Palladium-Catalyzed C–C Bond Formations *via* Activation of Carboxylic Acids and Their Derivatives

vom Fachbereich Chemie der Technischen Universität Kaiserslautern zur Verleihung des akademischen Grades 'Doktor der Naturwissenschaften' genehmigte Dissertation

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vorgelegt von

Bingrui Song, M.Sc.

geboren in Henan (China)

Betreuer

Prof. Dr. Lukas J. Gooßen

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Promotionskommission:

Vorsitzender:	Prof. Dr. Stefan Kubik
Berichterstatter:	Prof. Dr. Lukas J. Gooßen
Berichterstatter:	Prof. Dr. Werner R. Thiel

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Eidesstattliche Erklärung

Hiermit versichere ich, dass ich die vorliegende Arbeit eigenständig verfasst, keine anderen als die angegebenen Quellen und Hilfsmittel verwendet und Literaturzitate kenntlich gemacht habe. Ich erkläre außerdem, dass diese Arbeit weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Kaiserslautern, den _____ 2013 _____

Bingrui Song

Dedication

To my daughter Yinhao Song on the occasion of her birth

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Parts of this work have been published as following:

Publications

- B. Song, T. Knauber, L. J. Gooßen, *Angew. Chem. Int. Ed.* **2013**, *52*, 2954-2958: Decarboxylative Cross-Coupling of Mesylates Catalyzed by Copper/Palladium Systems with Customized Imidazolyl Phosphine Ligands.
- F. Collet, B. Song, F. Rudolphi, L. J. Gooßen, *Eur. J. Org. Chem.* **2011**, 6486-6501: Development of Decarboxylative Coupling Processes for the Synthesis of Azomethines and Ketones.
- B. Song, T. Himmler, L. J. Gooßen, *Adv. Synth. Catal.* **2011**, *353*, 1688-1694: Palladium/Copper-Catalyzed Di-α-arylation of Acetic Acid Esters.
- B. Song, F. Rudolphi, T. Himmler, L. J. Gooßen, *Adv. Synth. Catal.* **2011**, *353*, 1565-1574: Practical Synthesis of 2-Arylacetic Acid Esters via Palladium-Catalyzed Dealkoxycarbonylative Coupling of Malonates with Aryl Halides.
- F. Rudolphi, B. Song, L. J. Gooßen, *Adv. Synth. Catal.* **2011**, *353*, 337-342: Synthesis of Azomethines from α-Oxocarboxylates, Amines and Aryl Bromides via One-Pot Three-Component Decarboxylative Coupling.

Patents

- T. Himmler, L. J. Gooßen, F. Rudolphi, B. Song, WO/2012/066134, **2012**: Process for preparing aryl- and heteroarylacetic acid derivatives.
- A. Cotte, M. Gotta, L. J. Gooßen, F. Rudolphi, B. Song, WO/2012/116942, **2012**: Process for preparing azomethines from α-oxocarboxylates, amines and aryl bromides.

Abbreviation

Ac	Acetyl
acac	Acetylacetonate
AcOH	Acetic acid
Ad.	Adamantyl
Ar	Aryl
ASC	Advanced Synthesis and Catalysis
BINAP	Bis-(diphenylphosphino)-1,1'-binaphthaline
Bipy	2,2'-bipyridine
Bn	Benzyl
BOC	Di-*tert*-butylldicarbonate
Brett-Phos	2-(Dialkylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'biphenyl
Bz	Benzoyl
CEJ	Chemistry, A European Journal
COD	1,5-Cycloctadiene
Cy	Cyclohexyl
CM-Phos	2-[2-(Dicyclohexylphosphino)phenyl]-1-methyl-1H-indole
DavePhos	2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl
dba	Dibenzylidene acetone
DCE	1,2-Dichloroethane
DEM	Diethyl malonate
DFT	Density functional theory
(R,R)-DIOP	(4R,5R)-(-)-4,5-Bis(diphenylphosphanylmethyl)-2,2-dimethyl-1,3-dioxolane
DMA	N,N-Dimethylacetamide
DMF	N,N-Dimethylforamide
DMPU	N,N-Dimethylpropyleneurea
DPE-Phos	Bis(2-diphenylphosphinophenyl)ether
Dppe	1,1-Bis(diphenylphosphino)-ethane
Dppp	1,1-Bis(diphenylphosphino)-propane
DMSO	Dimethylsulfoxide
DTBP	Di-*tert*-butyl peroxide

EI	Electron Ionization
EJOC	European Journal of organic chemistry
Et	Ethyl
eq.	Equivalent
F-acac	Hexafluoroacetylacetonate
GC	Gas chromatography
HMPA	Hexamethylphosphoramide
IPr	1,3-bis(2,6-diisopropyl)-phenyl-imidazol-2-ylidene
IR	Infrared
JOC	Journal of Organic Chemistry
John-phos	2-(Biphenyl)dialkylphosphine
L	Ligand
M	Metal
MeCN	Acetonitrile
Me	Methyl
Mes	Mesityl
MS	Molecular sieves
*n*Bu	*n*-Butyl
NHC	N-Heterocyclic carbene
NMP	N-Methyl-2-pyrrolidone
*n*Pr	*n*-Propyl
Nu	Nucleophile
PCy_3	Tricyclohexyl phosphine
Ph	Phenyl
Phen.	1,10-Phenanthroline
Piv	Pivaloyl
PivOH	Pivalic acid
ppm	Parts per million
RT	Room temperature
Ru-Phos	2-Dicyclohexylphosphino-2',6'-di-isopropoxy-1,1'-biphenyl
SET	Single electron transfer
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TASF	Tris(dimethylaminosulfonium) difluorotrimethylsilicate
TBAB	Tetrabutylammonium bromide

TBAC	Tetrabutylammonium chloride
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-Butyl hydroperoxide
*t*Bu	Tertiary butyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMSO	Tetramethylenesulfoxide
Tol.	Toluene
μW	Microwave irradiation
X	Halide or pseudo halide
X-phos	2-(Dicyclohexylphosphino)-2’,4’,6’-isopropylbiphenyl

Structure Numbering

The chemical structures of each chapter are numbered separately for clearity and readability. In the experimental section, the number is composed of a second level chapter number followed by hyphen and a structure number of the molecule. For example, 2.2-**1a** represents compound **1a** in chapter 2.2. Identical chemical structures in different chapters are represented by different numbers.

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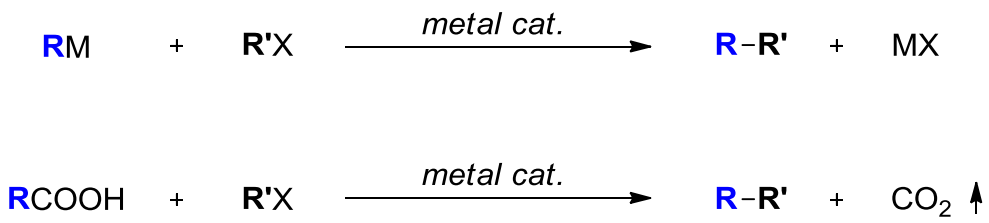
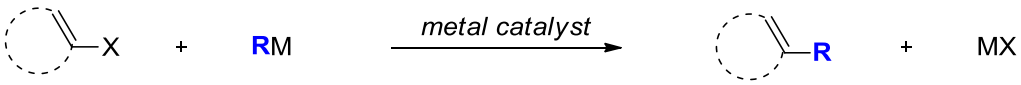
Chapter 1

General Introduction:
Modern Development of Transition-Metal-Catalyzed Coupling Reactions



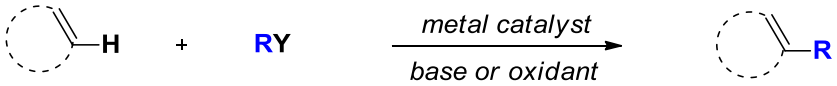
1.1 Transition metal-catalyzed coupling reactions

Metal-catalyzed coupling reactions have become one of the most important synthetic tools in modern organic synthesis.[1] Nowadays, more and more new synthetic transformations via metal-catalyzed coupling reactions have been invented.[2] As shown in scheme 1, a typical cross-coupling reaction involves a formal nucleophilic substitution at aryl and alkenyl halides or pseudohalides by an organometallic reagent. Transition metals such as Pd, Ni, Cu, Fe, Pt, Rh, Ru, etc. are the most effective catalysts for these reactions providing synthetic methodologies for the regioselective construction of new C-C and C-heteroatom bonds. In addition to metal-catalyzed cross-coupling reactions to form asymmetric C-C bonds, homocouplings to form symmetric biaryls or bisalkynes have also been developed.[3]



Scheme 1. Metal-catalyzed cross-coupling reactions.

More recently, the dehydrogenative couplings of hydrocarbons especially arenes bearing certain directing groups with carbon eletrophiles, organometallic reagents or other hydrocarbons have also been reported (Scheme 2).[4]

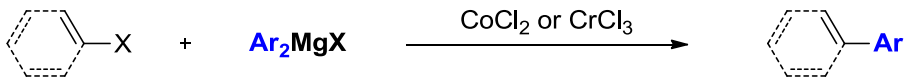


Scheme 2. Metal-catalyzed cross-coupling reactions.

1.1.1 Coupling reactions forming C–C bonds

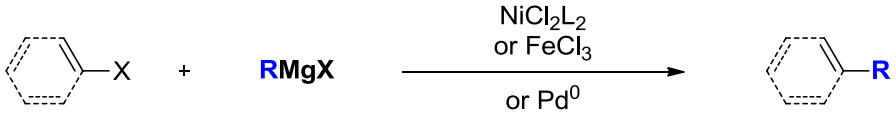
1.1.1.1 Cross-coupling of aryl / alkenyl (pseudo)halides with main group organometallic nucleophiles

In 1941, Kharasch reported the synthesis of asymmetric biarlys from arylmagnesium halides and aryl halides in the presence of catalytic amounts of cobalt (II) chloride (Scheme 3).[5] In another report, Kharasch cross-coupled aryl Grignard reagents with vinyl halides catalyzed by cobalt or chromium compounds (Scheme 3).[6]



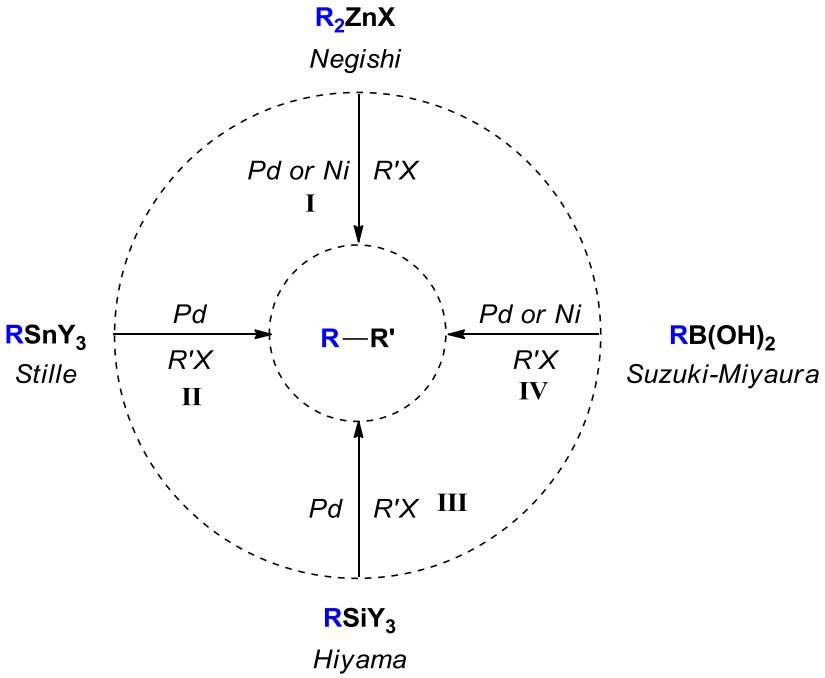
Scheme 3. Early examples of Grignard reagents in metal-catalyzed cross-coupling reactions.

