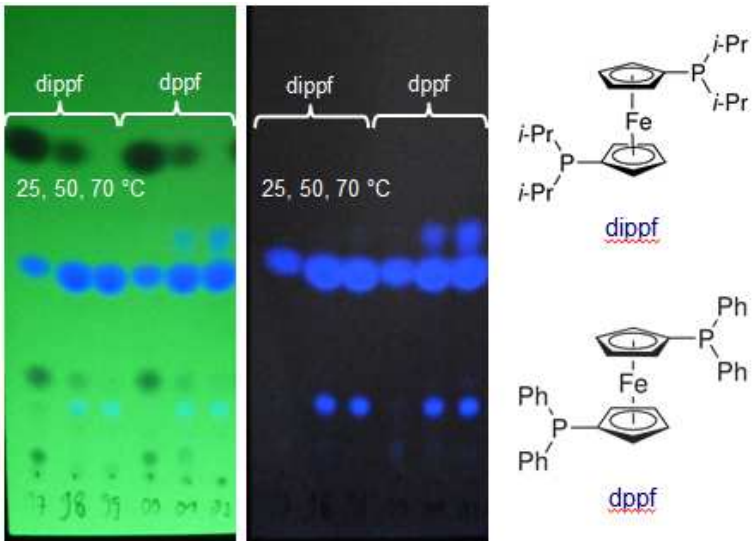
Since the separation on SiO_2 always led to the partial decomposition of the desired secondary amines, basic Al_2O_3 was used for the column chromatography. The synthesis of 9,9–dimethyl–*N*–(4–(9–phenyl–9*H*–carbazol–3–yl)phenyl)–9*H*–fluoren–2–amine (**4.3.2–3f**) was chosen as the model reaction.



4.3.2-1a **4.3.2-2a** **4.3.2-3f**

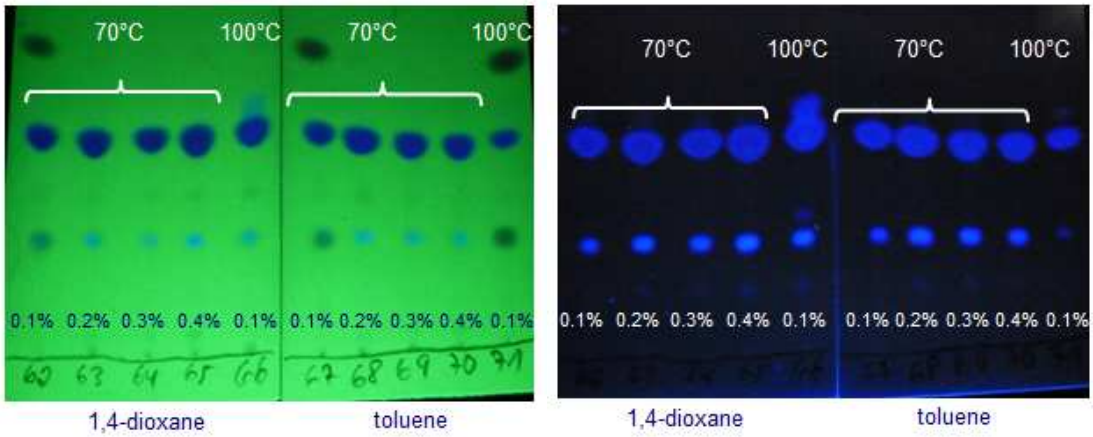
Influence of the reaction temperature: Comparison between dippf and dppf

The starting materials were completely consumed after 16 h at 70 °C. The reaction with dippf only led to the formation of the secondary amine. Dppf was far less selective.



Catalyst loading

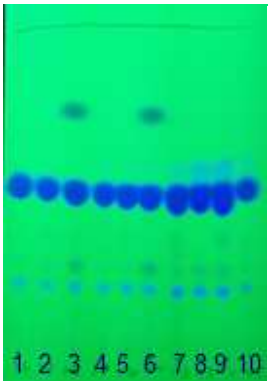
At 70 °C, 0.2 mol% of the Pd–catalyst was needed for the full conversion. The reaction also works in 1,4–dioxane and mixtures of toluene and 1,4–dioxane.



Ligand Screening

The catalyst screening was repeated for the synthesis of compound **4.3.2–3f**. The catalysts $Pd(dba)_2$/dippf and Pd(dippf)maleimide/dippf formed the desired product selectively at 70 °C

and 80 °C. The reaction with Pd(dippf)maleimide alone was not finished after 16 h. All other catalysts formed the diarylated product as byproduct (spot above the product) or were less reactive.



1 0.2 mol% $Pd(dba)_2$ + 0.2 mol% d*i*ppf
2 0.2 mol% Pd(d*i*ppf)maleimide + 0.2 mol% d*i*ppf
3 0.2 mol% Pd(d*i*ppf)maleimide

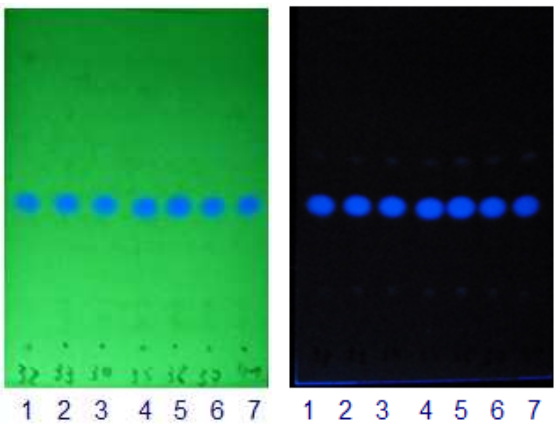
4 0.2 mol% $Pd(dba)_2$ + 0.2 mol% d*i*ppf, 80°C
5 0.2 mol% Pd(d*i*ppf)maleimide + 0.2 mol% d*i*ppf, 80°C
6 0.2 mol% Pd(d*i*ppf)maleimide, 80°C

7 0.2 mol% $Pd(dba)_2$ + 0.2 mol% dcyppf
8 0.2 mol% $Pd(dba)_2$ + 0.2 mol% dtBuppf
9 0.2 mol% $Pd(dba)_2$ + 0.2 mol% dppf
10 0.2 mol% $Pd(dba)_2$ + 0.2 mol% XantPhos

1 0.2 mol% $Pd(dba)_2$ + 0.2 mol% *t*BuJohnPhos
2 0.2 mol% $Pd(dba)_2$ + 0.2 mol% XPhos
3 0.2 mol% $Pd(dba)_2$ + 0.2 mol% CyBrettPhos
4 0.2 mol% $Pd(dba)_2$ + 0.2 mol% RuPhos
5 0.2 mol% $Pd(dba)_2$ + 0.2 mol% MorDalPhos
6 0.2 mol% $Pd(dba)_2$ + 0.2 mol% BINAP
7 0.2 mol% $Pd(PtBu_3)_2$
8 0.2 mol% $[Pd(\mu Br)(PtBu_3)]_2$
9 0.2 mol% (IPr)Pd(allyl)Cl
10 0.2 mol% (IPr)Pd(cinnamyl)Cl

Reactivity of Pd(dippf)maleimide

After these findings, the reactivity of Pd(dippf)maleimide was further investigated. As can be seen on the TLC plate, the addition of 0.1 mol% of d*i*ppf to 0.2 mol% Pd(dippf)maleimide is sufficient for the full conversion of the starting materials.



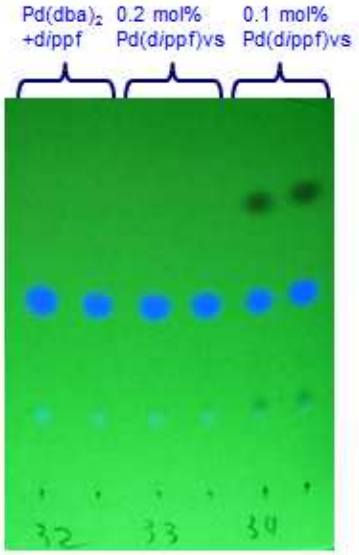
1 0.3 mol% Pd(dippf)maleimide + 0.15 mol% d*i*ppf, 70°C
2 0.3 mol% Pd(dippf)maleimide + 0.3 mol% d*i*ppf, 70°C
3 0.3 mol% Pd(dippf)maleimide + 0.15 mol% d*i*ppf, 80°C

4 0.2 mol% Pd(dippf)maleimide + 0.1 mol% d*i*ppf, 70°C
5 0.2 mol% Pd(dippf)maleimide + 0.2 mol% d*i*ppf, 70°C
6 0.2 mol% Pd(dippf)maleimide + 0.1 mol% d*i*ppf, 80°C

7 0.2 mol% Pd(dba)2 + 0.2 mol% d*i*ppf, 70°C

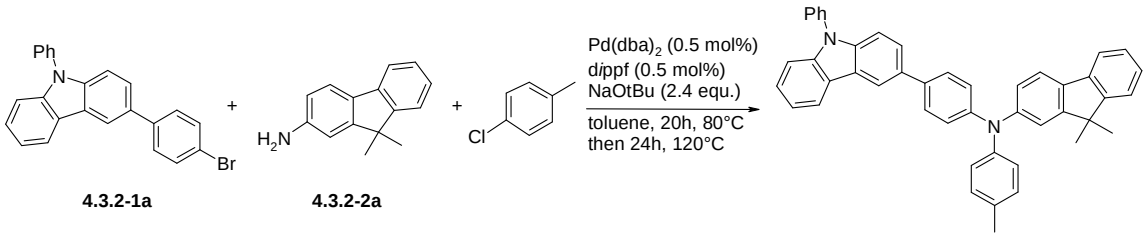
Pd(dippf)(vs)tol as catalyst solution

The TLC plate below shows, that the reaction can also be catalysed by the catalyst solution Pd(dippf)(vs)tol. While 0.1 mol% of palladium is not sufficient for the full conversion of the starting materials, 0.2 mol% of palladium led to the quantitative conversion after 16h.



One–pot synthesis of the tertiary amines

The following reaction was monitored by TLC:



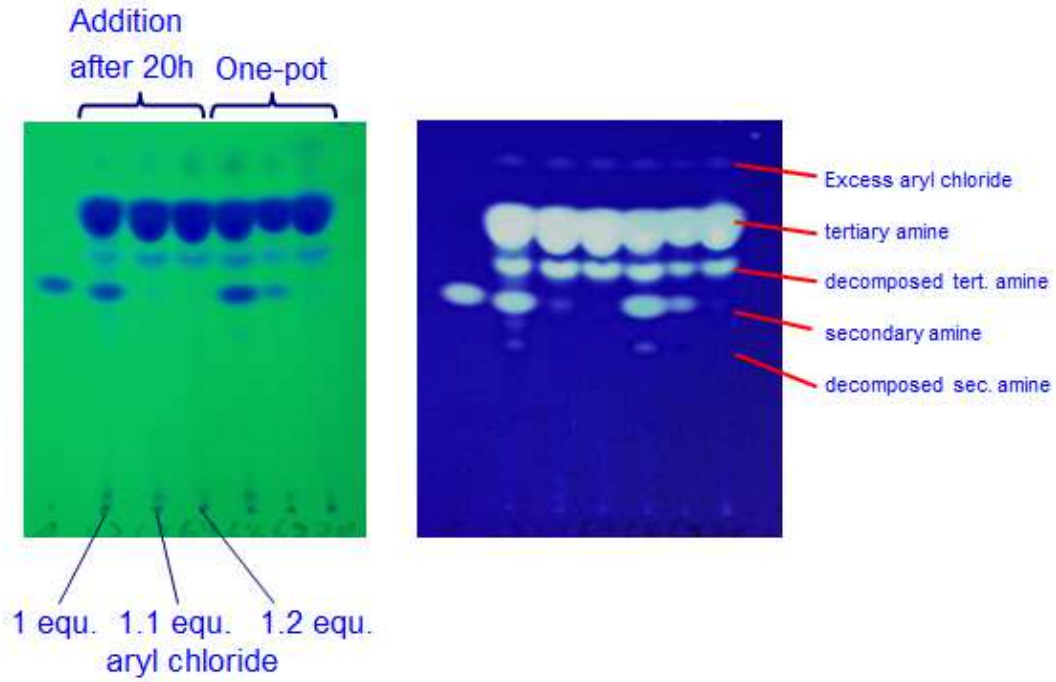
4.3.2-1a **4.3.2-2a**

The TLC plates show the following: First, the standard reaction without aryl chloride after 20 h. The secondary amine is formed selectively and without the diarylated byproduct.