Although such pioneering work has shown the concept of metal-catalyzed cross-coupling reactions, the synthetic utility of these findings has been underestimated and even forgotten until 30 years later. In 1972, Kumada[7] and Corriu[8] independently reported the Ni-catalyzed cross-coupling reaction of aryl halides with Grignard reagents—the so-called Kumada-Corriu reaction (Scheme 5). A similar transformation using iron complexes was also developed by Kochi[9] at almost the same time. Starting in 1975, the value of palladium complexes had been soon discovered, and their applications in Kumada-Corriu reactions allow the coupling of a much broader array of Grignard reagents.[10]



Scheme 5. Kumada-Corriu reaction under different catalysts.

Since the invention of Kumada-Corriu reaction, a great deal of research efforts has been focused on transition metal-catalyzed C–C bond forming reactions of aryl and alkenyl halides and various organometallic reagents (Scheme 6). The use of Grignard reagents limits the synthetic utility of Kumada-Corrriu reaction, due to the low tolerance towards functional groups resulting from the strong basicity.

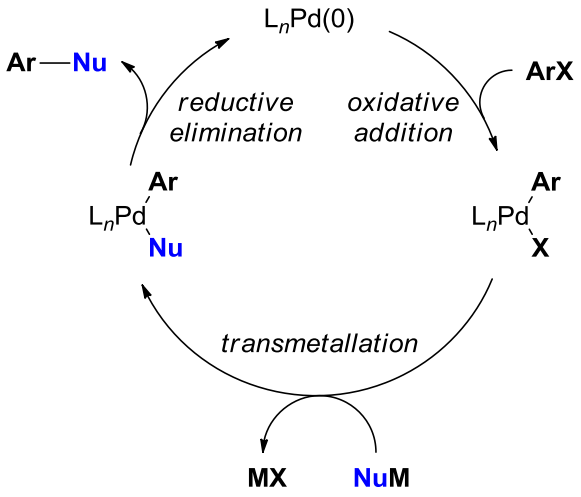


Scheme 6. Metal-catalyzed cross-coupling reactions of various organometallic reagents.

In order to improve the functional group tolerance of the Kumada-Corrriu coupling processes, other organometallic coupling partners containing less electropositive metals than lithium and

magnesium were later employed in the transition metal-catalyzed coupling reactions. In late 1970s, Negishi *et al.* sequently repoted the applications of organoaluminiums [11] and organozincs[12] in the coupling reactions of aryl and alkenyl halides. Their further extensive investigations showed that the best reaction results were obtained by using organozinc compounds in the presence of palladium(0) catalysts (Scheme 6, **I**).

In 1976, Eaborn fistly used organostannanes in the palladium-catalyzed coupling reactions.[13] In the following several years, Stille investigated the use of organotin compounds in the C–C bond forming reactions and significantly improved the yields under much milder reaction conditions. [14] The organotin reagents are stable to chromatography, water and oxygen, which make their purification much easier than other main group organometallic reagents. However, the formation of stoichiometric tin halides after the reaction limits their practical application in chemical industry (**II**). The organosilanes are less toxic, but are also less reactive. Therefore, their use in coupling reactions normally requires an activating agent such as the fluoride ion or a base (**III**).[15] In 1979, Suzuki and Miyaura reported the first Pd-catalyzed cross-coupling of 1-alkenylboranes with aryl halides (**IV**). [16] Nowadays, Suzuki-Miyaura reaction has become the most commonly used cross-coupling process because of its mild reaction conditions and high functional group tolerance. Moreover, boronic acids are environmentally safer and much less toxic than organostannanes, and the inorganic by-products are easily removed from the reaction mixture, making the reaction suitable for industrial processes.



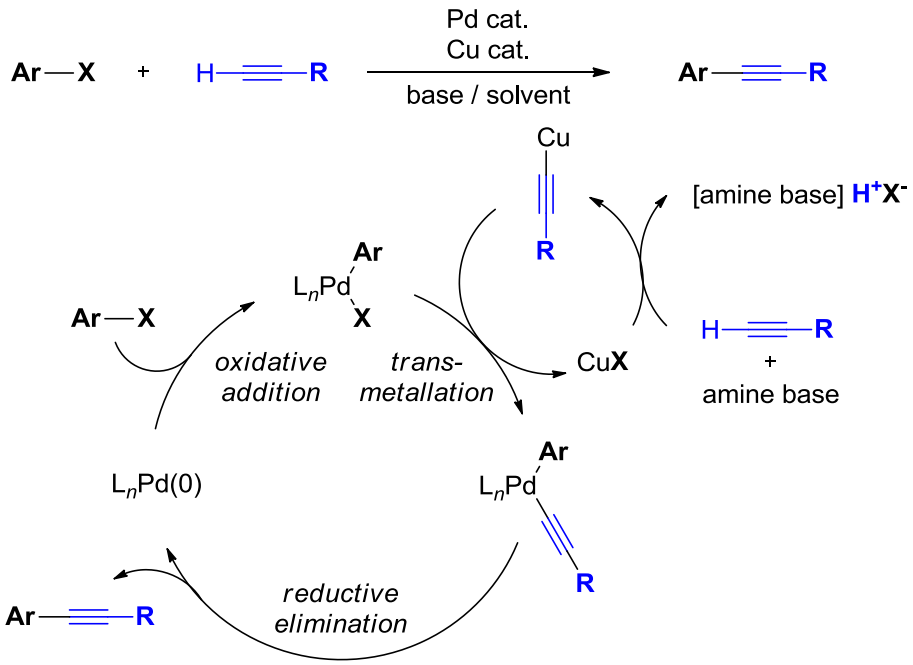
Scheme 7. General mechanism of Pd-catalyzed cross-coupling of main group organometallic nucleophiles.

As depicted in scheme 7, a typical palladium-catalyzed cross-coupling reaction of various organometallic reagents contains three stages: oxidative addition, transmetallation, and

reductive elimination. Initially, a low-valent palladium complex reacts with the aryl halide by oxidative addition to generate an arylpalladium (II) halide complex. The carbon fragment is then transferred from the organometallic reagents to the arylpalladium species forming a new organopalladium (II) complex. Finally, this complex undergoes reductive elimination to form the coupling product that contains a new carbon-carbon bond while regenerating the Pd(0) catalyst.

1.1.1.2 Cross-coupling of aryl / alkenyl (pseudo)halides with alkynes

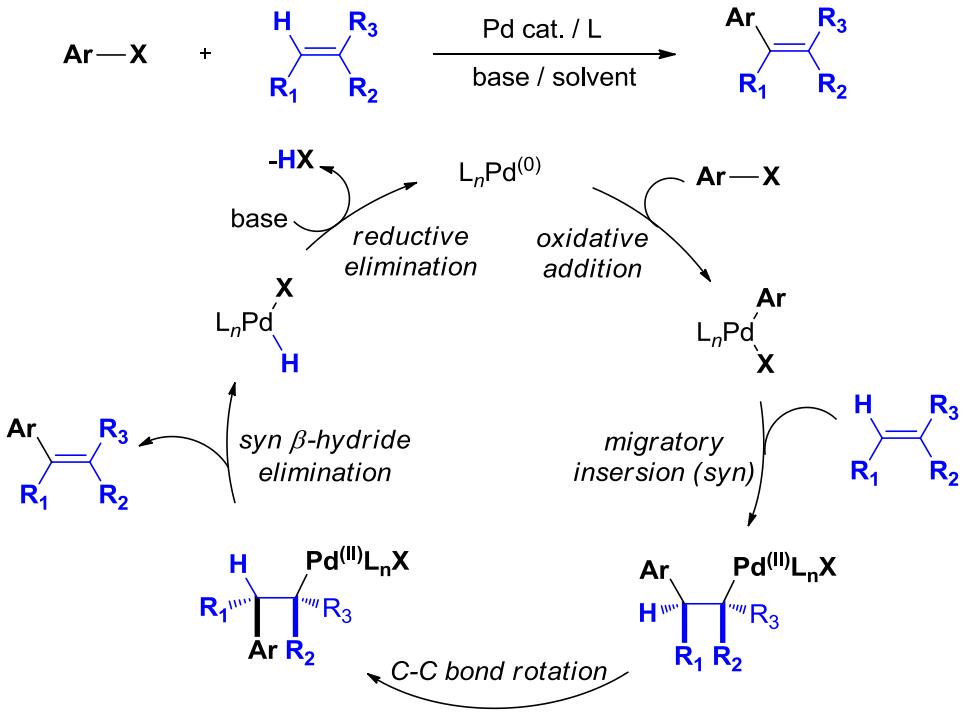
Terminal alkynes containing reactive C–H bonds (the pKa of phenylacetylene is 28.8,[17] similar to alkyl esters) can be reacted with aryl or vinyl halides in the presence of transition metal catalysts. In 1975, Cassar[18] and Heck[19] independently disclosed the alkyne coupling reactions in the presence of catalytic Ni(0) or Pd(0) complexes. At the same time, Sonogashira[20] discovered that the coupling of terminal alkynes and aryl halides could readily occur at room temperature in the presence of a bimetallic palladium / copper catalyst system (Scheme 8). The *in situ* generated copper acetylide, which takes the role of an organometallic reagent, reacts with the aryl palladium halide species forming the aryl-Pd-alkynyl intermediate, which undergoes reductive elimination, releasing the product and the palladium(0) catalyst.



Scheme 8. Sonogashira coupling of aryl/alkenyl halides with terminal alkynes.