Then 3 reactions with different amounts of the aryl chloride (1 equ., 1.1 equ. and 1.2 equ.) were added to the reaction mixture after 20 h, followed by 24 h at 120 °C. The full conversion of the secondary to the tertiary amine was only observed, when at least 1.1 equivalents of the third coupling partner, the aryl chloride, were added. The desired product is then accompanied by the excess aryl chloride that can easily be distilled off. The additional, light–blue signal underneath

the tertiary amine originates in the decomposition of small amounts of the product in SiO_2. Therefore, the column chromatography was performed on basic Al_2O_3.

Finally, in the last 3 reactions, all the starting materials were directly put together, heated to 80 °C for 20 h and then to 120 °C for 24 h. Again, 1 equ., 1.1 equ. and 1.2 equ. Of the aryl chloride were employed. In this case, only the reaction with 1.2 equivalents of the aryl chloride led to the full conversion of the intermediate secondary amine.



6.11.3. Synthesis of Pd(dippf)maleimide (4.3.2–8)

1,1′–Bis(diisopropylphosphino)ferrocene (dippf) (213 mg, 0.50 mmol) was dissolved in diethyl ether (5 mL) and a solution of palladium(0)–1,3–divinyl–1,1,3,3–tetramethyldisiloxane (0.5 mL, 10.87% palladium) was added. The orange solution was stirred at room temperature for 1h and maleimide (99.1 mg, 1.00 mmol) in diethyl ether (5 mL) was added at once. The mixture was brought in an ultrasonic bath, which resulted in the immediate precipitation of a yellow solid. After 10 minutes, the solid was allowed to settle and the supernatant was removed via syringe. The crude product was washed with diethyl ether (3 × 5 mL) and dried *in vacuo* (10^{-2} mbar) to obtain the title compound as yellow solid (291 mg, 0.47 mmol, 94%). Suitable crystals for the crystal structural analysis were obtained by cooling a saturated solution of the palladium complex in an acetonitrile/THF mixture (5:1) to –20°C for 24h.

^{1}H–NMR (400 MHz, dioxane–d_8): δ= 7.78 (s, 1H), 4.39–4.33 (m, 6H), 4.30 (m, 2H), 3.93 (dd, *J*=4.9 Hz, 1.4 Hz, 2H), 2.45–2.37 (m, 2H), 2.22 (dt, *J*=8.8 Hz, 2.0 Hz, 2H), 1.29 (d, *J*=7.0 Hz, 3H), 1.25 (d, *J*= 7.0 Hz, 3H), 1.21 (d, *J*=7.0 Hz, 3H), 1.17 (m, 6H), 1.13 (d, *J*=6.8Hz, 3H), 1.08 (d, *J*=7.0 Hz, 3H), 1.04 ppm (d, *J*=6.8 Hz, 3H); **^{13}C–NMR** (101 MHz, dioxane–d_8): δ= 177.2 (d, *J*=2.2 Hz, 1C), 81.5 (m, 1C), 74.9 (t, *J*=4.0 Hz, 2C), 73.4 (t, *J*=2.9 Hz, 2C), 70.8 (m, 4C), 51.6 (t, *J*=11.7 Hz, 2C), 27.1 (d, *J*=10.3 Hz, 1C), 27.0 (d, J=11.0 Hz, 1C), 25.7 (d, *J*=8.8 Hz, 1C), 25.6 (d, *J*=8.8 Hz, 1C), 21.0 (t, *J*=2.9 Hz, 2C), 20.5 (t, *J*=2.9 Hz, 2C), 20.0 (t, *J*=4.0 Hz, 2C), 19.8 ppm (t, *J*=1.5 Hz, 2C); **^{31}P–NMR** (162 MHz, dioxane–d_8): δ= 38.87 ppm (s, 2P); **CHN** Anal. Calcd. for $C_{26}H_{39}FeNO_2P_2Pd$: C 50.22, H 6.32, N 2.25; found: C 50.24, H 6.31, N 2.37.

6.11.4. Preparation of the Pd(dippf)(vs)tol toluene solution

The catalyst solution was prepared by the addition of a Pd(vs) solution (0.5 mL, 10.87% Pd) to dippf (214 mg, 0.50 mmol) in toluene (0.5 mL). The ^{31}P–NMR showed several different Pd(0)dippf species: ^{31}P–NMR (162 MHz, toluene–d_8): δ = 32.54, 32.31, 32.25, 32.22, 32.13, 32.07, 32.00, 31.81, 31.77 ppm.

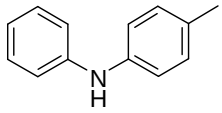
6.11.5. Synthesis of the secondary amines

Standard procedure for the synthesis of the diaryl amines

A dry 20 mL crimp cap vessel was charged with the aryl bromide (1.00 mmol), the primary amine (1.00 mmol), sodium *tert*–butoxide (118 mg, 1.20 mmol) and a magnetic stir bar and was kept *in vacuo* for 10 min. After three nitrogen–vacuum cycles, a stock solution of Pd(dippf)maleimide (1.24 mg, 0.002 mmol) and dippf (0.85 mg, 0.002 mmol) in dry, distilled toluene (2 mL) was added via syringe. The reaction mixture was stirred at 70°C for 20h, cooled to room temperature and diluted with dichloromethane (30 mL) and water (30 mL). The aqueous layer was separated and extracted with fresh dichloromethane (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* (40°C, 500 mbar). The crude product was further purified by flash chromatography (basic Al_2O_3, hexane:ethyl acetate or hexane/diethyl ether), yielding the corresponding amine (76–96%).

Synthesis of 4–methyl–N–phenylaniline (4.3.2–3a)

[CAS: 620–84–8]

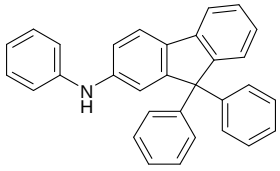


Compound **4.3.2–3a** was prepared following the standard procedure, starting from 4–bromotoluene (**4.3.2–1a**) (175 mg, 1.00 mmol, 126 µL) and aniline (**4.3.2–2a**) (93.1 mg, 1.00 mmol, 91.2 µL). After column chromatography (hexane:ethyl acetate = 4:1), **4.3.2–3a** was obtained as colourless solid (172 mg, 0.94 mmol, 94%).

^{1}H–NMR (400 MHz, chloroform–*d*): δ= 7.36 (m, 2H), 7.23–7.17 (m, 2H), 7.14–7.09 (m, 4H), 7.01 (tt, *J*=1.1 Hz, 7.3 Hz, 1H), 5.66 (s, 1H), 2.43 ppm (s, 3H); **^{13}C–NMR** (101 MHz, chloroform–*d*) δ= 143.9, 140.2, 130.8, 129.8 (2C), 129.2 (2C), 120.2, 118.8 (2C), 116.8 (2C), 20.6 ppm; **MS** (70 eV): m/z (%): 183 [M^+] (44), 182 (100), 167 (12), 91 (10), 63 (6), 51 (14), 50 (10).

Synthesis of N,9,9–triphenyl–9H–fluoren–2–amine (4.3.2–3b)

[CAS: 860465–14–1]



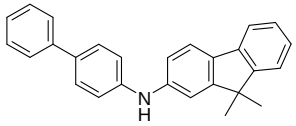
Compound **4.3.2–3b** was prepared following the standard procedure, starting from bromobenzene (**4.3.2–1b**) (159 mg, 1.00 mmol, 106 µL) and 9,9–diphenyl–9*H*–fluoren–2–amine (**4.3.2–2b**) (333 mg, 1.00 mmol). After column chromatography (hexane:ethyl acetate = 9:1), **4.3.2–3b** was obtained as colourless solid (390 mg, 0.95 mmol, 95%).

m.p. 197–198 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.56; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ= 8.37 (s, 1H), 7.76 (d, *J*=8.0 Hz, 2H), 7.37 (d, *J*=7.7 Hz, 1H), 7.33 (t, *J*=7.5 Hz, 1H), 7.30–7.17 (m, 9H), 7.16–7.09 (m, 5H), 7.06 (d, *J*=1.9 Hz, 1H), 7.02 (d, *J*=7.7 Hz, 2H), 6.81 ppm (t, *J*=7.4 Hz, 1H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ= 152.1, 149.9, 145.8 (2C), 143.4,

143.0, 140.1, 131.2, 129.2 (2C), 128.4 (4C), 127.7 (4C), 127.6, 126.6 (2C), 126.2, 125.8, 121.3, 120.0, 129.3, 116.9 (2C), 115.7, 114.1, 64.8 ppm; **IR** ν = 3388 (w), 1595 (m), 1489 (m), 1451 (m), 1351 (w), 1314 (s), 1236 (w), 752 (vs), 723 (s), 699 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{31}H_{23}N$: C 90.92, H 5.66, N 3.42; found: C 90.97, H 5.46, N 3.49.

Synthesis of N–([1,1'–biphenyl]–4–yl)–9,9–dimethyl–9H–fluoren–2–amine (4.3.2–3c)

[CAS: 897671–69–1]

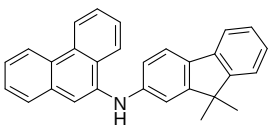


Compound **4.3.2–3c** was prepared following the standard procedure, starting from 4–bromo–1,1'–biphenyl (**4.3.2–1c**) (259 mg, 1.00 mmol) and 9,9–dimethyl–9*H*–fluoren–2–amine (**4.3.2–2c**) (209 mg, 1.00 mmol). After column chromatography (hexane:diethyl ether = 2:1), **4.3.2–3c** was obtained as colourless solid (323 mg, 0.89 mmol, 89%).

m.p. 140–141 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.58; **^{1}H–NMR** (400 MHz, chloroform–*d*) δ = 7.72 – 7.63 (m, 4H), 7.59 (m, 2H), 7.51 – 7.44 (m, 3H), 7.37 (m, 2H), 7.32 (t, *J*=7.0 Hz, 1H), 7.25 (br. s, 1H), 7.22 (d, *J*=8.3 Hz, 2H), 7.13 (br. d, *J*=7.5 Hz, 1H), 5.92 (br. s, 1H), 1.54 ppm (s, 6H); **^{13}C–NMR** (101 MHz, chloroform–*d*) δ = 155.3, 153.1, 142.7, 142.1, 140.8, 139.2, 133.5, 132.8, 128.7 (2C), 128.0 (2C), 126.9, 126.6, 126.5 (2C), 126.1, 122.4, 120.8, 119.1, 117.6 (2C), 117.2, 112.6, 46.8, 27.2 ppm (2C); **IR** ν = 3372 (m), 2954 (w), 1604 (m), 1521 (m), 1461 (m), 1308 (s), 828 (s), 766 (vs), 732 (vs), 701 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{27}H_{23}N$: C 89.71, H 6.41, N 3.87; found: C 89.69, H 6.27, N 3.84.

Synthesis of N–(9,9–dimethyl–9H–fluoren–2–yl)phenanthren–9–amine (4.3.2–3d)

[CAS: 1372778–26–1]

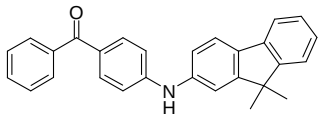


Compound **4.3.2–3d** was prepared following the standard procedure, starting from 9–bromophenanthrene (**4.3.2–1d**) (268 mg, 1.00 mmol) and 9,9–dimethyl–9*H*–fluoren–2–amine

(**4.3.2–2c**) (209 mg, 1.00 mmol). After column chromatography (hexane:diethyl ether = 2:1), **4.3.2–3d** was obtained as tan solid (335 mg, 0.87 mmol, 87%).

m.p. 132–133 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.63; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ= 8.86 (m, 1H), 8.72 (m, 1H), 8.42 (s, 1H), 8.37 (dd, *J*=8.2 Hz, 1.1 Hz, 1H), 7.77–7.65 (m, 5H), 7.63 (s, 1H), 7.51 (m, 2H), 7.45 (d, *J*=7.5 Hz, 1H), 7.32 (d, *J*=2.0 Hz, 1H), 7.27 (dt, *J*=7.5 Hz, 1.1 Hz, 1H), 7.20 (dt, *J*=7.3 Hz, 1.0 Hz, 1H), 7.13 (dd, *J*=8.3 Hz, 2.0 Hz, 1H), 1.40 ppm (s, 6H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ= 154.7, 152.7, 144.6, 139.0, 137.8, 132.5, 131.0, 130.8, 127.5, 127.1, 127.1, 127.0, 126.9, 126.6, 126.4, 125.8, 124.5, 123.3, 123.3, 122.6, 122.5, 120.9, 118.9, 116.8, 112.4, 111.7, 46.3, 27.1 ppm (2C); **IR** ν = 1610 (w), 1600 (w), 1461 (m), 1447 (m), 1424 (w), 1319 (m), 1300 (m), 1233 (w), 734 (vs), 722 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{29}H_{23}N$: C 90.35, H 6.01, N 3.63; found: C 89.98, H 6.31, N 3.49.

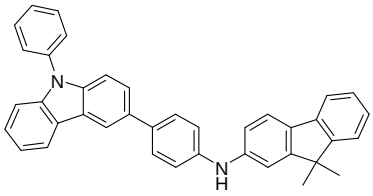
Synthesis of (4–((9,9–dimethyl–9H–fluoren–2–yl)amino)phenyl)(phenyl)methanone (4.3.2–3e)



Compound **4.3.2–3e** was prepared following the standard procedure, starting from 4–bromobenzophenone (**4.3.2–1e**) (269 mg, 1.00 mmol) and 9,9–dimethyl–9*H*–fluoren–2–amine (**4.3.2–2c**) (209 mg, 1.00 mmol). After column chromatography (hexane:diethyl ether = 1:2), **4.3.2–3e** was obtained as yellow solid (296 mg, 0.76 mmol, 76%).

m.p. 206–207°C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.38; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ= 9.08 (s, 1H), 7.80–7.45 (m, 10H), 7.41–7.35 (m, 1H), 7.33–7.13 (m, 5H), 1.43 ppm (s, 6H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ= 193.6, 154.8, 152.9, 148.7, 140.6, 138.5 (2C), 132.9, 132.4 (2C), 131.5, 129.0 (2C), 128.3 (2C), 127.0, 126.7, 126.4, 122.6, 120.9, 119.3, 118.6, 114.1, 113.9 (2C), 46.4, 26.9 ppm (2C); **IR** ν = 3345 (m), 1587 (m), 1563 (s), 1444 (m), 1313 (s), 1280 (vs), 1148 (s), 830 (m), 731 (vs), 698 cm^{-1} (s); **CHN** Anal. Calcd. for $C_{28}H_{23}NO$: C 86.34, H 5.95, N 3.60; found: C 86.05, H 6.10, N 3.52.

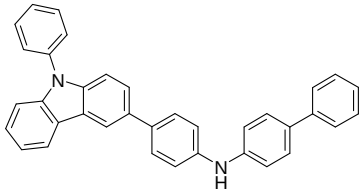
Synthesis of 9,9–dimethyl–N–(4–(9–phenyl–9H–carbazol–3–yl)phenyl)–9H–fluoren–2–amine (4.3.2–3f) [CAS: 1354653–33–0]



Compound **4.3.2–3f** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol) and 9,9–dimethyl–9*H*–fluoren–2–amine (**4.3.2–2c**) (209 mg, 1.00 mmol). After column chromatography (hexane:diethyl ether = 1:1), **4.3.2–3f** was obtained as colourless solid (496 mg, 0.94 mmol, 94%).

m.p. 196–197 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.47; **^{1}H–NMR** (400 MHz, chloroform–*d*) δ = 8.41 (d, *J*=1.3 Hz, 1H), 8.26 (d, *J*=7.8 Hz, 1H), 7.75–7.60 (m, 9H), 7.55–7.44 (m, 5H), 7.41–7.21 (m, 6H), 7.13 (d, *J*=7.0 Hz, 1H), 5.91 (s, 1H), 1.55 ppm (s, 6H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ = 154.8, 152.6, 143.1, 142.3, 140.5, 139.1, 139.0, 136.9, 132.6, 132.1, 130.7, 130.2 (2C), 127.6, 127.5 (2C), 126.9, 126.6 (2C), 126.3, 125.8, 124.6, 123.4, 123.0, 122.5, 120.9, 120.8, 120.1, 118.8, 117.6, 117.2 (2C), 115.7, 111.1, 109.9, 109.7, 46.3, 27.1 ppm (2C); **IR** ν = 1598 (m), 1500 (s), 1451 (s), 1303 (m), 1230 (s), 804 (vs), 750 (s), 744 (s), 731 (vs), 699 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{39}H_{30}N_2$: C 88.94, H 5.74, N 5.32; found: C 88.79, H 5.86, N 5.19.

Synthesis of N–(4–(9–phenyl–9H–carbazol–3–yl)phenyl)–[1,1'–biphenyl]–4–amine (4.3.2–3g) [CAS: 1160294–96–1]

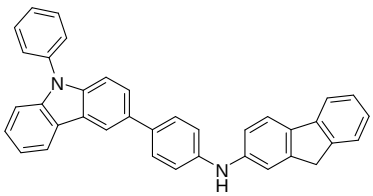


Compound **4.3.2–3g** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol) and [1,1'–biphenyl]–4–amine (**4.3.2–2d**) (169 mg, 1.00 mmol). After column chromatography

(hexane:diethyl ether = 1:1), **4.3.2–3g** was obtained as colourless solid (462 mg, 0.95 mmol, 95%).

m.p. 179–180 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.48; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ = 8.53 (d, *J*=1.3 Hz, 1H), 8.47 (s, 1H), 8.35 (d, *J*=7.5 Hz, 1H), 7.74–7.53 (m, 12H), 7.47–7.38 (m, 5H), 7.34–7.19 ppm (m, 6H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ = 143.0, 142.9, 141.9, 140.5, 140.1, 139.1, 136.9, 132.6, 132.5, 131.2, 130.2 (2C), 128.9 (2C), 127.6, 127.5 (2C), 127.4 (2C), 126.6 (2C), 126.4 (2C), 125.8 (2C), 124.7, 123.4, 123.0, 120.8, 120.1, 117.7, 117.5 (2C), 116.8, 110.0, 109.7 ppm; **IR** ν = 1597 (s), 1501 (vs), 1474 (s), 1451 (vs), 1303 (m), 1231 (s), 1178 (m), 807 (vs), 757 (vs), 698 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{36}H_{26}N_2$: C 88.86, H 5.39, N 5.76; found: C 88.49, H 5.39, N 5.68.

Synthesis of N–(4–(9–phenyl–9H–carbazol–3–yl)phenyl)–9H–fluoren–2–amine (4.3.2–3h)

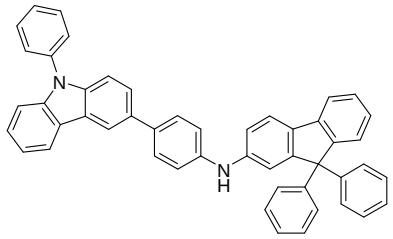


Compound **4.3.2–3h** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol) and 9*H*–fluoren–2–amine (**4.3.2–2e**) (181 mg, 1.00 mmol). After column chromatography (hexane:diethyl ether = 1:1), **4.3.2–3h** was obtained as colourless solid (460 mg, 0.92 mmol, 92%).

m.p. 192–193 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.46; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ = 8.54 (d, *J*=1.5 Hz, 1H), 8.44 (s, 1H), 8.35 (d, *J*=7.8 Hz, 1H), 7.77–7.63 (m, 9H), 7.55 (m, 1H), 7.51 (d, *J*=7.5 Hz, 1H), 7.47–7.36 (m, 4H), 7.31 (m, 2H), 7.26 (d, *J*=8.8 Hz, 2H), 7.20 (dt, *J*=7.5 Hz, 1.3 Hz, 1H), 7.15 (dd, *J*=8.3 Hz, 2.0 Hz, 1H), 3.87 ppm (s, 2H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ = 144.6, 142.7, 142.3, 142.2, 141.5, 140.5, 139.1, 136.9, 133.3, 132.6, 132.2, 130.2 (2C), 127.6, 127.5 (2C), 126.7, 126.6 (2C), 126.4, 125.3, 124.9, 124.7, 123.4, 123.0, 120.8, 120.7, 120.1, 118.8, 117.6, 117.4 (2C), 117.3, 115.9, 113.1, 110.0, 109.7 ppm; **IR** ν =

1596 (m), 1499 (s), 1451 (vs), 1317 (m), 1226 (m), 1178 (m), 815 (s), 767 (s), 740 (vs), 731 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{37}H_{26}N_2$: C 89.13, H 5.26, N 5.62; found: C 88.83, H 5.25, N 5.54.

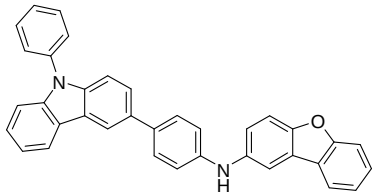
Synthesis of 9,9–diphenyl–N–(4–(9–phenyl–9H–carbazol–3–yl)phenyl)–9H–fluoren–2–amine (4.3.2–3i) [CAS: 1447838–87–0]



A dry 20 mL crimp cap vessel was charged with 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol), 9,9–diphenyl–9*H*–fluoren–2–amine (**4.3.2–2b**) (333 mg, 1.00 mmol), sodium *tert*–butoxide (118 mg, 1.20 mmol) and a magnetic stir bar and was kept *in vacuo* for 10min, followed by three nitrogen–vacuum cycles. A stock solution of Pd(dippf)maleimide (1.24 mg, 0.002 mmol) and dippf (0.85 mg, 0.002 mmol) in dry, distilled toluene (3 mL) was added via syringe and the mixture was stirred at 70°C for 24h until TLC analytics showed full conversion of the starting materials. After cooling to room temperature, diethyl ether (15 mL) was added and the precipitate was filtered off, washed with water (15 mL), ethanol (15 mL) and diethyl ether (15 mL). The crude product was recrystallized from hot toluene and dried *in vacuo* (70°C, 10^{-3} mbar) for 24 h to yield the title compound **4.3.2–3i** as colourless solid (605 mg, 0.93 mmol, 93%).

m.p. 270–271 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.33; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ = 8.55 (d, *J*=7.5 Hz, 2H), 8.34 (d, *J*=7.8 Hz, 1H), 7.77 (t, *J*=8.8 Hz, 2H), 7.70–7.58 (m, 7H), 7.50 (m, 1H), 7.44–7.13 ppm (m, 21H); **^{13}C–NMR** (101 MHz, dioxane–d_8) δ = 153.8, 151.6, 147.3 (2C), 144.6, 142.9, 142.1, 141.3, 140.8, 138.8, 134.9, 134.1, 133.3, 130.7 (2C), 129.1 (4C), 129.1 (4C), 129.0, 128.7 (2C), 128.3, 128.1, 128.0 (2C), 127.3 (2C), 127.1, 126.8, 126.8, 125.6, 124.8, 124.5, 121.9, 121.2, 120.8, 120.0, 118.7 (2C), 116.9, 115.9, 110.7, 110.6, 66.3 ppm; **IR** ν = 3413 (w), 1596 (m), 1475 (m), 1455 (s), 1320 (m), 1227 (m), 761 (vs), 753 (vs), 746 (vs), 697 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{49}H_{34}N_2$: C 90.43, H 5.27, N 4.30; found: C 90.15, H 5.52, N 4.18.