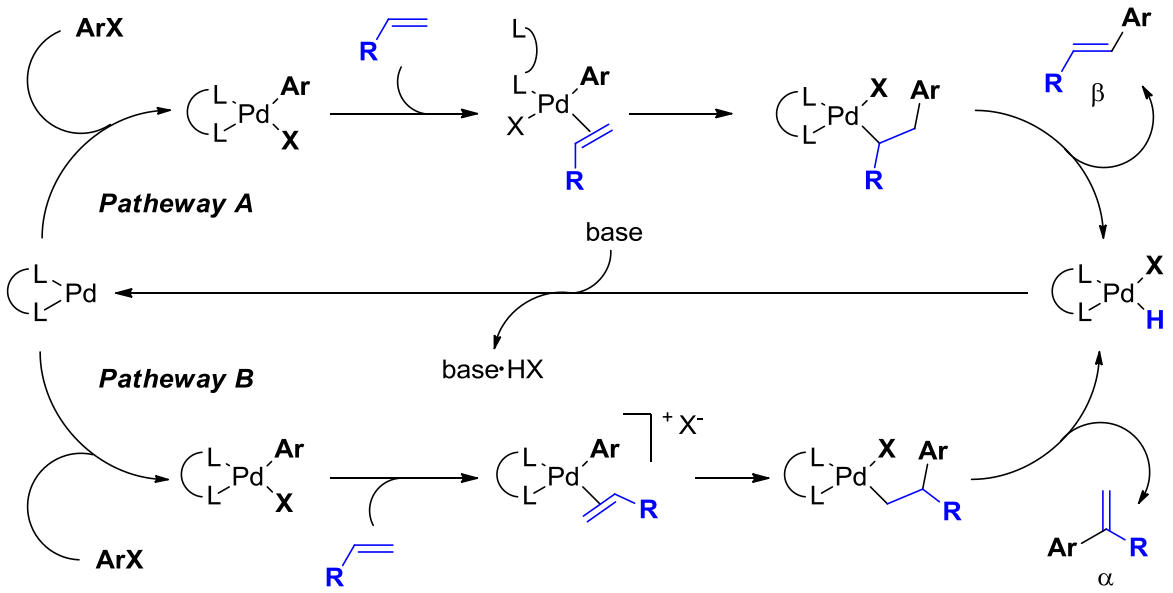
1.1.1.3 Cross-coupling of aryl / alkenyl (pseudo)halides with alkenes

The coordination of olefin to palladium species allows the coupling between olefins and aryl or alkenyl halides. Indeed, Mizoroki[21] and Heck[22] independently reported the Pd-catalyzed cross-coupling of olefins with organohalides. Electron-deficient olefins such as styrene or acrylate derivatives show particularly high reactivity in the coupling reaction of aryl halides, leading to the aryl-vinyl compounds. Due to its high functional group tolerance and mild conditions, the Mizoroki-Heck reaction has become one of the most widely used methods that forms carbon-carbon bonds in organic synthesis. However, the coupling reactions of aryl halides with sterically congested olefins is difficult, especially the reactions of cycloalkenes are particularly slow or may even be inhibited because the C-C bond rotation of the vinylic palladium intermediate is not possible (Scheme 9).



Scheme 9. Mizoroki-Heck coupling of aryl/alkenyl halides with alkenes.

In principle, two regioisomeric products could be generated during the Heck reaction. The coupling reactions of aryl halides with electron-deficient olefins, such as acrylates and acrylonitriles, normally give rise to the linear β-arylated products. However, when replacing halides by triflates and employing a bidentate ligand, electron-rich olefins bearing a heteroatom adjacent to the C=C double bond could be regioselectively arylated on the α-carbon. The introduction of stoichiometric amounts of halide scavengers such as silver or thallium salts could also lead to the α-arylated product.

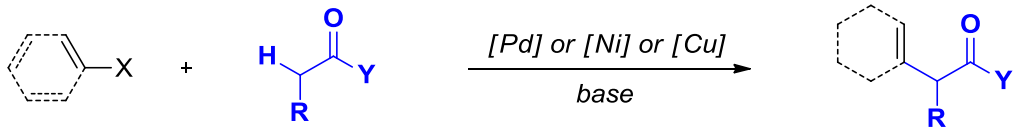


Scheme 10. Regioselectivity in Mizoroki-Heck reaction.

These observations could be explained by two competing reactions pathways, each leading to a different regioselectivity in Mizoroki-Heck coupling reactions.[23] As illustrated by the simplified mechanism in Scheme 10, the *β* product is generated via the neutral pathway A, which is triggered by the dissociation of a neutral ligand from Pd^{II}. In the ionic pathway B, a cationic palladium intermediate is formed through the replacement of the halide ligand by the olefin, yielding the *α*-arylated product. Therefore the use of aryl triflates in Mizoroki-Heck couplings favors the ionic pathway because of the liability of the Pd-OTf bond.[24] Ionic liquids such as imidazolium salts have also proved to be effective for the *α*-regioselective Mizoroki-Heck coupling reactions due to the electrostatic interactions.[25]

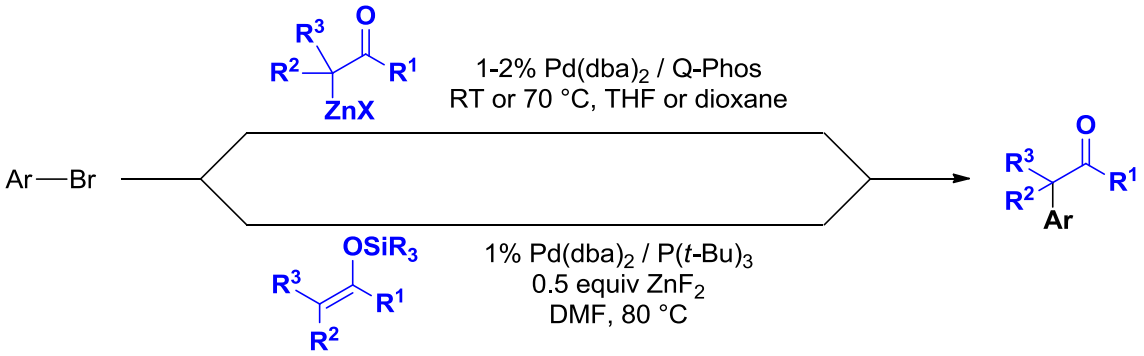
1.1.1.4 Cross-coupling of aryl / alkenyl (pseudo)halides with enolates

Carbonyl compounds could function as nucleophiles which are coupled with aryl or vinyl halides in the presence of appropriate bases and transition metal catalysts (Scheme 11). In the first stage of these coupling processes, enolates of ketones, esters, amides, aldehydes, nitriles, malonates, cyanoacetates, cyclic 1,3-diketones, and nitroalkanes are *in situ* generated by treating them with an appropriate strong base, normally MHMDS or MO*t*Bu (M = Li, Na or K).[26] This metal enolate then reacts with the aryl palladium halide complex generated from the oxidative addition, forming the aryl-palladium-enolate complex, which undergoes reductive elimination, forming α-arylated carbonyl products and liberating the initial catalyst.



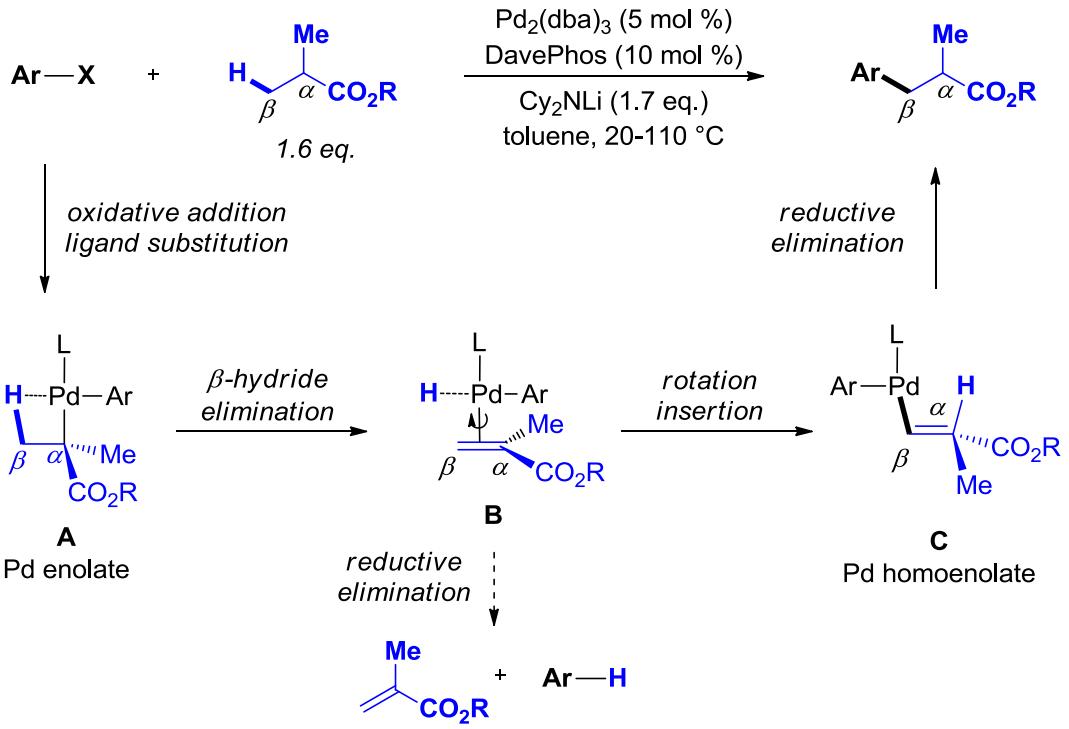
Scheme 11. Transition metal-catalyzed coupling of enolates.

Nowadays, the coupling chemistry of enolates with organohalides has been intensively investigated. It turned out to be a versatile methodology for the α-functionalization of carbonyl compounds. However, the requirement of extremely strong bases in most cases greatly limits their synthetic utilities. These drawbacks are somewhat addressed by the introduction of zinc[27] and silicon[28] enolates into the reaction system, whereas these variant procedures require one more step for the syntheses of the organometallic reagents and the coupling of silicon enolates usually needs an activator such as fluorides (Scheme 12).



Scheme 12. Pd-catalyzed couling of zinc and silyl enolates with aryl bromides.

More recently, Baudion and his coworkers developed a novel method for the β-arylation of esters (Scheme 13).[29] The key to this β-regioselectivity is the rearrangement of the palladium enolate A to the palladium homoenolate C, from which reductive elimination occurs more readily. The use of α-branched esters and sterically congested aryl halides further increases the regioselectivity. When amino esters were used as the coupling partners, this reaction could be even extended to longer-range (γ to ζ) arylations.[30]



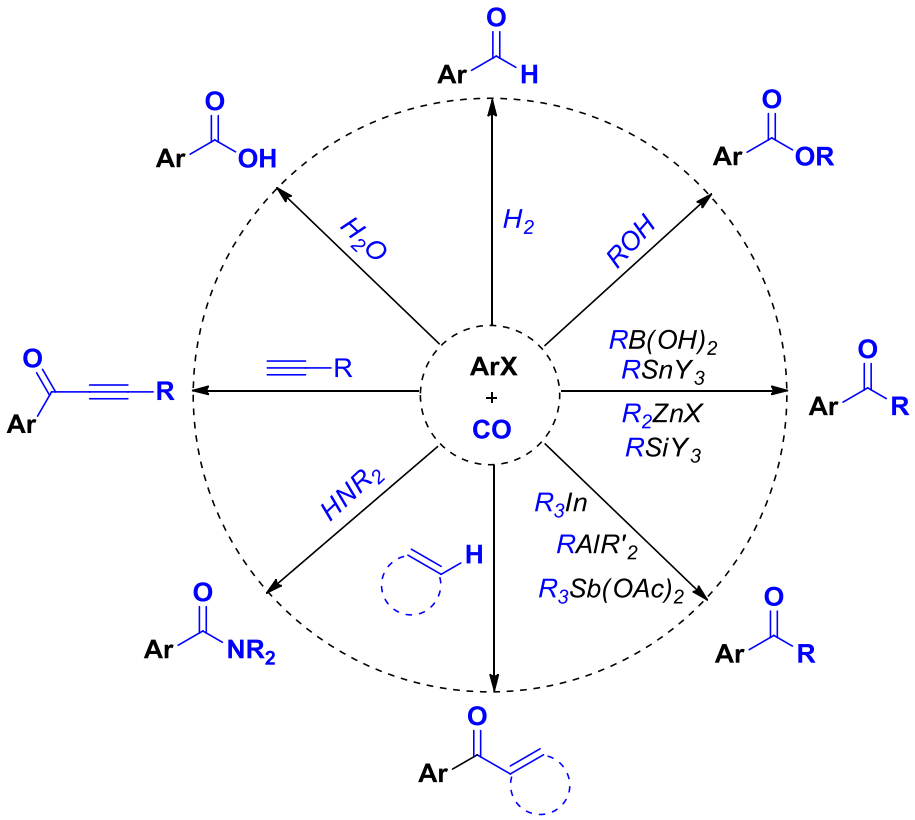
Scheme 13. Pd-catalyzed β-arylation of esters.

1.1.1.5 Carbonylative cross-coupling reactions

In 1974, Heck disclosed a series of reports on carbonylative cross-coupling reactions.[31] Aryl and vinyl halides react with carbon monoxide in the presence of a palladium catalyst to form acylpalladium intermediates, which are then treated with nucleophiles such as alcohols and amines to generate the corresponding carbonyl products (Scheme 14). Replacing of the nucleophiles with hydrogen, a reductive carbonylation process occurs, affording the corresponding aldehydes.

Scheme 14. Heck carbonylations.

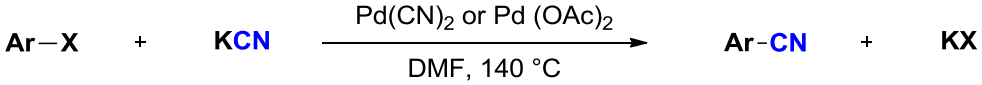
The efficient and convenient construction of carbonyl compounds is of great interest for organic chemists. Since its discovery, substantial contributions have been made to the development of the carbonylative coupling reactions. Nowadays carbon monoxide has become the most important C1 building block to introduce a carbonyl group into the parent molecules. As shown in Scheme 15, by treating carbon electrophiles with various nucleophiles including organometallic reagents and hydrocarbons, a vast range of carbonyl products can be readily realized.[32]



Scheme 15. Pd-catalyzed carbonylative cross-coupling reactions.

1.1.1.6 Cross-coupling of aryl / alkenyl (pseudo)halides with cyanide

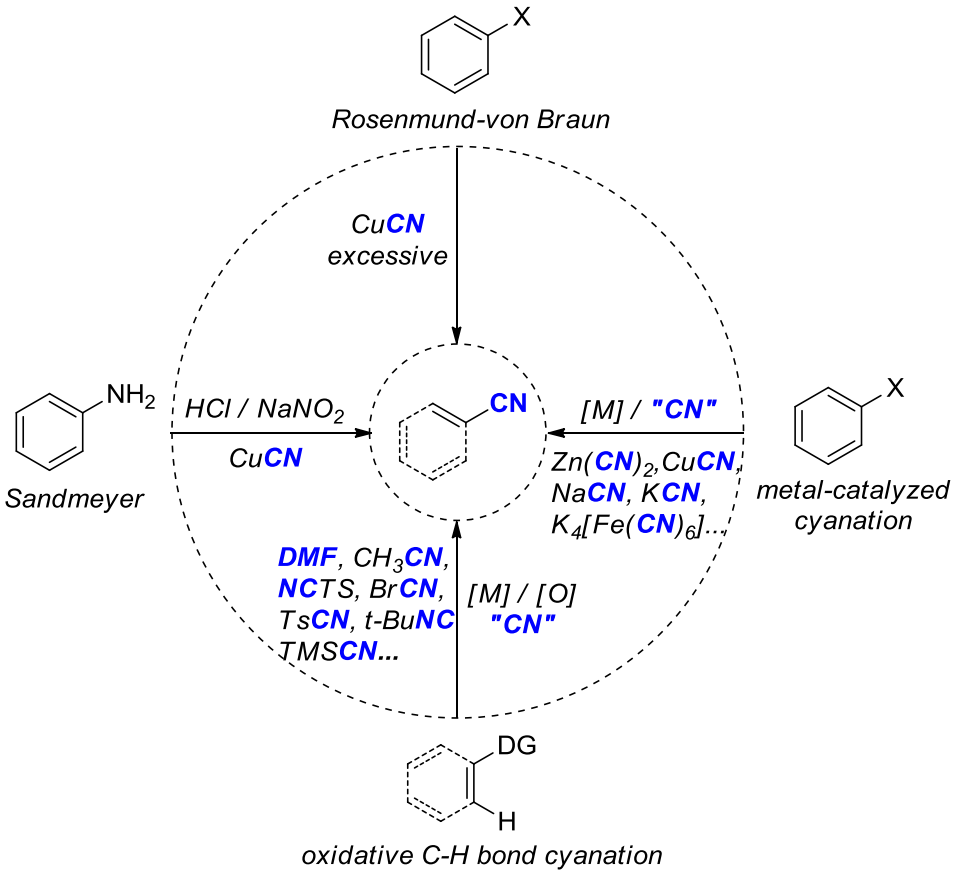
Nitriles are important synthons, e.g. for the synthesis of carboxylic acid derivatives and heterocycles. Moreover, the nitrile group is widely present in a number of fine chemicals and biologically active agents such as dyes, herbicides, agrochemicals, pharmaceuticals, and natural products. Benzonitriles are traditionally prepared from diazo compounds via the Sandmeyer reaction.[33] An alternative process is the Rosenmund-von Braun reaction from aryl halides in the presence of excessive cuprous cyanide.[34] In 1973, Sakakibara and his coworkers demonstrated the first palladium-catalyzed cyanation of aryl halides using potassium cyanide as cyanide source (Scheme 16).[35]



Scheme 16. Pd-catalyzed cyanation of aryl halides.

Transition metal complexes of the platinum group, especially palladium or nickel complexes are the most efficient catalysts for cyanation reactions (Scheme 17). The commonly used cyanating reagents consist of metal cyanide salts or complexes such as NaCN, KCN, CuCN, $Zn(CN)_2$, $(RO)_2BCN$, and $K_4[Fe(CN)_6]$. [36] Direct oxidative cyanation reactions of

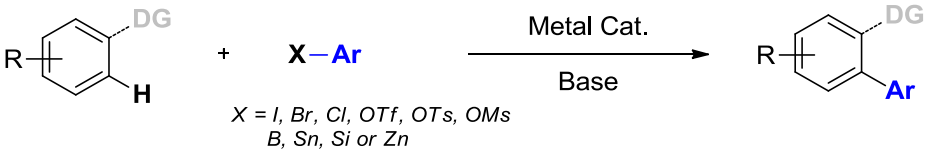
hydrocarbons in the presence of an appropriate oxidant were also established in the past decade. A directing group bearing an adjacent heteroatom dramatically promotes the cyanation, and organo cyanides such as trimethylsiylcyanide, NCTS, BrCN, TsCN, isocyanides, acetonitrile and DMF represent the most efficient cyanating reagents for C–H bond activation processes.[37]



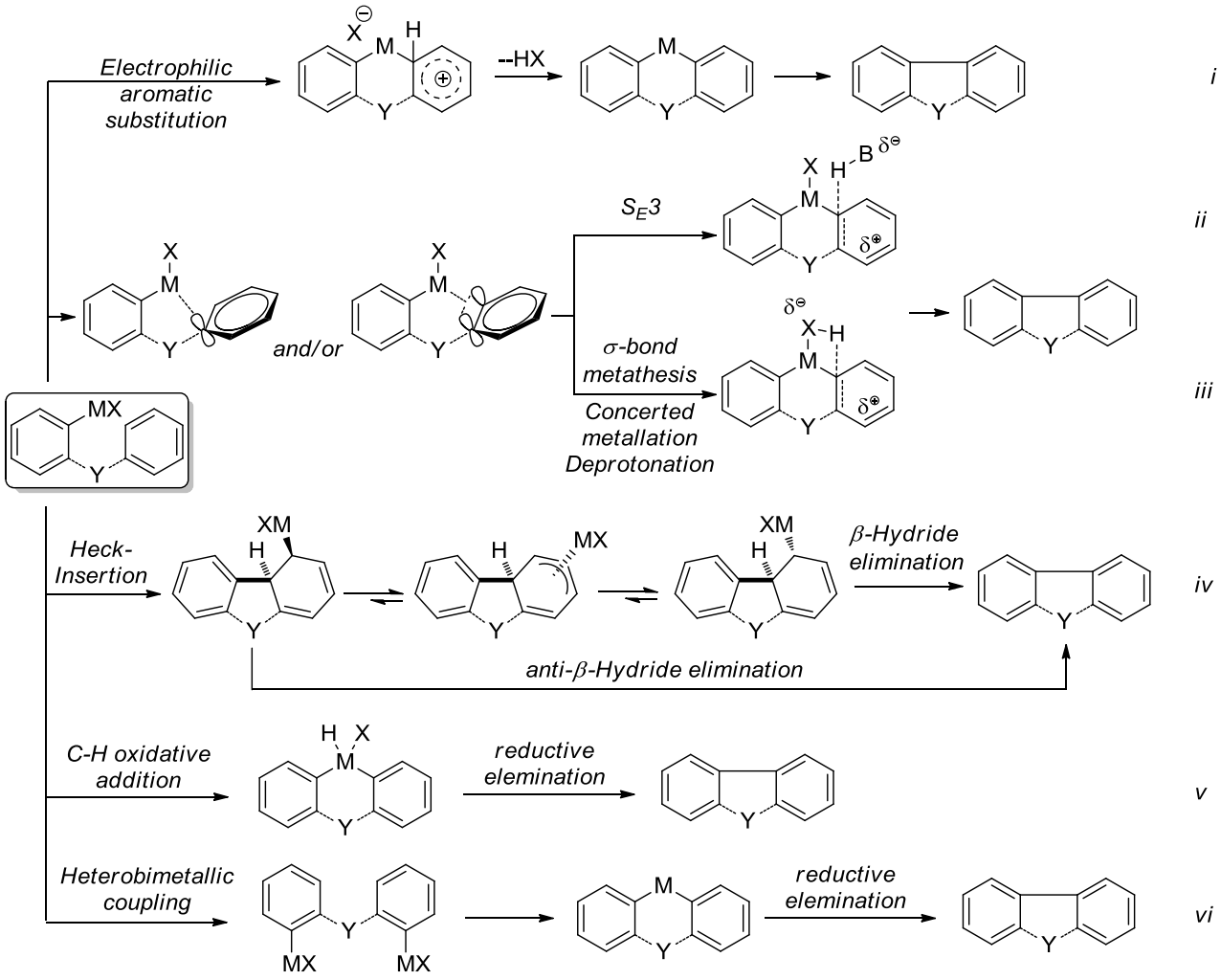
Scheme 17. Cyanation reactions.