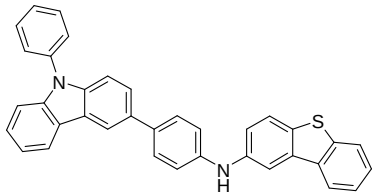
Synthesis of N–(4–(9–phenyl–9H–carbazol–3–yl)phenyl)dibenzo[b,d]furan–2–amine (4.3.2–3j)



Compound **4.3.2–3j** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol) and 2–dibenzofuranamine (**4.3.2–2f**) (183 mg, 1.00 mmol). After column chromatography (hexane:diethyl ether = 1:1), **4.3.2–3j** was obtained as colourless solid (442 mg, 0.88 mmol, 88%).

m.p. 153–154 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.43; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ = 8.72 (s, 1H), 8.55 (d, *J*=1.5 Hz, 1H), 8.35 (d, *J*=7.8 Hz, 1H), 7.99–7.93 (m, 2H), 7.77–7.62 (m, 7H), 7.60 (d, *J*=8.0 Hz, 1H), 7.54 (m, 1H), 7.47–7.27 (m, 9H), 7.16 ppm (dd, *J*=8.5 Hz, 1.8 Hz, 1H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ = 157.1, 155.3, 144.0, 141.6, 140.5, 139.2, 136.9, 133.0, 132.5, 130.2 (2C), 127.6, 127.5 (2C), 126.6 (2C), 126.4, 125.6, 124.7, 124.2, 123.4, 123.0 (2C), 121.6, 120.8, 120.1, 119.7, 118.0 (2C), 117.7, 115.5, 113.1, 111.2, 110.0, 109.7, 97.9 ppm; **IR** ν = 1636 (w), 1598 (m), 1500 (s), 1456 (vs), 1327 (m), 1235 (m), 1123 (m), 808 (s), 746 (vs), 694 cm^{-1} (s); **CHN** Anal. Calcd. for $C_{36}H_{24}N_2O$: C 86.38, H 4.83, N 5.60; found: C 86.02, H 5.04, N 5.43.

Synthesis of N–(4–(9–phenyl–9H–carbazol–3–yl)phenyl)dibenzo[b,d]thiophen–2–amine (4.3.2–3k)

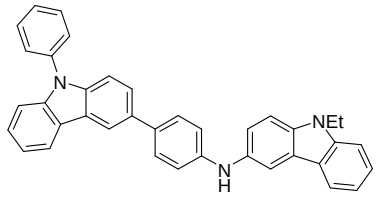


Compound **4.3.2–3k** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol) and 2–dibenzothiophenamine (**4.3.2–2g**) (199 mg, 1.00 mmol). After column chromatography

(hexane:diethyl ether = 1:1), **4.3.2–3k** was obtained as colourless solid (496 mg, 0.96 mmol, 96%).

m.p. 121–122 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.43; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ = 8.54 (d, *J*=1.5 Hz, 1H), 8.51 (s, 1H), 8.35 (d, *J*=7.5 Hz, 1H), 8.25 (m, 1H), 8.07 (d, *J*=2.0 Hz, 1H), 7.99 (m, 1H), 7.89 (d, *J*=8.5 Hz, 1H), 7.75–7.63 (m, 7H), 7.55 (m, 1H), 7.48 (m, 2H), 7.45–7.37 (3H), 7.36–7.27 ppm (m, 4H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ = 142.7, 141.0, 140.5, 139.5, 139.1, 136.9, 136.0, 134.9, 132.6, 132.1, 130.2 (2C), 129.7, 127.6, 127.5 (2C), 126.9, 126.6 (2C), 126.4, 124.7, 124.5, 123.6, 123.4, 123.1, 123.0, 121.9, 120.8, 120.1, 119.0, 117.6, 116.8 (2C), 110.0, 109.7, 109.2 ppm; **IR** ν = 1599 (s), 1500 (vs), 1472 (vs), 1452 (vs), 1228 (vs), 802 (vs), 759 (vs), 745 (s), 730 (vs), 697 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{36}H_{24}N_2S$: C 83.69, H 4.68, N 5.42, S 6.21; found: C 83.40, H 4.76, N 5.35, S 6.31.

Synthesis of 9–ethyl–N–(4–(9–phenyl–9H–carbazol–3–yl)phenyl)–9H–carbazol–3–amine (4.3.2–3l)

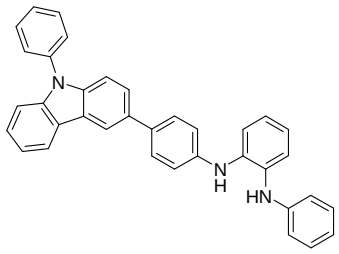


Compound **4.3.2–3l** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol) and 9–ethyl–9*H*–carbazol–2–amine (**4.3.2–2h**) (221 mg, 1.00 mmol). After column chromatography (hexane:ethyl acetate = 2:1), **4.3.2–3l** was obtained as tan solid (502 mg, 0.95 mmol, 95%).

m.p. 139–140 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.42; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ = 8.50 (d, *J*=1.5 Hz, 1H), 8.33 (d, *J*=7.8 Hz, 1H), 8.14 (s, 1H), 8.11 (d, *J*=7.5 Hz, 1H), 7.96 (d, *J*=2.0 Hz, 1H), 7.72–7.61 (m, 7H), 7.58–7.51 (m, 3H), 7.46–7.37 (m, 4H), 7.35–7.27 (m, 2H), 7.17–7.11 (m, 3H), 4.41 (q, *J*=7.0 Hz, 2H), 1.31 ppm (t, *J*=7.0 Hz, 3H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ = 144.6, 142.7, 142.3, 142.2, 141.5, 140.5, 139.1, 136.9, 133.3, 132.6, 132.2, 130.2 (2C), 127.6, 127.5 (2C), 126.7, 126.6 (2C), 126.4, 125.3, 124.9, 124.7, 123.4, 123.0, 120.8, 120.7, 120.1, 118.8, 117.6, 117.4 (2C), 117.3, 115.9, 113.1, 110.0, 109.7,

36.5 ppm; **IR** ν = 1597 (m), 1490 (s), 1472 (vs), 1450 (vs), 1326 (m), 1299 (m), 1227 (vs), 799 (s), 744 (s), 697 cm^{-1} (s); **CHN** Anal. Calcd. for $C_{38}H_{29}N_3$: C 86.50, H 5.54, N 7.96; found: C 86.32, H 5.63, N 7.90.

Synthesis of N^1–phenyl–N^2–(4–(9–phenyl–9H–carbazol–3–yl)phenyl)benzene–1,2–diamine (4.3.2–3m)



Compound **4.3.2–3m** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol) and N^1–phenylbenzene–1,2–diamine (**4.3.2–2i**) (188 mg, 1.00 mmol). After column chromatography (hexane:ethyl acetate = 2:1), **4.3.2–3m** was obtained as tan solid (423 mg, 0.84 mmol, 84%).

m.p. 92–93 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.53; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ = 8.49 (d, *J*=1.5 Hz, 1H), 8.33 (d, *J*=7.8 Hz, 1H), 7.72–7.61 (m, 7H), 7.53 (m, 1H), 7.46–7.37 (m, 4H), 7.36 (s, 1H), 7.34–7.26 (m, 3H), 7.19 (m, 2H), 7.10 (d, *J*=8.5 Hz, 2H), 6.99 (dd, *J*=8.7 Hz, 0.9 Hz, 2H), 6.94 (m, 2H), 6.76 ppm (m, 1H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ = 144.5, 143.4, 140.5, 139.0, 136.9, 134.6 (2C), 132.7, 131.6, 130.2 (2C), 129.0 (2C), 127.6, 127.3 (2C), 126.6 (2C), 126.3, 124.6, 123.4, 123.0, 122.1, 122.0, 120.8, 120.1, 119.9 (2C), 119.0, 117.5, 116.7 (2C), 116.2 (2C), 109.9, 109.6 ppm; **IR** ν = 1592 (m), 1498 (s), 1475 (s), 1452 (s), 1300 (m), 1231 (m), 1177 (w), 804 (m), 743 (vs), 695 cm^{-1} (s); **CHN** Anal. Calcd. for $C_{36}H_{27}N_3$: C 86.20, H 5.43, N 8.38; found: C 85.82, H 5.62, N 8.22.

6.11.6. Synthesis of tertiary amines

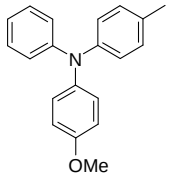
Standard procedure for the synthesis of tertiary amines

A dry 20 mL crimp cap vessel was charged with the aryl bromide (1.00 mmol), the primary amine (1.00 mmol), sodium *tert*–butoxide (235 mg, 2.40 mmol) and a magnetic stir bar and was

kept *in vacuo* for 10 min. After three nitrogen–vacuum cycles, a stock solution of Pd(dippf)maleimide (3.11 mg, 0.005 mmol) and dippf (2.13 mg, 0.005 mmol) in dry, distilled toluene (2 mL) was added via syringe. The reaction mixture was stirred at 80 °C for 20 h, whereupon a solution of the second aryl halide (1.10 mmol) in toluene (0.5 mL) was added via syringe. The temperature was increased to 120 °C and the mixture was stirred for another 24 h, then allowed to cool to room temperature and diluted with dichloromethane (30 mL) and water (30 mL). The aqueous layer was separated from the organic layer and extracted with fresh dichloromethane (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* (40 °C, 500 mbar). The crude product was further purified by flash chromatography (basic Al_2O_3, hexane/ethyl acetate), yielding the corresponding tertiary amines (75–96%).

Synthesis of 4–methoxy–N–phenyl–N–(p–tolyl)aniline (4.3.2–9a)

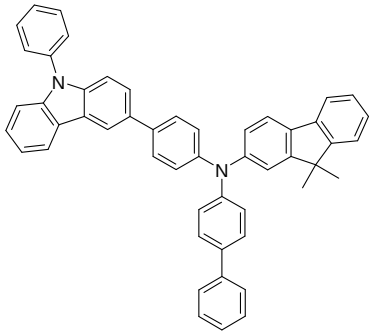
[CAS: 97126–56–2]



Compound **4.3.2–9a** was prepared following the standard procedure, starting from 4–bromotoluene (**4.3.2–1a**) (175 mg, 1.00 mmol, 126 µL), aniline (**4.3.2–2a**) (93.1 mg, 1.00 mmol, 91.2 µL) and 1–bromo–4–methoxybenzene (**4.3.2–1g**) (206 mg, 1.10 mmol, 138 µL). After column chromatography (hexane:ethyl acetate = 4:1), **4.3.2–9a** was obtained as colourless solid (276 mg, 0.95 mmol, 95%).

^{1}H–NMR (400 MHz, chloroform–*d*) δ = 7.26 (m, 2H), 7.17–7.03 (m, 8H), 6.97 (m, 1H), 6.90 (m, 2H), 3.86 (s, 3H), 2.38 ppm (s, 3H); **^{13}C–NMR** (101 MHz, chloroform–*d*) δ = 155.8, 148.4, 145.5, 141.0, 131.8, 129.7 (2C), 128.9 (2C), 126.9 (2C), 123.8 (2C), 122.0 (2C), 121.1, 114.6 (2C), 55.4, 20.7 ppm; **MS** (70 eV): m/z (%): 290 [M^+] (20), 289 (92), 275 (22), 274 (100), 77 (6), 51 (7), 50 (5).

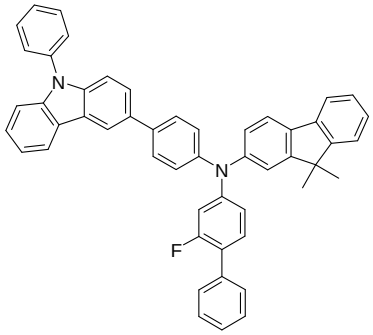
Synthesis of N–([1,1'–biphenyl]–4–yl)–9,9–dimethyl–N–(4–(9–phenyl–9H–carbazol–3-yl)phenyl)–9H–fluoren–2–amine (4.3.2–9b) [CAS: 1242056–42–3]



Compound **4.3.2–9b** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol), 9,9–dimethyl–9*H*–fluoren–2–amine (**4.3.2–2c**) (209 mg, 1.00 mmol) and 4–bromo–1,1'–biphenyl (**4.3.2–1c**) (262 mg, 1.10 mmol). After column chromatography (hexane:ethyl acetate = 4:1), **4.3.2–9b** was obtained as beige solid (624 mg, 0.92 mmol, 92%).

m.p. 155–156 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.63; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ= 5.58 (d, *J*=1.5 Hz, 1H), 8.34 (d, *J*=7.8 Hz, 1H), 7.79–7.60 (m, 13H), 7.54 (m, 2H), 7.47–7.37 (m, 5H), 7.36–7.24 (m, 5H), 7.19 (d, *J*=8.8 Hz, 2H), 7.15 (d, *J*=8.5 Hz, 2H), 7.06 (dd, *J*=8.0 Hz, 2.0 Hz, 1H), 1.39 ppm (s, 6H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ= 154.9, 153.2, 146.8, 146.4, 145.9, 140.6, 139.5, 139.4, 138.2, 136.8, 135.4, 134.1, 134.1, 132.0, 130.2 (2C), 128.9 (2C), 127.7 (2C), 127.7, 127.6 (2C), 127.1, 127.0, 126.7, 126.6 (2C), 126.4, 126.2 (2C), 124.9, 124.3, 123.6, 123.4, 123.4 (2C), 122.9, 122.7, 121.2, 120.8, 120.2, 119.6, 118.8, 118.2, 110.0, 109.7, 99.5, 46.5, 26.8 ppm (2C); **IR** ν = 1599 (m), 1484 (s), 1474 (s), 1458 (s), 1449 (vs), 1298 (m), 1232 (s), 760 (s), 735 (vs), 696 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{51}H_{38}N_2$: C 90.23, H 5.64, N 4.13; found: C 90.27, H 5.46, N 4.10.

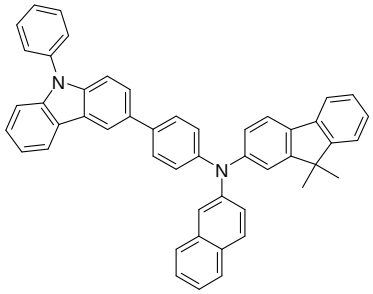
Synthesis of N–(2–fluoro–[1,1'–biphenyl]–4–yl)–9,9–dimethyl–N–(4–(9–phenyl–9H-carbazol–3–yl)phenyl)–9H–fluoren–2–amine (4.3.2–9c)



Compound **4.3.2–9c** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol), 9,9–dimethyl–9*H*–fluoren–2–amine (**4.3.2–2c**) (209 mg, 1.00 mmol) and 4–bromo–2–fluoro–1,1'–biphenyl (**4.3.2–1h**) (282 mg, 1.10 mmol). After column chromatography (hexane:ethyl acetate = 9:1), **4.3.2–9c** was obtained as beige solid (655 mg, 0.94 mmol, 94%).

m.p. 171–172 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.62; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ = 8.58 (d, *J*=1.5 Hz, 1H), 8.33 (d, *J*=7.8 Hz, 1H), 7.77 (m, 4H), 7.69 (m, 3H), 7.62 (m, 2H), 7.53 (m, 4H), 7.46–7.22 (m, 13H), 7.1 (dd, *J*=8.3 Hz, 2.0 Hz, 1H), 6.89 (dd, *J*=8.5 Hz, 2.3 Hz, 1H), 6.82 (dd, *J*=13.3 Hz, 2.3 Hz, 1H), 1.39 ppm (s, 6H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ = 159.5 (d, J=245.8 Hz, 1C), 155.1, 153.3, 148.5 (d, J=10.3 Hz, 1C), 145.6, 145.1, 140.6, 139.5, 138.1, 136.8, 136.4, 135.0, 135.0 (d, J=1.5 Hz, 1C), 131.8, 131.2 (d, J=5.9 Hz, 1C), 130.2 (2C), 128.6 (2C), 128.4 (d, J=3.7 Hz, 2C), 127.9 (2C), 127.7, 127.3, 127.1, 127.0, 126.6 (2C), 126.5, 125.1 (2C), 125.0, 124.4, 123.4, 122.9, 122.7, 121.4, 121.0 (d, J=13.9 Hz, 1C), 120.8, 120.2, 119.8, 119.7, 118.3, 117.7 (d, J=1.5 Hz, 1C), 110.0, 109.7, 108.4 (d, J=25.7 Hz, 1C), 46.6, 26.7 ppm (2C); **^{19}F–NMR** (376.5 MHz, DMSO–d_6) δ = -116.70 ppm (s, 1F); **IR** ν = 1600 (m), 1501 (m), 1474 (s), 1458 (s), 1449 (s), 1310 (m), 1232 (m), 759 (s), 736 (s), 696 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{51}H_{37}FN_2$: C 87.90, H 5.35, N 4.02; found: C 87.77, H 5.50, N 3.93.

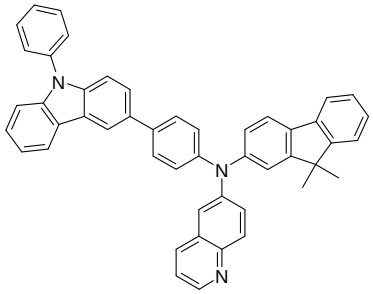
Synthesis of 9,9–dimethyl–N–(naphthalen–2–yl)–N–(4–(9–phenyl–9H–carbazol–3-yl)phenyl)–9H–fluoren–2–amine (4.3.2–9d)



Compound **4.3.2–9d** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol), 9,9–dimethyl–9*H*–fluoren–2–amine (**4.3.2–2c**) (209 mg, 1.00 mmol) and 2–bromonaphthalene (**4.3.2–1i**) (230 mg, 1.10 mmol). After column chromatography (hexane:ethyl acetate = 9:1), **4.3.2–9d** was obtained as beige solid (628 mg, 0.96 mmol, 96%).

m.p. 196–197 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.62; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ= 8.58 (m, 1H), 8.33 (d, *J*=7.8 Hz, 1H), 7.84 (m, 2H), 7.77–7.60 (m, 10H), 7.57–7.47 (m, 3H), 7.46–7.35 (m, 5H), 7.34 (d, *J*=2.0 Hz, 1H), 7.33–7.23 (m, 4H), 7.19 (d, *J*=8.5 Hz, 2H), 7.05 (dd, *J*=8.3 Hz, 2.0 Hz, 1H), 1.36 ppm (s, 6H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ= 154.9, 153.2, 146.6, 146.1, 145.0, 140.6, 139.4, 138.3, 136.8, 135.4, 134.1, 134.0, 131.9, 130.2 (2C), 129.7, 129.1, 127.7 (2C), 127.7, 127.5, 127.1, 126.9, 126.7, 126.6 (2C), 126.5, 126.4, 124.9, 124.6, 124.2 (2C), 124.0, 123.4, 123.3, 122.9, 122.7, 121.2, 120.8, 120.2, 119.6 (2C), 118.5, 118.2, 110.0, 109.7, 46.5, 26.7 ppm (2C); **IR** ν = 1597 (m), 1501 (m), 1458 (s), 1449 (s), 1299 (m), 1229 (m), 807 (m), 745 (s), 735 (vs), 697 cm^{-1} (m); **CHN** Anal. Calcd. for $C_{49}H_{36}N_2$: C 90.15, H 5.56, N 4.29; found: C 89.93, H 5.70, N 4.14.

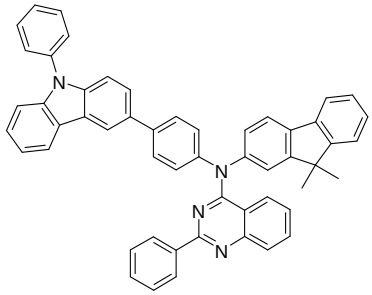
Synthesis of N–(9,9–dimethyl–9H–fluoren–2–yl)–N–(4–(9–phenyl–9H–carbazol–3-yl)phenyl)quinolin–6–amine (4.3.2–9e)



Compound **4.3.2–9e** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol), 9,9–dimethyl–9*H*–fluoren–2–amine (**4.3.2–2c**) (209 mg, 1.00 mmol) and 6–chloroquinoline (**4.3.2–1j**) (182 mg, 1.10 mmol). After column chromatography (hexane:ethyl acetate = 2:1), **4.3.2–9e** was obtained as yellow solid (595 mg, 0.91 mmol, 91%).

m.p. 168–169 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.14; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ= 8.74 (dd, *J*=4.3 Hz, 1.8 Hz, 1H), 8.58 (d, *J*=1.5 Hz, 1H), 8.33 (d, *J*=7.8 Hz, 1H), 8.14 (m, 1H), 7.93 (m, 1H), 7.78–7.60 (m, 9H), 7.56–7.47 (m, 4H), 7.45–7.35 (m, 5H), 7.34–7.20 (m, 5H), 7.08 (dd, *J*=8.3 Hz, 2.0 Hz, 1H), 1.37 ppm (s, 6H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ= 155.0, 153.2, 148.7, 146.3, 145.7, 145.4, 144.6, 140.5, 139.4, 138.2, 136.8, 135.8, 134.7, 134.4, 131.8, 130.2 (2C), 130.1, 129.0, 127.8 (2C), 127.6, 127.1, 126.8, 126.8, 126.6 (2C), 126.4, 124.9, 124.5 (2C), 123.6, 123.4, 122.9, 122.7, 121.7, 121.2, 120.8, 120.1, 119.6, 118.9, 118.3, 118.2, 110.0, 109.7, 46.7, 26.7 ppm (2C); **IR** ν = 1599 (m), 1497 (s), 1474 (s), 1458 (vs), 1448 (vs), 1299 (s), 1231 (vs), 758 (s), 735 (vs), 696 cm^{-1} (s); **CHN** Anal. Calcd. for $C_{48}H_{35}N_3$: C 88.18, H 5.40, N 6.43; found: C 88.06, H 5.62, N 6.20.

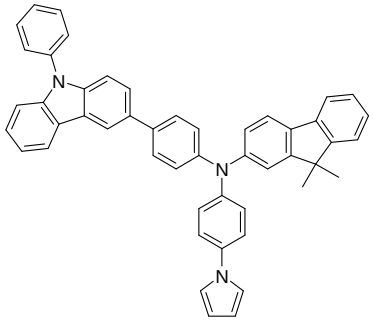
Synthesis of N–(9,9–dimethyl–9H–fluoren–2–yl)–2–phenyl–N–(4–(9–phenyl–9H-carbazol–3–yl)phenyl)quinazolin–4–amine (4.3.2–9f)



Compound **4.3.2–9f** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol), 9,9–dimethyl–9*H*–fluoren–2–amine (**4.3.2–2c**) (209 mg, 1.00 mmol) and 4–chloro–2–phenylquinazoline (**4.3.2–1k**) (273 mg, 1.10 mmol). After column chromatography (hexane:ethyl acetate = 4:1), **4.3.2–9f** was obtained as yellow solid (549 mg, 0.75 mmol, 75%).

m.p. 206–207 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.56; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ = 8.67 (d, *J*=1.5 Hz, 1H), 8.36 (d, *J*=7.8 Hz, 1H), 8.23 (dd, *J*=8.0 Hz, 1.8 Hz, 2H), 7.95 (d, *J*=8.0 Hz, 1H), 7.85 (dd, *J*=8.3 Hz, 5.3 Hz, 3H), 7.82–7.52 (m, 10H), 7.46–7.23 (m, 13H), 7.14 (dd, *J*=8.2 Hz, 1.9 Hz, 1H), 1.38 ppm (s, 6H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ = 162.7, 158.7, 154.6, 153.5, 152.9, 145.9, 145.3, 140.6, 139.6, 138.0, 137.8, 137.7, 136.7, 135.9, 133.0, 131.4, 130.4, 130.2 (2C), 128.7, 128.3, 127.8 (2C), 127.7 (3C), 127.2, 127.1, 126.7 (2C), 126.6, 126.6 (2C), 126.5, 125.8, 125.5, 125.0, 124.9, 123.5, 122.9, 122.8, 121.2, 121.0, 120.9, 120.2, 120.0, 118.5, 116.4, 110.0, 109.7, 46.5, 26.6 ppm (2C); **IR** ν = 1484 (vs), 1474 (vs), 1457 (s), 1375 (vs), 1331 (vs), 1232 (s), 759 (vs), 736 (vs), 707 (vs), 698 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{53}H_{38}N_4$: C 87.09, H 5.24, N 7.67; found: C 86.78, H 5.48, N 7.55.