1.1.1.7 Direct arylation via C–H bond activation

In the presence of an appropriate metal catalyst, the C–H bond of an arene could be cleaved, replacing of the hydrogen atom by an organo electrophile or a metallic nucleophile, resulting in the formation of a new C–C bond (Scheme 18).[38] From the economical and ecological standpoint, the direct arylation of hydrocarbons is particularly attractive to organic chemists, since this provides a versatile pathway to biaryl compounds. A rapidly growing number of reports contribute to the development of C–H bond activation chemistry.[39]



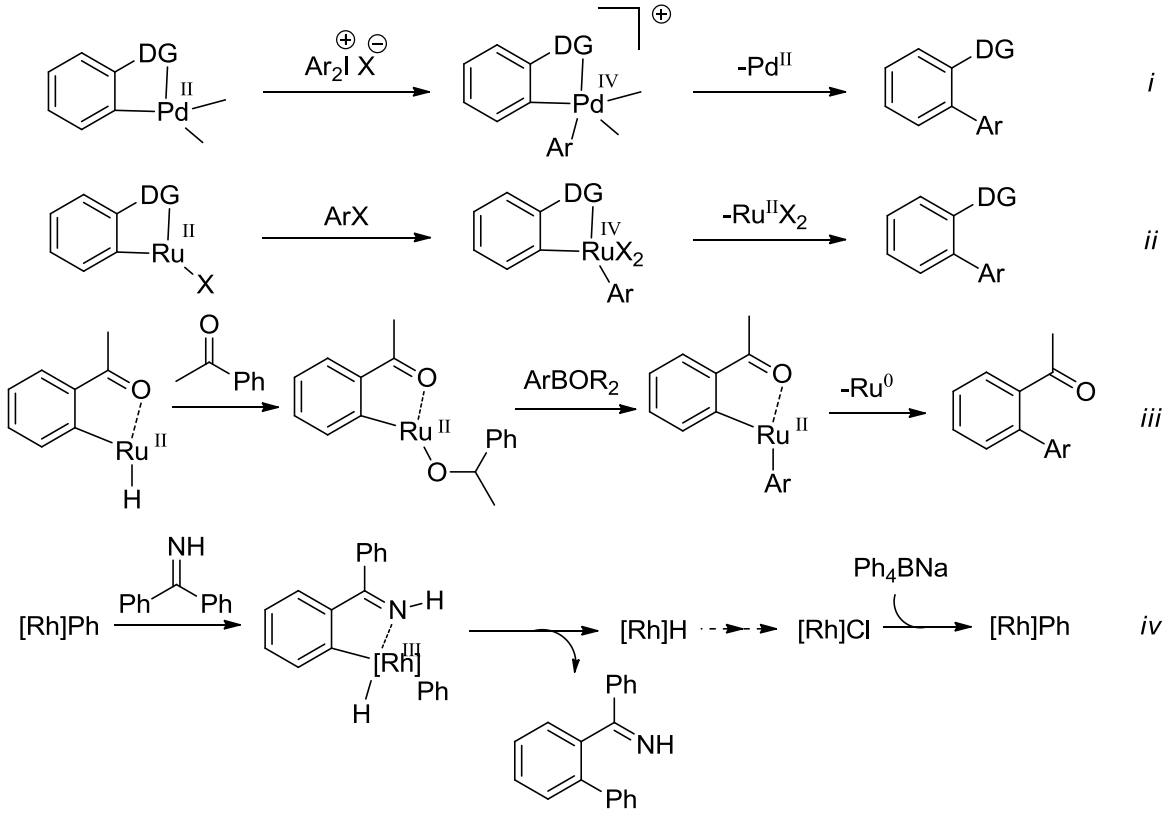
Scheme 18. Cross-coupling of arenes with aryl electrophiles or aryl organometallic reagents.



Scheme 19. Intramolecular and intermolecular coupling of an arylmetal halide complex with an arene.

A great diversity of mechanisms for the direct arylation processes are postulated. In general, such coupling reactions are initiated by or involve the oxidative addition of aryl halides to a metal catalyst, forming an arylmetal halide complex. This organometallic species is then coupled with another arene or heteroarene at the position where the C–H bond is cleaved. As depicted in Scheme 19, six general pathways have been proposed: (i) an electrophilic substitution on the arene by the metal species (S_EAr);[40] (Scheme 19, ii) a concerted S_E3 process facilitated by a base;[41] (Scheme 19, iii) σ–bond metathesis[42] or a concerted metallation-deprotonation;[43] (Scheme 19, iv) a Heck-type insertion on the arene, either through a formal anti-hydride elimination or by several isomerizations followed by a syn β-hydride elimination;[44] (Scheme 19, v) an direct oxidative addition of the arene C–H bond;[45] (Scheme 19, vi) a process in that a second metal-aryl species is involved.[46] The mechanistic

details for each catalytic system depend on the substrate, transition metal, solvent, base, and ligand. Arylation reactions of arenes bearing a directing group which can form a five or six membered ring through the coordination of oxygen or nitrogen to the transition metal may occur via even complicated mechanisms, involving several organometallic species.

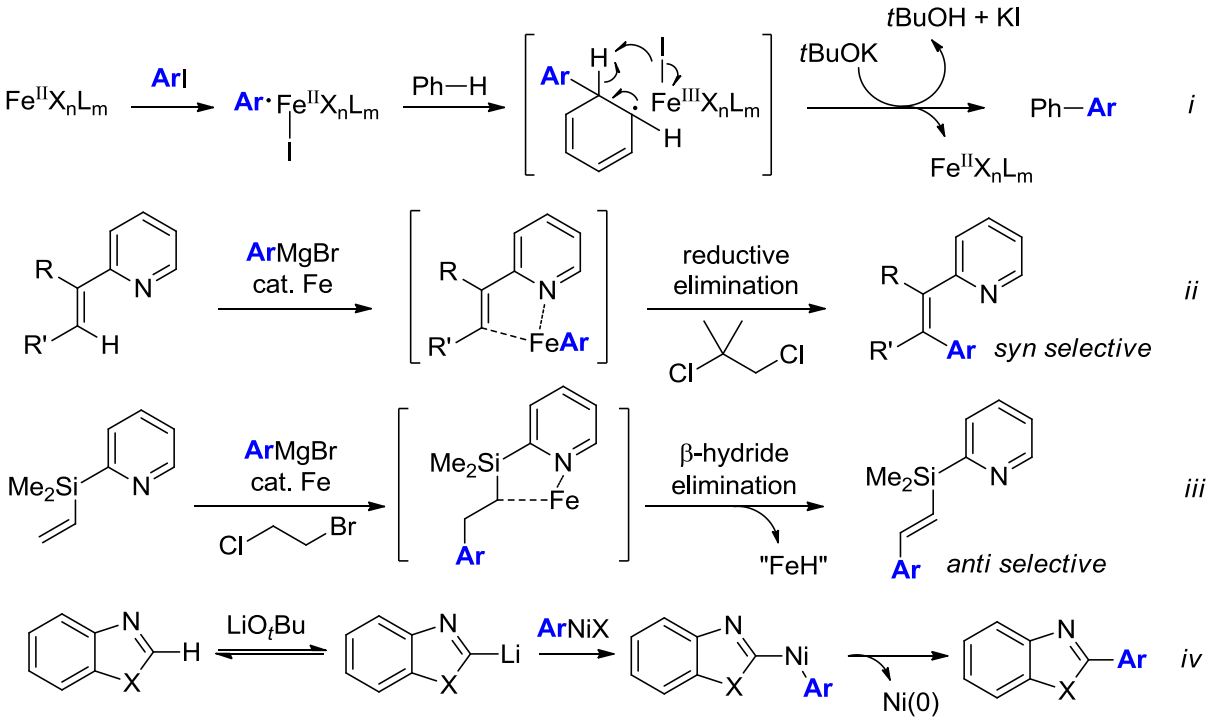


Scheme 20. Pd, Ru and Rh intermediates in the direct arylation processes.

Many transition metals can catalyze the direct arylation of arenes. Complexes of Pd, Ru and Rh are the most versatile and widely used catalysts for these processes.[47] The reactions catalyzed by palladium complexes occur through a mechanism involving Pd(0) and Pd(II) intermediates, while the reactions using hypervalent aryl iodine reagents as electrophiles are expected to proceed via a catalytic cycle containing Pd(II) and Pd(IV) species (Scheme 20, i).[48] Ruthenium-catalyzed cross-coupling reactions of arenes with aryl halides or sulfonates are also believed to undergo a catalytic cycle involving Ru(II) and Ru(IV) intermediates (Scheme 20, ii).[49] However, a mechanism involving Ru(0) and Ru(II) is also proposed when the arenes are coupled with arylboronic esters (Scheme 20, iii).[50] As for the rhodium-catalyzed direct arylations, a catalytic cycle containing a combination of Rh(I) and Rh(III) intermediates is proposed (Scheme 20, iv).[51]

Recently, the use of the first-row transition metals in the direct arylation of arenes and heteroarenes has also been reported. In contrast to the late transition metals, Fe, Cu and Ni

catalysts are abundant and less expensive, making their use in organic synthesis more attractive.[52]

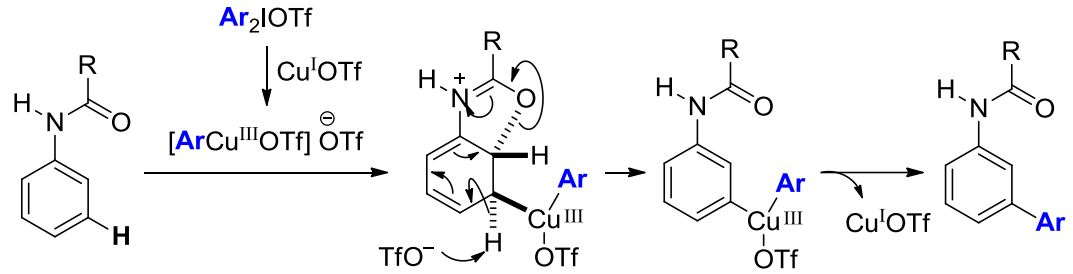


Scheme 21. Fe and Ni intermediates in the direct arylation reactions.

Both aryl halides and arylmetallic reagents have been used in iron-catalyzed direct arylation reactions. The coupling of arenes with aryl halides is proposed to involve an SET (single-eletron-transfer) process, in which an aryliron(III) radical species is generated from an iron(II) species and aryl iodide (Scheme 21, i).[53] The iron-catalyzed arylation of activated arenes and alkenes by using organozinc and Grignard reagents respectively were also established (Scheme 21, ii). The mechanism of the iron-catalyzed arylation of arenes with arylzinc compounds remains unclear at this stage,[54] while the couplings of alkenes bearing directing groups are thought to occur via either the reductive elimination of a five-membered metallacylce (Scheme 21, ii)[55] or the Heck-type carbometallation followed by β-hydride elimination (Scheme 21, iii).[56]

In the Ni-catalyzed arylation of heteroarenes, the acidic C–H bonds could be cleaved by LiO(*t*Bu) forming a heteroaryllithium compound, which undergoes transmetallation with the *in situ* generated arylnickel halide complex to form the corresponding diaryl-nickel species followed by the reductive elimination giving the biaryls and nickel(0) catalyst (Scheme 21, iv).[57]

In contrast to the routinely established Pd-catalyzed *ortho*-arylation of arenes containing directing groups, the use of a copper catalyst allows the direct arylation at the *meta*-position of arenes and indoles.[58] The mechanism involves a highly electrophilic Cu(III)-aryl species generated from a hypervalent aryliodium reagent, activating the aromatic ring sufficiently to permit an anti-oxy-cupration of the carbonyl group of an acetamide across the 2,3 positions on the arene ring (Scheme 22).