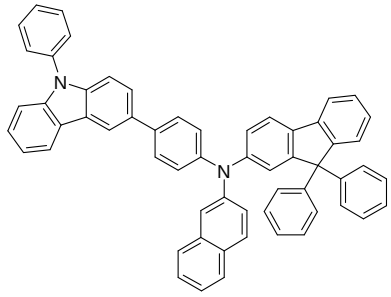
Synthesis of N–(4–(1H–pyrrol–1–yl)phenyl)–9,9–dimethyl–N–(4–(9–phenyl–9H-carbazol–3–yl)phenyl)–9H–fluoren–2–amine (4.3.2–9g)



Compound **4.3.2–9g** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol), 9,9–dimethyl–9*H*–fluoren–2–amine (**4.3.2–2c**) (209 mg, 1.00 mmol) and 1–(4–chlorophenyl)–1*H*–pyrrole (**4.3.2–1l**) (199 mg, 1.10 mmol). After column chromatography (hexane:ethyl acetate = 9:1), **4.3.2–9g** was obtained as colourless solid (633 mg, 0.95 mmol, 95%).

m.p. 173–174 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.64; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ = 8.57 (d, *J*=1.5 Hz, 1H), 8.34 (d, *J*=7.5 Hz, 1H), 7.77–7.62 (m, 9H), 7.57–7.48 (m, 4H), 7.47–7.37 (m, 3H), 7.34–7.24 (m, 6H), 7.16 (d, *J*=8.8 Hz, 4H), 7.03 (dd, *J*=8.2 Hz, 2.1 Hz, 1H), 6.25 (t, *J*=2.1 Hz, 2H), 1.39 ppm (s, 6H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ = 154.9, 153.2, 146.6, 146.0, 144.6, 140.6, 139.4, 138.3, 136.8, 135.3, 135.1, 133.9, 132.0, 130.2 (2C), 127.7 (2C), 127.7, 127.1, 126.7, 126.6 (2C), 126.5, 124.9 (2C), 123.7 (2C), 123.4, 123.0, 122.9, 122.7, 121.2, 120.8, 120.6 (2C), 120.2, 119.6, 118.9 (2C), 118.2, 118.2 (2C), 110.3 (2C), 110.0, 109.7, 46.5, 26.8 ppm (2C); **IR** ν = 1599 (w), 1512 (vs), 1501 (s), 1449 (s), 1311 (m), 1232 (m), 1069 (m), 735 (s), 723 (vs), 698 cm^{-1} (s); **CHN** Anal. Calcd. for $C_{49}H_{37}N_3$: C 88.12, H 5.58, N 6.29; found: C 88.07, H 5.75, N 6.19.

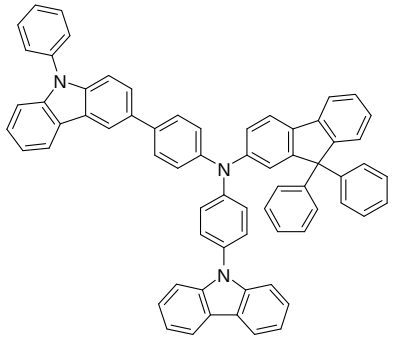
Synthesis of N–(naphthalen–2–yl)–9,9–diphenyl–N–(4–(9–phenyl–9H–carbazol–3-yl)phenyl)–9H–fluoren–2–amine (4.3.2–9h)



Compound **4.3.2–9h** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol), 9,9–diphenyl–9*H*–fluoren–2–amine (**4.3.2–2b**) (333 mg, 1.00 mmol) and 2–bromonaphthalene (**4.3.2–1i**) (230 mg, 1.10 mmol). After column chromatography (hexane:ethyl acetate = 9:1), **4.3.2–9h** was obtained as beige solid (743 mg, 0.96 mmol, 96%).

m.p. 185–186 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.54; **^{1}H–NMR** (400 MHz, DMSO–d_6) δ = 8.48 (s, 1H), 8.27 (d, *J*=7.5 Hz, 1H), 7.77–7.65 (m, 4H), 7.61–7.47 (m, 8H), 7.47–7.40 (m, 2H), 7.38–7.20 (m, 8H), 7.19–6.95 ppm (m, 16H); **^{13}C–NMR** (101 MHz, DMSO–d_6) δ = 151.9, 150.3, 146.9, 145.5, 145.3 (2C), 144.6, 140.5, 139.4 (2C), 136.7, 135.8, 134.5, 133.9, 131.8, 130.1 (2C), 129.7, 129.7, 129.0, 128.2 (4C), 127.6 (br. s, 6C), 127.4, 127.0, 126.8, 126.6 (2C), 126.5 (3C), 126.4 (2C), 125.9, 124.8, 124.6, 124.5 (2C), 123.8, 123.4, 123.0, 122.9, 121.5, 121.1, 120.7, 120.1, 119.8, 119.6, 118.1, 109.9, 109.7, 64.8 ppm; **IR** ν = 1596 (m), 1501 (m), 1474 (m), 1452 (s), 1295 (m), 1281 (m), 1231 (m), 805 (m), 743 (vs), 696 cm^{-1} (vs); **CHN** Anal. Calcd. for $C_{59}H_{40}N_2$: C 91.21, H 5.19, N 3.61; found: C 91.07, H 5.45, N 3.47.

Synthesis of N–(4–(9H–carbazol–9–yl)phenyl)–9,9–diphenyl–N–(4–(9–phenyl–9H-carbazol–3–yl)phenyl)–9H–fluoren–2–amine (4.3.2–9i)



Compound **4.3.2–9i** was prepared following the standard procedure, starting from 3–(4–bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (398 mg, 1.00 mmol), 9,9–diphenyl–9*H*–fluoren–2–amine (**4.3.2–2b**) (333 mg, 1.00 mmol) and 9–(4–bromophenyl)–9*H*–carbazole (**4.3.2–1m**) (414 mg, 1.10 mmol). After column chromatography (hexane:ethyl acetate = 4:1), **4.3.2–9i** was obtained as beige solid (849 mg, 0.95 mmol, 95%).

m.p. 192–193 °C; **Rf** (SiO_2, hexane:ethyl acetate = 4:1): 0.52; **^{1}H–NMR** (400 MHz, dioxane–d_8) δ = 8.45 (s, 1H), 8.23 (d, *J*=7.8 Hz, 1H), 8.16 (d, *J*=7.8 Hz, 2H), 7.76–7.53 (m, 9H), 7.48–7.35 (m, 12H), 7.34–7.14 ppm (m, 20H); **^{13}C–NMR** (101 MHz, dioxane–d_8) δ = 153.8, 152.0, 148.3, 147.8, 146.9, 146.9 (2C), 142.2, 141.9 (2C), 141.0, 140.8, 138.7, 137.8, 136.2, 133.7, 132.6, 130.7 (2C), 129.1 (4C), 129.0 (4C), 129.0, 128.7 (2C), 128.4, 128.2, 128.0 (2C), 127.9, 127.5 (2C), 127.1, 127.0, 126.7 (2C), 125.8 (2C), 125.8 (2C), 125.3 (2C), 124.9, 124.6, 124.4, 124.1 (2C), 123.2, 122.0, 121.2, 121.1 (2C), 121.0, 120.6 (2C), 120.6, 119.1, 110.9, 110.7, 110.6 (2C), 66.4 ppm; **IR** ν = 1598 (m), 1509 (s), 1475 (m), 1451 (vs), 1306 (m), 1286 (m), 1232 (m), 747 (vs), 724 (s), 699 cm^{-1} (s); **CHN** Anal. Calcd. for $C_{67}H_{45}N_3$: C 90.21, H 5.08, N 4.71; found: C 89.99, H 5.18, N 4.72.

6.11.7. Preparative scale syntheses

Preparative scale synthesis of 9,9–dimethyl–N–(4–(9–phenyl–9H–carbazol–3–yl)phenyl)-9H–fluoren–2-amine (4.3.2–3f) with Pd(dippf)maleimide

3–(4–Bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (7.97 g, 20.0 mmol), 9,9–dimethyl–9*H*–fluoren–2–amine (**4.3.2–2c**) (4.17 g, 20.0 mmol), sodium *tert*–butoxide (2.35 g, 24.0 mmol), dippf (8.5 mg, 0.02 mmol) and a magnetic stir bar were added to a dry flask with equipped reflux condenser, gas inlet and overpressure valve and kept *in vacuo* for 10 min. After three nitrogen–vacuum cycles, the degassed, distilled toluene (30 mL) and a solution of Pd(dippf)maleimide (24.9 mg, 0.04 mmol) in toluene (10 mL) were added. The reaction mixture was heated to 70 °C for 20 h and was then allowed to cool to room temperature. Water (60 mL) was added and the mixture was extracted with dichloromethane (150 mL). The organic layer was separated, dried over $MgSO_4$ (5 g), filtered through a short plug of basic aluminum oxide and concentrated *in vacuo* (40 °C, 10 mbar). The slightly yellow residue was washed with diethyl ether (3 × 20 mL) and dried *in vacuo* (10^{-2} mbar) for 2 h. The title compound was obtained as colourless solid (10.2 g, 19.4 mmol, 97%). The analytical data matched those described before.

Preparative scale synthesis of 9,9–dimethyl–N–(4–(9–phenyl–9H–carbazol–3–yl)phenyl)-9H–fluoren–2–amine (4.3.2–3f) with a Pd(dippf)(vs)tol solution

3–(4–Bromophenyl)–9–phenyl–9*H*–carbazole (**4.3.2–1f**) (7.97 g, 20.0 mmol), 9,9–dimethyl–9*H*–fluoren–2–amine (**4.3.2–2c**) (4.17 g, 20.0 mmol), sodium *tert*–butoxide (2.35 g, 24.0 mmol) and a magnetic stir bar were added to a dry flask with equipped reflux condenser, gas inlet and overpressure valve and kept *in vacuo* for 10 min, followed by three nitrogen–vacuum cycles. A catalyst stock solution was prepared by mixing dippf (214 mg, 0.50 mmol), toluene (0.5 mL) and a solution of palladium(0)–1,3–divinyl–1,1,3,3-tetramethyldisiloxane (0.5 mL, 10.87% palladium). Dry, distilled toluene (40 mL) and the catalyst solution (100 µL, 0.04 mmol palladium) were added to the solid reactants. The reaction mixture was stirred at 70 °C for 20 h and was then allowed to cool to room temperature. Water (60 mL) was added and the mixture was extracted with dichloromethane (150 mL). The organic layer was separated, dried over $MgSO_4$ (5 g), filtered through a short plug of basic aluminum oxide and concentrated *in vacuo* (40 °C, 10 mbar). The slightly yellow residue was washed with

diethyl ether (3 × 20 mL) and dried *in vacuo* (10^{-2} mbar) for 2h. The title compound was obtained as colourless solid (9,71 g, 18.4 mmol, 92%). The analytical data matched those described before.