Scheme 22. Cu-catalyzed *meta*-arylation of phenyl acetamide.

Controlling the regioselectivity in the direct cross-coupling reaction of unreactive arenes still remains as a big challenge, although unprecedented achievement have been made in the past two decades. Conventionally, the arenes or heteroarenes that undergo direct arylation contain either a directing group (DG) or an eletron bias controlled by an eletron-withdrawing or eletron-donationg group for directing the coupling to a specific C–H bond (Figure 1).

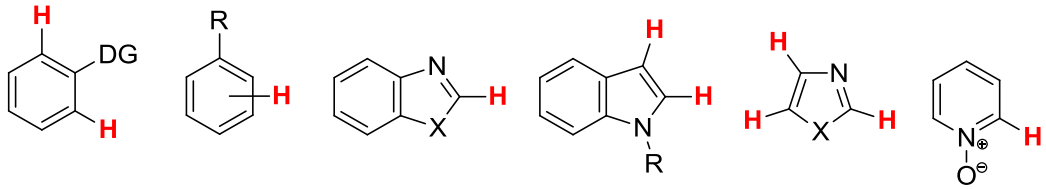


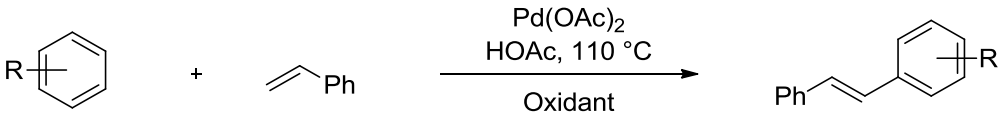
Figure 1. The hydrogens of arenes and heteroarenes those are susceptible to cleavage.

The introduction of directing groups allows the activation of the C–H bonds on the *ortho* positions, frequently resulting in the formation of *ortho*-diarylated byproducts, which can be suppressed by blocking one of the *ortho*-positions or bulky substituents in one of the *meta*-positions. The installations and removal of these directing groups cause additional synthetic steps. In the direct coupling of arenes or heteroarenes without directing groups, the regioselectivity is highly dependent on the substrates' inherent electronic properties. As shown in Figure 1, high regioselectivity in the directing couplings can be easily achieved for heteroarenes containing only one acidic C–H bonds, such as benzoxazole, benzothiazole and benzimidazole. However, most of the arenes and heteroarenes contain more than one reactive C-H bonds. As for these compounds, the regioselectivies have been partially obtained in

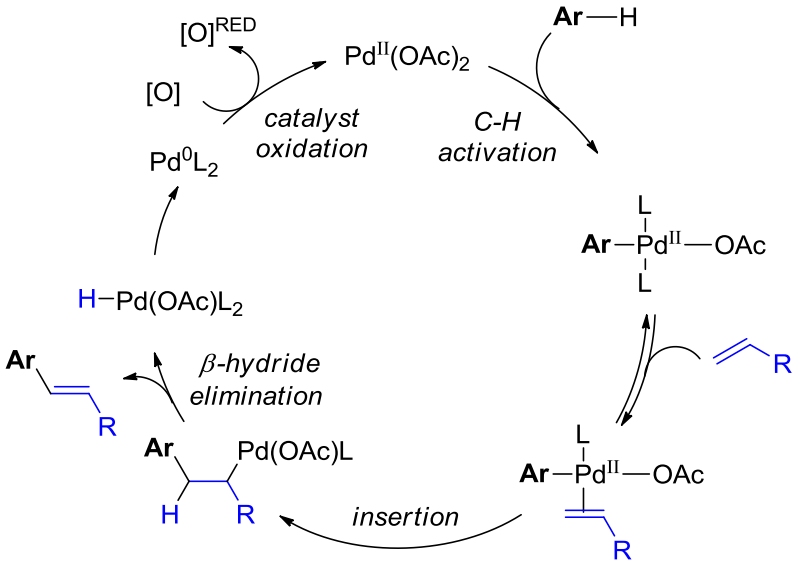
certain cases by changing the reaction solvent, adding co-catalysts, or by conducting the reaction with more sterically hindered catalysts or sterically congested substrates.

1.1.1.8 Oxidative cross-coupling via C–H bond activation

The oxidative coupling of two hydrocarbons by simultaneously activating two different carbon-hydrogen bonds is a straightforward approach to the C–C bond formations In the late 1960s, Fujiwara and his co-workers reported a series of seminal work on the synthesis of aryl olefins from arenes and alkenes.[59] Although a stoichiometric amounts of palladium salts are required for the complete transformation, the catalytic coupling could also be realized with oxidants, such as $Cu(OAc)_2$ or O_2 (Scheme 23).



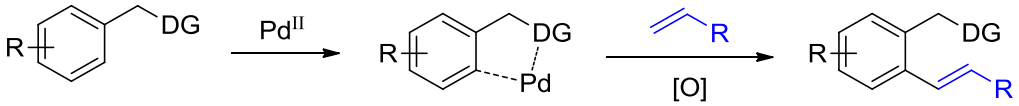
Scheme 23. Direct arylation of olefins.



Scheme 24. Mechanism of the Fujiwara coupling reaction.

As depicted in Scheme 24, the coupling process is initiated by the activation of the C–H bond of an arene to form an aryl palladium intermediate, to which the olefin can coordinate. Subsequent carbopalladation of the olefin leads to an alkyl palladium complex that undergoes syn-β-hydride elimination, affording the arylated olefins. The palladium(II) catalyst is regenerated through the oxidation of palladium(0) species after the reductive elimination. An oxidant in stoichiometric quantity is required for the completion of the catalytic cycle. Commonly used reagents include copper salts, silver salts, benzoquinone, O_2, $K_2S_2O_8$, and peroxides.

Since the arene substrates often contain multiple C–H bonds, the control of the regioselectivity becomes a challenging task for organic chemists. In the early studies, the regioselectivity was regulated by the electronic nature of the substrates chosen. [60] Nowadays, the ortho-selective alkenylation of aromatic rings could be easily achieved by the introduction of a directing group prior to the coupling reaction (Scheme 25).[61]



Scheme 25. Selective oxidative alkenylation of arenes containing directing groups.

More recently, the oxidative cross-coupling of two simple arenes have also been realized. As shown in Figure 2, the coupling partners are usually electron-rich arenes, arenes bearing directing groups such as pyridine, amides, carbamates, and other aza-rings, and pyridine N-oxides, and arenes containing strong electron-withdrawing groups.[62]

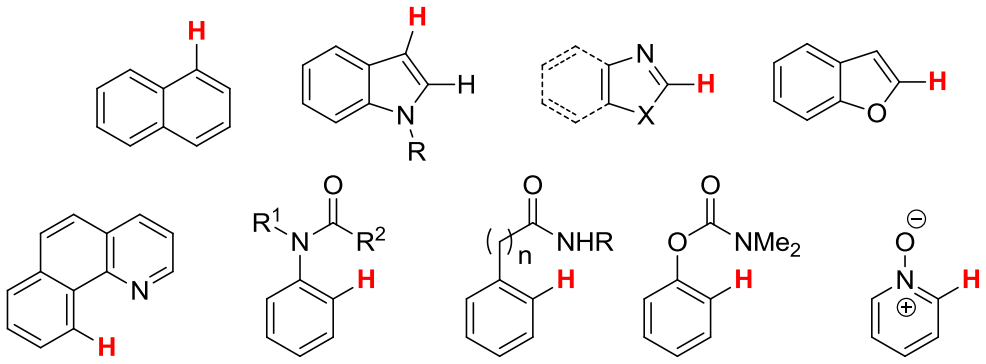
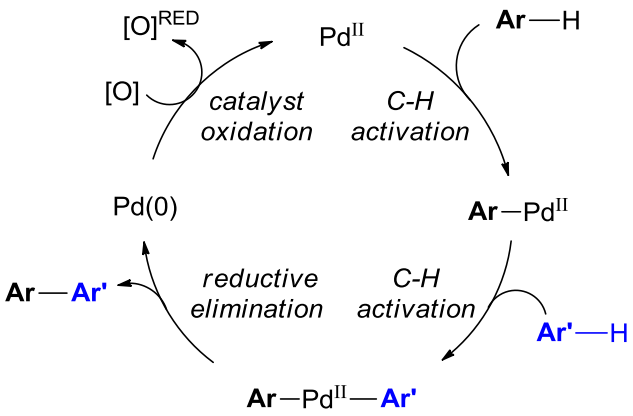


Figure 2. Coupling partners in tandem direct arylations.

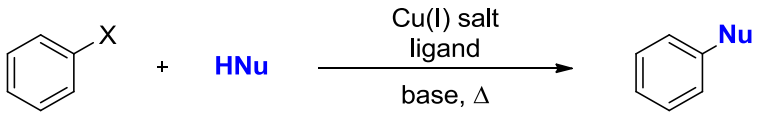
A general mechanism for the Pd-catalyzed tandem direct arylation is depicted in Scheme 26. A diaryl palladium intermediate is formed after subsequent activation of two different C–H bonds. After reductive elimination, the corresponding biaryl is generated along with the Pd(0) species which is finally re-oxidized to the initial Pd(II) catalyst. However, the mechanisms of the direct coupling of two C–H bonds can differ greatly from each other, depending on the reaction conditions and substrates chosen. An alternative mechanism involves the Pd(II) and Pd(IV) intermediates, especially when strong oxidants such as persulfate salts[63] are used in the coupling reactions.



Scheme 26. General mechanism for tandem direct arylation.

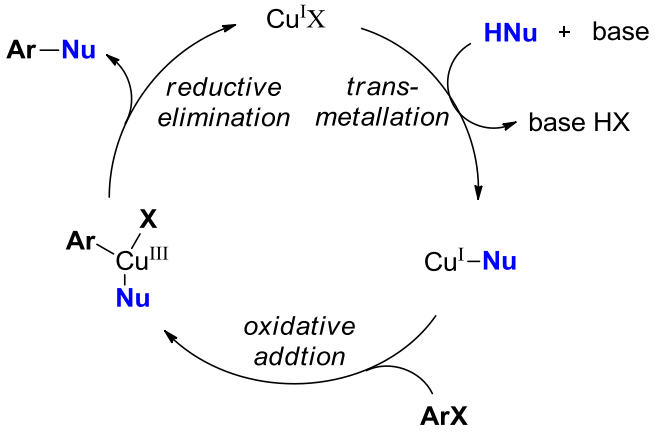
1.1.2 Coupling reactions forming Carbon–heteroatom bonds

Carbon(sp^2)-heteroatom bonds occur frequently in complicated molecules and therefore their construction is one of the most important tasks for organic chemists. The classic method involving the copper-mediated cross-coupling of aryl halides and heteroatom nucleophiles was developed by Ullmann in the 1900s.[64] Substantial efforts with the aim to improve the efficiency and compatibility have been done to this coupling reaction.[65] Nowadays, the Ullmann-type coupling reactions allow the carbon-heteroatom bond formations at much milder conditions compared to the prototypes and only catalytic copper salt is usually required for the transformations (Scheme 27).[66]



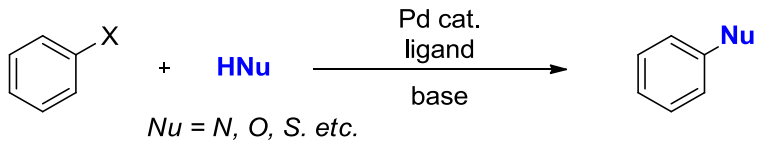
Scheme 27. Ullmann-type cross-couplings.