7. Kristallographische Daten

Pd(dippf)maleimide (4.3.2–8)

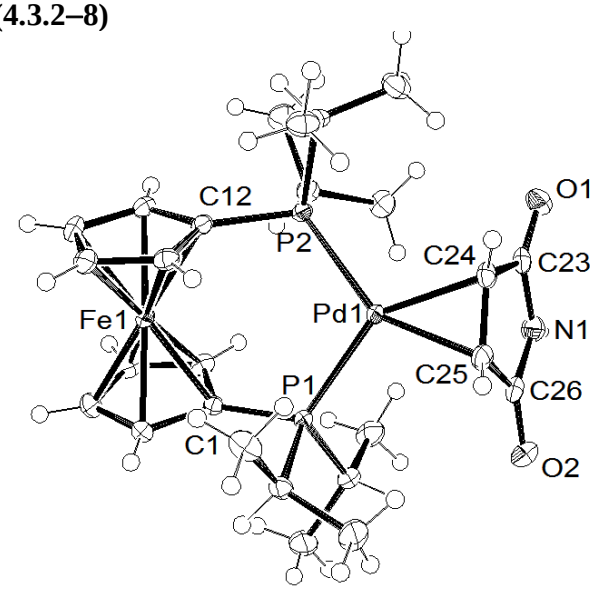


Table 1. Crystal data and structure refinement for 13071o.

Empirical formula	C26 H39 Fe N O2 P2 Pd	
Formula weight	621.77	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 10.27050(10) Å	α= 90°.
	b = 11.51790(10) Å	β= 95.4520(10)°.
	c = 22.5794(3) Å	γ = 90°.
Volume	2658.94(5) $Å^3$	
Z	4	
Density (calculated)	1.553 Mg/m^3	
Absorption coefficient	1.366 mm^{-1}	
F(000)	1280	
Crystal size	0.28 x 0.22 x 0.12 mm^3	
Theta range for data collection	2.75 to 30.00°.	
Index ranges	–14<=h<=12, –16<=k<=16, –31<=l<=29	
Reflections collected	17419	
Independent reflections	7746 [R(int) = 0.0216]	
Completeness to theta = 30.00°	99.8%	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.8533 and 0.7010	
Refinement method	Full–matrix least–squares on F^2	
Data / restraints / parameters	7746 / 0 / 315	
Goodness–of–fit on F^2	1.072	
Final R indices [I>2sigma(I)]	R1 = 0.0264, wR2 = 0.0527	
R indices (all data)	R1 = 0.0310, wR2 = 0.0542	
Largest diff. peak and hole	0.437 and –0.628 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 13071o. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Fe(1)	11721(1)	–644(1)	3561(1)	14(1)
C(1)	9830(2)	–69(1)	3506(1)	14(1)
C(2)	9928(2)	–1050(2)	3124(1)	18(1)
C(3)	10417(2)	–2007(2)	3473(1)	23(1)
C(4)	10623(2)	–1646(2)	4073(1)	24(1)
C(5)	10266(2)	–455(2)	4099(1)	18(1)
P(1)	9310(1)	1396(1)	3303(1)	13(1)
C(6)	8753(2)	1238(2)	2502(1)	19(1)
C(7)	9918(2)	1237(2)	2128(1)	26(1)
C(8)	7789(2)	2193(2)	2287(1)	35(1)
C(9)	7754(2)	1514(2)	3656(1)	20(1)
C(10)	8003(2)	1677(2)	4327(1)	27(1)
C(11)	6821(2)	496(2)	3501(1)	30(1)
C(12)	13014(2)	689(1)	3722(1)	16(1)
C(13)	12877(2)	404(2)	3101(1)	18(1)
C(14)	13246(2)	–773(2)	3033(1)	22(1)
C(15)	13606(2)	–1237(2)	3605(1)	23(1)
C(16)	13471(2)	–346(2)	4030(1)	19(1)
P(2)	12626(1)	2102(1)	4014(1)	14(1)
C(17)	12602(2)	1811(2)	4823(1)	18(1)
C(18)	13941(2)	1618(2)	5163(1)	26(1)
C(19)	11847(2)	2751(2)	5125(1)	25(1)
C(20)	14192(2)	2883(2)	3951(1)	19(1)
C(21)	14428(2)	3036(2)	3300(1)	25(1)
C(22)	14253(2)	4066(2)	4263(1)	27(1)
Pd(1)	10727(1)	2934(1)	3553(1)	12(1)
C(23)	10645(2)	5094(2)	4175(1)	20(1)
O(1)	11402(1)	5475(1)	4582(1)	26(1)
C(24)	10905(2)	4785(2)	3563(1)	19(1)
C(25)	9683(2)	4454(2)	3256(1)	20(1)
C(26)	8670(2)	4559(2)	3674(1)	22(1)
O(2)	7495(1)	4407(1)	3592(1)	29(1)
N(1)	9327(2)	4893(1)	4217(1)	23(1)

Table 3. Bond lengths [Å] and angles [°] for 13071o.

Fe(1)–C(5)	2.0250(17)	C(12)–C(16)	1.437(2)
Fe(1)–C(16)	2.0277(17)	C(12)–P(2)	1.8148(17)
Fe(1)–C(12)	2.0401(17)	C(13)–C(14)	1.420(2)
Fe(1)–C(1)	2.0447(16)	C(13)–H(13)	0.9500
Fe(1)–C(13)	2.0450(17)	C(14)–C(15)	1.415(3)
Fe(1)–C(4)	2.0459(18)	C(14)–H(14)	0.9500
Fe(1)–C(15)	2.0462(17)	C(15)–C(16)	1.420(2)
Fe(1)–C(2)	2.0581(17)	C(15)–H(15)	0.9500
Fe(1)–C(3)	2.0605(18)	C(16)–H(16)	0.9500
Fe(1)–C(14)	2.0624(17)	P(2)–C(17)	1.8592(17)
C(1)–C(2)	1.431(2)	P(2)–C(20)	1.8604(17)
C(1)–C(5)	1.440(2)	P(2)–Pd(1)	2.3277(4)
C(1)–P(1)	1.8155(17)	C(17)–C(18)	1.527(2)
C(2)–C(3)	1.418(3)	C(17)–C(19)	1.529(2)
C(2)–H(2)	0.9500	C(17)–H(17)	1.0000
C(3)–C(4)	1.414(3)	C(18)–H(18A)	0.9800
C(3)–H(3)	0.9500	C(18)–H(18B)	0.9800
C(4)–C(5)	1.423(3)	C(18)–H(18C)	0.9800
C(4)–H(4)	0.9500	C(19)–H(19A)	0.9800
C(5)–H(5)	0.9500	C(19)–H(19B)	0.9800
P(1)–C(6)	1.8542(17)	C(19)–H(19C)	0.9800
P(1)–C(9)	1.8560(17)	C(20)–C(21)	1.523(2)
P(1)–Pd(1)	2.3273(4)	C(20)–C(22)	1.532(3)
C(6)–C(8)	1.528(3)	C(20)–H(20)	1.0000
C(6)–C(7)	1.529(3)	C(21)–H(21A)	0.9800
C(6)–H(6)	1.0000	C(21)–H(21B)	0.9800
C(7)–H(7A)	0.9800	C(21)–H(21C)	0.9800
C(7)–H(7B)	0.9800	C(22)–H(22A)	0.9800
C(7)–H(7C)	0.9800	C(22)–H(22B)	0.9800
C(8)–H(8A)	0.9800	C(22)–H(22C)	0.9800
C(8)–H(8B)	0.9800	Pd(1)–C(25)	2.1285(17)
C(8)–H(8C)	0.9800	Pd(1)–C(24)	2.1401(17)
C(9)–C(10)	1.526(3)	C(23)–O(1)	1.227(2)
C(9)–C(11)	1.533(3)	C(23)–N(1)	1.386(2)
C(9)–H(9)	1.0000	C(23)–C(24)	1.475(2)
C(10)–H(10A)	0.9800	C(24)–C(25)	1.427(3)
C(10)–H(10B)	0.9800	C(24)–H(24)	0.94(2)
C(10)–H(10C)	0.9800	C(25)–C(26)	1.474(3)
C(11)–H(11A)	0.9800	C(25)–H(25)	0.91(2)
C(11)–H(11B)	0.9800	C(26)–O(2)	1.216(2)
C(11)–H(11C)	0.9800	C(26)–N(1)	1.396(2)
C(12)–C(13)	1.434(2)	N(1)–H(1N)	0.83(2)
C(5)–Fe(1)–C(16)	109.64(7)	C(12)–Fe(1)–C(13)	41.10(7)
C(5)–Fe(1)–C(12)	108.49(7)	C(1)–Fe(1)–C(13)	111.84(7)
C(16)–Fe(1)–C(12)	41.38(7)	C(5)–Fe(1)–C(4)	40.92(7)
C(5)–Fe(1)–C(1)	41.44(6)	C(16)–Fe(1)–C(4)	107.97(8)
C(16)–Fe(1)–C(1)	140.05(7)	C(12)–Fe(1)–C(4)	135.09(7)
C(12)–Fe(1)–C(1)	111.45(6)	C(1)–Fe(1)–C(4)	69.24(7)
C(5)–Fe(1)–C(13)	137.58(7)	C(13)–Fe(1)–C(4)	176.16(8)
C(16)–Fe(1)–C(13)	68.73(7)	C(5)–Fe(1)–C(15)	139.04(7)

C(16)–Fe(1)–C(15)	40.80(7)	C(4)–C(5)–C(1)	108.52(15)
C(12)–Fe(1)–C(15)	69.21(7)	C(4)–C(5)–Fe(1)	70.33(10)
C(1)–Fe(1)–C(15)	179.15(7)	C(1)–C(5)–Fe(1)	70.01(9)
C(13)–Fe(1)–C(15)	68.25(7)	C(4)–C(5)–H(5)	125.7
C(4)–Fe(1)–C(15)	110.72(8)	C(1)–C(5)–H(5)	125.7
C(5)–Fe(1)–C(2)	68.54(7)	Fe(1)–C(5)–H(5)	125.5
C(16)–Fe(1)–C(2)	175.77(7)	C(1)–P(1)–C(6)	102.16(8)
C(12)–Fe(1)–C(2)	142.56(7)	C(1)–P(1)–C(9)	101.80(8)
C(1)–Fe(1)–C(2)	40.81(6)	C(6)–P(1)–C(9)	103.15(8)
C(13)–Fe(1)–C(2)	115.28(7)	C(1)–P(1)–Pd(1)	118.95(5)
C(4)–Fe(1)–C(2)	68.07(7)	C(6)–P(1)–Pd(1)	116.03(6)
C(15)–Fe(1)–C(2)	138.34(7)	C(9)–P(1)–Pd(1)	112.62(6)
C(5)–Fe(1)–C(3)	68.31(7)	C(8)–C(6)–C(7)	110.06(16)
C(16)–Fe(1)–C(3)	135.64(7)	C(8)–C(6)–P(1)	111.68(13)
C(12)–Fe(1)–C(3)	175.30(7)	C(7)–C(6)–P(1)	110.79(12)
C(1)–Fe(1)–C(3)	68.67(7)	C(8)–C(6)–H(6)	108.1
C(13)–Fe(1)–C(3)	143.53(7)	C(7)–C(6)–H(6)	108.1
C(4)–Fe(1)–C(3)	40.27(8)	P(1)–C(6)–H(6)	108.1
C(15)–Fe(1)–C(3)	110.72(8)	C(6)–C(7)–H(7A)	109.5
C(2)–Fe(1)–C(3)	40.29(7)	C(6)–C(7)–H(7B)	109.5
C(5)–Fe(1)–C(14)	177.35(7)	H(7A)–C(7)–H(7B)	109.5
C(16)–Fe(1)–C(14)	68.29(7)	C(6)–C(7)–H(7C)	109.5
C(12)–Fe(1)–C(14)	68.87(7)	H(7A)–C(7)–H(7C)	109.5
C(1)–Fe(1)–C(14)	139.27(7)	H(7B)–C(7)–H(7C)	109.5
C(13)–Fe(1)–C(14)	40.45(7)	C(6)–C(8)–H(8A)	109.5
C(4)–Fe(1)–C(14)	140.87(8)	C(6)–C(8)–H(8B)	109.5
C(15)–Fe(1)–C(14)	40.29(7)	H(8A)–C(8)–H(8B)	109.5
C(2)–Fe(1)–C(14)	113.64(7)	C(6)–C(8)–H(8C)	109.5
C(3)–Fe(1)–C(14)	114.31(7)	H(8A)–C(8)–H(8C)	109.5
C(2)–C(1)–C(5)	106.44(15)	H(8B)–C(8)–H(8C)	109.5
C(2)–C(1)–P(1)	128.20(13)	C(10)–C(9)–C(11)	111.23(16)
C(5)–C(1)–P(1)	125.34(13)	C(10)–C(9)–P(1)	111.44(12)
C(2)–C(1)–Fe(1)	70.10(9)	C(11)–C(9)–P(1)	113.06(12)
C(5)–C(1)–Fe(1)	68.54(9)	C(10)–C(9)–H(9)	106.9
P(1)–C(1)–Fe(1)	124.85(8)	C(11)–C(9)–H(9)	106.9
C(3)–C(2)–C(1)	108.72(16)	P(1)–C(9)–H(9)	106.9
C(3)–C(2)–Fe(1)	69.94(10)	C(9)–C(10)–H(10A)	109.5
C(1)–C(2)–Fe(1)	69.09(9)	C(9)–C(10)–H(10B)	109.5
C(3)–C(2)–H(2)	125.6	H(10A)–C(10)–H(10B)	109.5
C(1)–C(2)–H(2)	125.6	C(9)–C(10)–H(10C)	109.5
Fe(1)–C(2)–H(2)	126.9	H(10A)–C(10)–H(10C)	109.5
C(4)–C(3)–C(2)	108.41(16)	H(10B)–C(10)–H(10C)	109.5
C(4)–C(3)–Fe(1)	69.31(10)	C(9)–C(11)–H(11A)	109.5
C(2)–C(3)–Fe(1)	69.77(10)	C(9)–C(11)–H(11B)	109.5
C(4)–C(3)–H(3)	125.8	H(11A)–C(11)–H(11B)	109.5
C(2)–C(3)–H(3)	125.8	C(9)–C(11)–H(11C)	109.5
Fe(1)–C(3)–H(3)	126.7	H(11A)–C(11)–H(11C)	109.5
C(3)–C(4)–C(5)	107.91(16)	H(11B)–C(11)–H(11C)	109.5
C(3)–C(4)–Fe(1)	70.42(10)	C(13)–C(12)–C(16)	106.38(15)
C(5)–C(4)–Fe(1)	68.75(10)	C(13)–C(12)–P(2)	123.79(13)
C(3)–C(4)–H(4)	126.0	C(16)–C(12)–P(2)	129.82(13)
C(5)–C(4)–H(4)	126.0	C(13)–C(12)–Fe(1)	69.63(10)
Fe(1)–C(4)–H(4)	126.4	C(16)–C(12)–Fe(1)	68.85(10)