The general mechanism of the copper-catalyzed cross-couplings to form aromatic C–X bonds involves Cu(I) and Cu(III) intermediates (Scheme 28).[67] The coupling reaction occurs by the formation of an organocopper complex though the anion exchange between a halide and a heteroatom ligand, followed by the oxidative addition of the aryl halide to form an arylcopper complex. This Cu(III) intermediate undergoes reductive elimination releasing the coupling product and the initial Cu(I) halide complex.

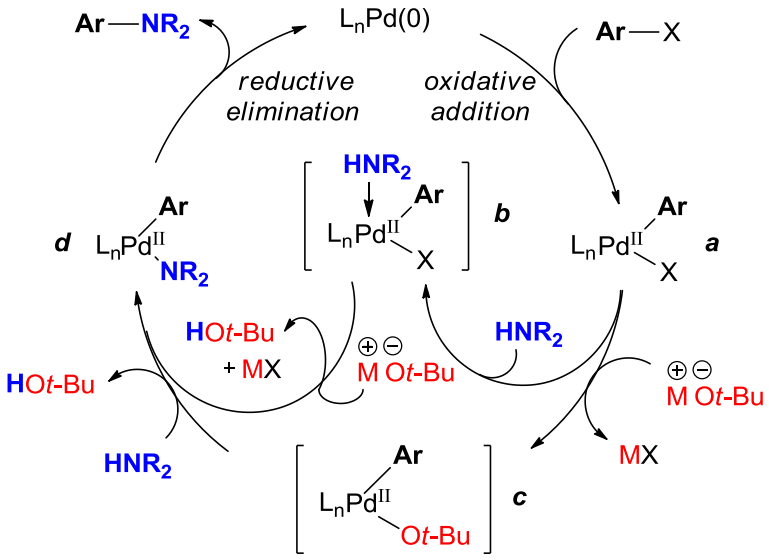


Scheme 28. General mechanism for Ullmann-type coupling reaction.

The Pd-catalyzed cross-coupling reactions of aryl halides and sulfonates with heteroatom nucleophiles in the presence of a stoichiometric amount of a strong base were established by Buchwald and Hartwig in the mid-1990s (Scheme 29).[68] Compared to the copper-catalyzed protocol, the palladium-catalyzed variant allows the C–N and C–O bond formations under milder reaction conditions and therefore shows higher functional group tolerance.[69] Moreover, by applying the appropriate ligands, unreactive organo electrophiles such as aryl chlorides,[70] aryl tosylates,[71] even aryl meslyates[72] can be coupled with amines or alcohols.



Scheme 29. Buchwald-Hartwig cross-couplings.



Scheme 30. General mechanism for Buchwald-Hartwig coupling reaction.

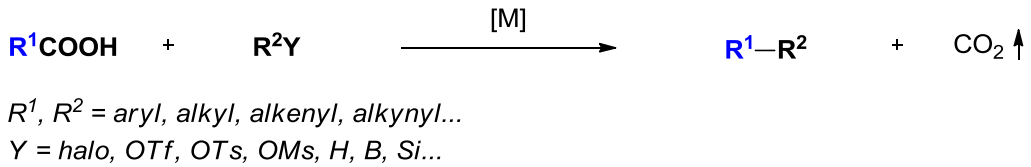
As dipected in scheme 30, the cross-coupling reaction between amines and aryl halides starts with the formation of an aryl palladium halide complex (**a**) through the oxidative addition of the aryl halide to the palladium(0) catalyst. An aryl palladium amide (**d**) is then formed via either deprotonation of the palladium-coordinated amine (**b**) by a strong base or the protonation of the palladium-alkoxide intermediate (**c**) by the amine. After reductive elimination of this aryl palladium-amido complex, the corresponding arylamine product is finally formed along with the regeneration of the palladium(0) catalyst.

1.2 Carboxylic acids and their derivatives in coupling reactions

Conventionally, C–C bond can be efficiently and conveniently constructed via the cross-coupling reactions between organometallic reagents and aryl halides or pseudohalides in the presence of transition metal catalysts. However, these traditional metal-catalyzed coupling reactions suffer from using stoichiometric amounts of organometallic compounds which are usually prepared from organohalogen compounds after several synthetic steps.[7-14]

C–C bond can be alternatively formed through the cross-coupling reactions of hydrocarbons containing acidic C–H bonds with carbon eletrophiles or even hydrocarbons. The synthetic strategies involving C–H bond activation draw on high atom economy, whereas the protocols frequently require pre-embedded directing groups in order to achieve high regioselectivity. Although traceless directing C–H bond transformations have been developed recently, they can only be applied for specific substrates.[73]

Another important alternative to the construction of carbon frameworks involves the transition metal-catalyzed decarboxylative cross-coupling of carboxylic acids with organo electrophiles or nucleophiles under redox or oxidative conditions (Scheme 31).

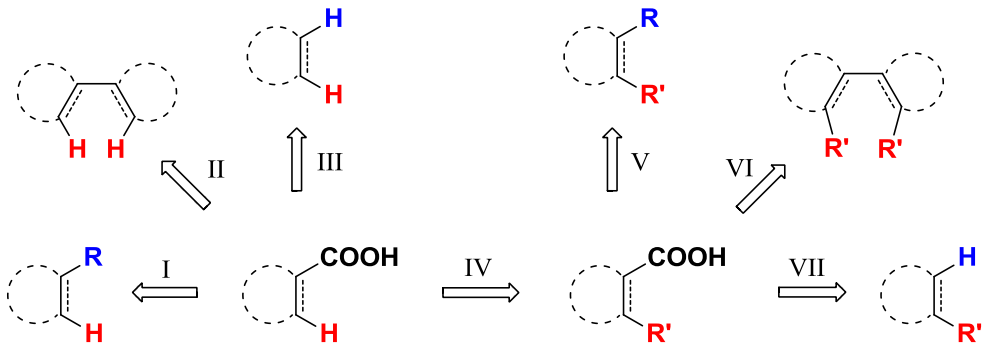


Scheme 31. Decarboxylative cross-couplings.

Decarboxylative cross-coupling reactions have recently emerged as a powerful methodology for the regioselective construction of C–C and C–heteroatom bonds.[74] The key advantage over traditional cross-coupling reactions is that they draw on stable and easily available carboxylic acids as sources of carbon nucleophiles rather than expensive and sensitive organometallic reagents. Within the last decade, a rapidly growing number of decarboxylative reactions have been discovered including decarboxylative Heck reactions, allylations, redox-neutral cross-

coupling reactions, oxidative coupling reactions, C–H arylations, homo-couplings, and Chan-Lam-type reactions.

Carboxylic acids can be versatile starting materials for many important building blocks in addition to the traditional synthetic strategies (Scheme 32). In principle, a carboxylic acid can undergo cross-coupling with a carbon eletrophile or a heteroatom-nucleophile, affording a new C–C or C–heteroatom bond (I). When an carboxylic acid undergoes decarboxylative homocoupling, the corresponding biaryl, bialkenyl or bialkynyl compound will be formed (II). The protodecarboxylation of a carboxylic acid can also ocurr, yielding a hydrocarbon (III). When the carboxyl group is used as a directing group, the adjacent C–H bod can be activated, foriming a new C–C or C–heteroatom bond at the *ortho*-position of the molecule (IV).[75] If necessary, this new carboxylic acid can further undergo the three afore-mentioned decarboxylative processes, affording the demanding products (V, VI and VII).

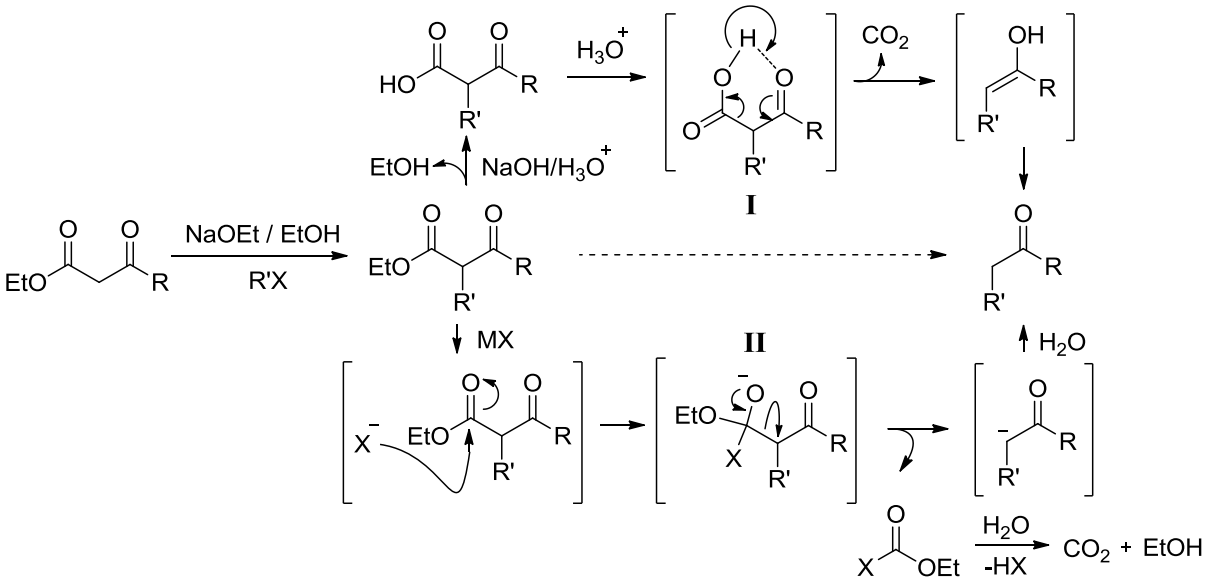


Scheme 32. Synthetic strategies involving decarboxylative coupling reactions.