P(2)–C(12)–Fe(1)	125.28(9)
C(14)–C(13)–C(12)	108.74(16)
C(14)–C(13)–Fe(1)	70.43(10)
C(12)–C(13)–Fe(1)	69.27(9)
C(14)–C(13)–H(13)	125.6
C(12)–C(13)–H(13)	125.6
Fe(1)–C(13)–H(13)	126.2
C(15)–C(14)–C(13)	108.11(16)
C(15)–C(14)–Fe(1)	69.24(10)
C(13)–C(14)–Fe(1)	69.11(10)
C(15)–C(14)–H(14)	125.9
C(13)–C(14)–H(14)	125.9
Fe(1)–C(14)–H(14)	127.3
C(14)–C(15)–C(16)	108.15(16)
C(14)–C(15)–Fe(1)	70.47(10)
C(16)–C(15)–Fe(1)	68.90(10)
C(14)–C(15)–H(15)	125.9
C(16)–C(15)–H(15)	125.9
Fe(1)–C(15)–H(15)	126.3
C(15)–C(16)–C(12)	108.62(16)
C(15)–C(16)–Fe(1)	70.30(10)
C(12)–C(16)–Fe(1)	69.77(10)
C(15)–C(16)–H(16)	125.7
C(12)–C(16)–H(16)	125.7
Fe(1)–C(16)–H(16)	125.8
C(12)–P(2)–C(17)	102.69(8)
C(12)–P(2)–C(20)	100.62(8)
C(17)–P(2)–C(20)	104.74(8)
C(12)–P(2)–Pd(1)	114.24(6)
C(17)–P(2)–Pd(1)	115.11(6)
C(20)–P(2)–Pd(1)	117.42(6)
C(18)–C(17)–C(19)	110.44(15)
C(18)–C(17)–P(2)	115.17(13)
C(19)–C(17)–P(2)	111.39(12)
C(18)–C(17)–H(17)	106.4
C(19)–C(17)–H(17)	106.4
P(2)–C(17)–H(17)	106.4
C(17)–C(18)–H(18A)	109.5
C(17)–C(18)–H(18B)	109.5
H(18A)–C(18)–H(18B)	109.5
C(17)–C(18)–H(18C)	109.5
H(18A)–C(18)–H(18C)	109.5
H(18B)–C(18)–H(18C)	109.5
C(17)–C(19)–H(19A)	109.5
C(17)–C(19)–H(19B)	109.5
H(19A)–C(19)–H(19B)	109.5
C(17)–C(19)–H(19C)	109.5
H(19A)–C(19)–H(19C)	109.5
H(19B)–C(19)–H(19C)	109.5
C(21)–C(20)–C(22)	109.72(15)
C(21)–C(20)–P(2)	110.37(12)
C(22)–C(20)–P(2)	113.14(12)
C(21)–C(20)–H(20)	107.8
C(22)–C(20)–H(20)	107.8
P(2)–C(20)–H(20)	107.8
C(20)–C(21)–H(21A)	109.5
C(20)–C(21)–H(21B)	109.5
H(21A)–C(21)–H(21B)	109.5
C(20)–C(21)–H(21C)	109.5
H(21A)–C(21)–H(21C)	109.5
H(21B)–C(21)–H(21C)	109.5
C(20)–C(22)–H(22A)	109.5
C(20)–C(22)–H(22B)	109.5
H(22A)–C(22)–H(22B)	109.5
C(20)–C(22)–H(22C)	109.5
H(22A)–C(22)–H(22C)	109.5
H(22B)–C(22)–H(22C)	109.5
C(25)–Pd(1)–C(24)	39.07(7)
C(25)–Pd(1)–P(1)	105.36(5)
C(24)–Pd(1)–P(1)	144.25(5)
C(25)–Pd(1)–P(2)	148.79(5)
C(24)–Pd(1)–P(2)	109.77(5)
P(1)–Pd(1)–P(2)	105.856(15)
O(1)–C(23)–N(1)	124.27(17)
O(1)–C(23)–C(24)	128.93(17)
N(1)–C(23)–C(24)	106.79(16)
C(25)–C(24)–C(23)	106.89(16)
C(25)–C(24)–Pd(1)	70.03(10)
C(23)–C(24)–Pd(1)	103.14(11)
C(25)–C(24)–H(24)	125.2(14)
C(23)–C(24)–H(24)	120.8(14)
Pd(1)–C(24)–H(24)	118.6(14)
C(24)–C(25)–C(26)	107.93(16)
C(24)–C(25)–Pd(1)	70.91(10)
C(26)–C(25)–Pd(1)	103.31(11)
C(24)–C(25)–H(25)	125.5(15)
C(26)–C(25)–H(25)	120.2(15)
Pd(1)–C(25)–H(25)	116.9(15)
O(2)–C(26)–N(1)	124.25(18)
O(2)–C(26)–C(25)	129.85(18)
N(1)–C(26)–C(25)	105.90(16)
C(23)–N(1)–C(26)	112.29(16)
C(23)–N(1)–H(1N)	120.3(17)
C(26)–N(1)–H(1N)	125.9(17)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 13071o. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Fe(1)	14(1)	13(1)	17(1)	0(1)	1(1)	2(1)
C(1)	12(1)	13(1)	17(1)	0(1)	2(1)	–1(1)
C(2)	17(1)	15(1)	22(1)	–2(1)	0(1)	–2(1)
C(3)	22(1)	12(1)	34(1)	0(1)	2(1)	–3(1)
C(4)	22(1)	22(1)	27(1)	11(1)	2(1)	0(1)
C(5)	16(1)	22(1)	16(1)	2(1)	2(1)	1(1)
P(1)	12(1)	13(1)	15(1)	–1(1)	–1(1)	1(1)
C(6)	22(1)	18(1)	16(1)	–1(1)	–5(1)	0(1)
C(7)	33(1)	28(1)	18(1)	1(1)	2(1)	–7(1)
C(8)	43(1)	30(1)	28(1)	1(1)	–18(1)	12(1)
C(9)	14(1)	21(1)	24(1)	–2(1)	1(1)	2(1)
C(10)	21(1)	37(1)	25(1)	–3(1)	6(1)	5(1)
C(11)	17(1)	31(1)	44(1)	–7(1)	6(1)	–4(1)
C(12)	12(1)	17(1)	19(1)	1(1)	0(1)	1(1)
C(13)	14(1)	23(1)	19(1)	0(1)	4(1)	0(1)
C(14)	17(1)	26(1)	24(1)	–7(1)	6(1)	2(1)
C(15)	19(1)	20(1)	30(1)	–4(1)	1(1)	8(1)
C(16)	15(1)	21(1)	21(1)	–1(1)	–2(1)	5(1)
P(2)	11(1)	15(1)	15(1)	1(1)	0(1)	1(1)
C(17)	20(1)	18(1)	16(1)	2(1)	–1(1)	0(1)
C(18)	26(1)	32(1)	20(1)	2(1)	–6(1)	4(1)
C(19)	26(1)	28(1)	21(1)	–2(1)	7(1)	2(1)
C(20)	12(1)	21(1)	22(1)	2(1)	0(1)	–1(1)
C(21)	20(1)	29(1)	24(1)	5(1)	2(1)	–5(1)
C(22)	25(1)	23(1)	33(1)	–3(1)	3(1)	–7(1)
Pd(1)	12(1)	11(1)	13(1)	0(1)	0(1)	1(1)
C(23)	24(1)	11(1)	25(1)	–1(1)	1(1)	3(1)
O(1)	27(1)	23(1)	27(1)	–8(1)	0(1)	–3(1)
C(24)	23(1)	12(1)	23(1)	2(1)	2(1)	1(1)
C(25)	24(1)	15(1)	19(1)	3(1)	–2(1)	5(1)
C(26)	23(1)	13(1)	28(1)	0(1)	–2(1)	7(1)
O(2)	19(1)	29(1)	39(1)	–2(1)	–4(1)	7(1)
N(1)	21(1)	23(1)	25(1)	–7(1)	4(1)	3(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 13071o.

	x	y	z	U(eq)
H(2)	9703	–1059	2706	22
H(3)	10579	–2763	3328	27
H(4)	10943	–2115	4401	28
H(5)	10308	9	4448	22
H(6)	8296	474	2445	23
H(7A)	9604	1139	1707	40
H(7B)	10507	595	2254	40
H(7C)	10390	1975	2182	40
H(8A)	8197	2954	2365	53
H(8B)	7003	2133	2499	53
H(8C)	7549	2105	1859	53
H(9)	7303	2231	3493	24
H(10A)	7183	1889	4490	41
H(10B)	8648	2295	4414	41
H(10C)	8336	951	4511	41
H(11A)	7250	–233	3632	46
H(11B)	6591	472	3070	46
H(11C)	6026	597	3704	46
H(13)	12587	918	2786	22
H(14)	13251	–1179	2667	26
H(15)	13888	–2009	3691	28
H(16)	13653	–422	4449	23
H(17)	12102	1072	4856	22
H(18A)	14412	2359	5204	39
H(18B)	14444	1067	4945	39
H(18C)	13829	1306	5559	39
H(19A)	11781	2537	5541	37
H(19B)	10968	2825	4918	37
H(19C)	12309	3493	5108	37
H(20)	14916	2392	4144	22
H(21A)	13711	3488	3096	37
H(21B)	14469	2273	3111	37
H(21C)	15256	3446	3274	37
H(22A)	15097	4434	4216	40
H(22B)	14156	3958	4687	40
H(22C)	13545	4562	4085	40
H(1N)	9040(20)	4840(20)	4546(11)	34
H(24)	11600(20)	5130(20)	3386(10)	34
H(25)	9460(20)	4520(20)	2858(10)	34

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