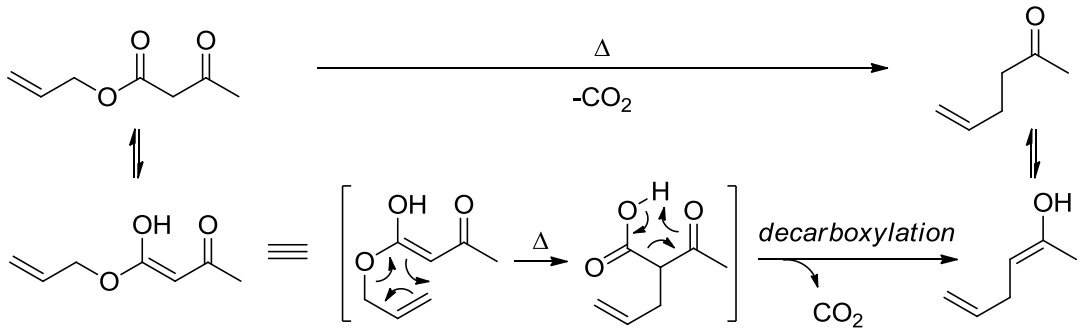
1.2.1 Decarboxylative couplings forming C–C bonds

In classic organic synthesis, alkylation of β-ketoesters and other active methylene compounds followed by decarboxylation is a useful route to α-alkylated ketones or esters (Scheme 33).[76] The decarboxylation step occurs either via a zwitterionic tautomer in which the carbonyl is protonated and the carboxyl group is deprotonated (I),[77] or trhough the Krapcho process involving the reaction of esters with alkali metal salt (II).[78]

Upon heating, allylic β-keto esters can be converted into γ,δ-unsaturated ketones via a decarboxylative Claisen rearrangement (Scheme 34). This reaction was discovered by Carroll in 1940,[79] and many different variations have been disclosed especially after 1990. Recent developments of this reaction focused on the low-temperature processes through modification of the precursor β-keto esters and the high syn/anti selectivities.[80]

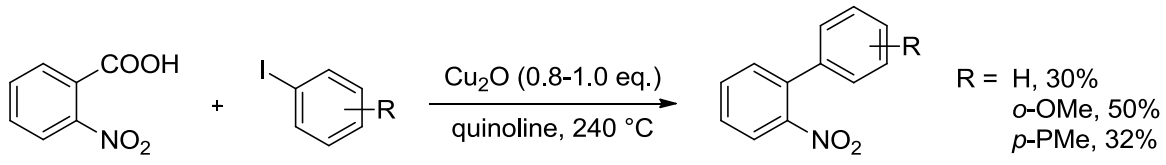


Scheme 33. Preparation of α-alkylated ketones or esters via tandem alkylation and decarboxylation.



Scheme 34. Decarboxylation process in Carroll rearrangement.

In 1966, Nilsson described the first biaryl synthesis via metal-mediated decarboxylative coupling of aryl carboxylic acid with aryl iodide (Scheme 35).[81] The rationale of this reaction is based on the assumption that the Ullmann-type biaryl synthesis and the copper-catalyzed decarboxylation of aromatic acids proceed via a common intermediate.

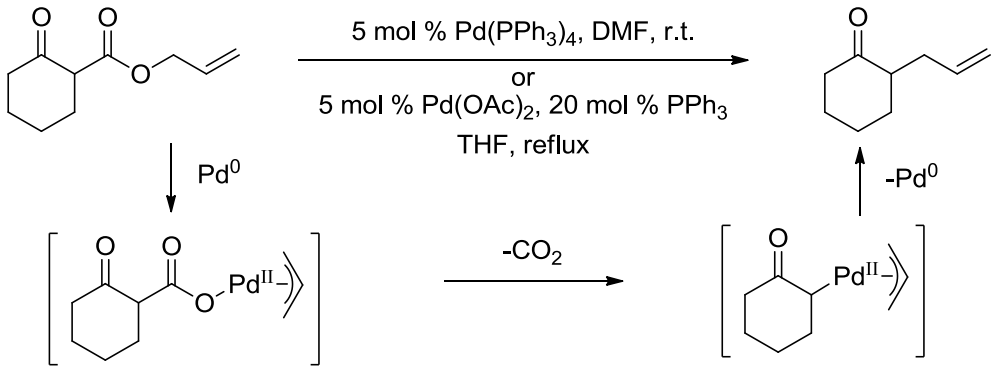


Scheme 35. Copper-mediated decarboxylative cross-coupling of aromatic carboxylic acids with aryl iodides.

Although this new coupling reaction demonstrated the feasibility of the use of carboxylic acids as coupling partners in biaryls synthesis, this reaction suffers from using excessive amount of copper catalyst, expensive aryl iodides and high reaction temperatures. Having

been seen as a typical variant of the Ullmann-type couplings, the copper-mediated decarboxylative cross-coupling reaction has not received much attention until the recent establishment of the catalytic processes.

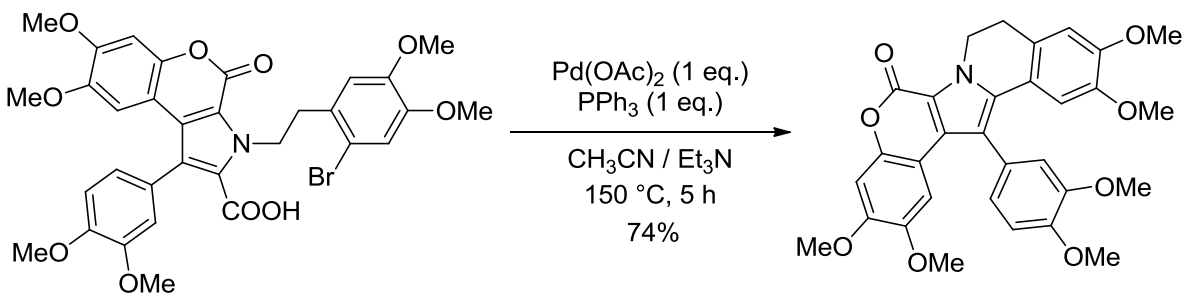
In 1980, Tsuji [82] and Saegusa [83] independently developed the palladium-catalyzed decarboxylative allylation reactions (Scheme 36). In the presence of palladium catalysts, the β-keto allyl esters undergo decarboxylation via a carboxylate-palladium-allyl complex to form the γ,δ-unsaturated ketones.



Scheme 36. Pd-catalyzed Tsuji-Saegusa decarboxylative allylation.

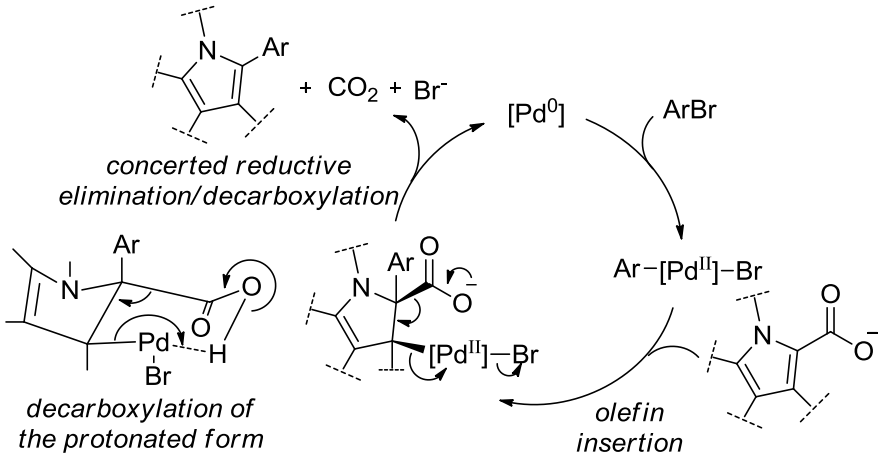
Compared to the Carroll rearrangement, the palladium-catalyzed decarboxylative allylation occurs via different mechanisms and takes place readily under much milder condition. Since its discovery, the decarboxylative allylations have received significant attention by organic chemists, while the substrate scope of the current methods is limited to the acidic hydrocarbons. [84] The further improvement of decarboxylative allylation includes the exploration of a wide variety of nucleophiles and the development of a broader scope of asymmetric allylation is also required.

In 1997, Steglich reported a seminal Heck-type intramolecular arylation reaction involving the decarboxylative palladation of pyrrolyl carboxylic acid in the total synthesis of lamellarin G (Scheme 37).[85]



Scheme 37. Decarboxylative palladation of pyrrolyl carboxylic acid.

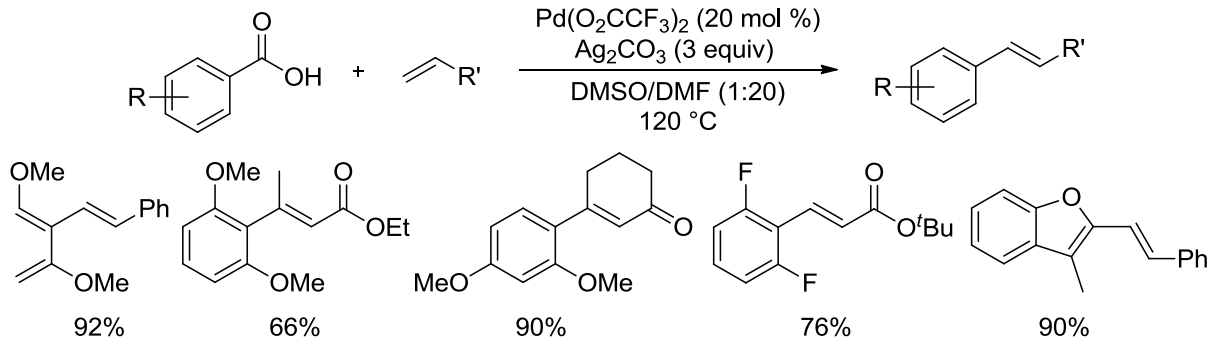
The reaction was proposed to occur through a α-heteroatom-subsituted olefin insertion by the aryl palladium bromide complex followed by the concerted reductive elimination and decarboxylation (Scheme 38).[86]



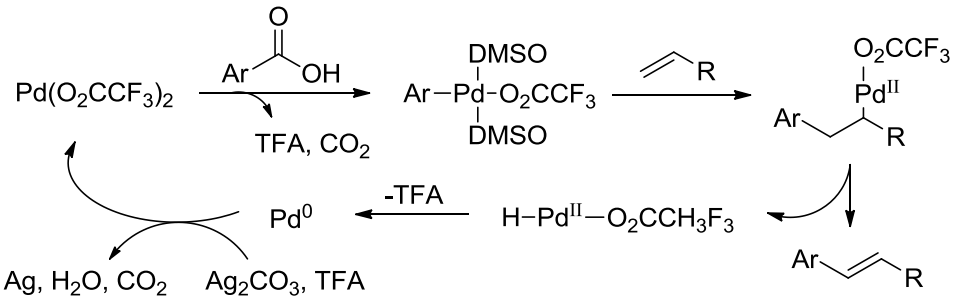
Scheme 38. Proposed mechanism for the intramolecular Heck-type decarboxylative arylation.

1.2.1.1 Cross-coupling of carboxylic acids with alkenes

The first palladium-catalyzed oxidative Heck-type decarboxylative cross-coupling reaction was disclosed by Myers in 2002 (Scheme 39).[87] In the presence of palladium catalyst, *ortho*-substituted carboxylic acids undergo decarboxylation to form aryl palladium (II) species which insert into the alkene double bond to generate an alkyl palladium (II) complex. After β-hydride elimination of this palladium intermediate, the arylated olefin is formed along with the palladium (0) species, which is oxidized by silver salt to regenerate the palladium (II) catalyst (Scheme 40).[88]



Scheme 39. Decarboxylative Heck-type couplings.

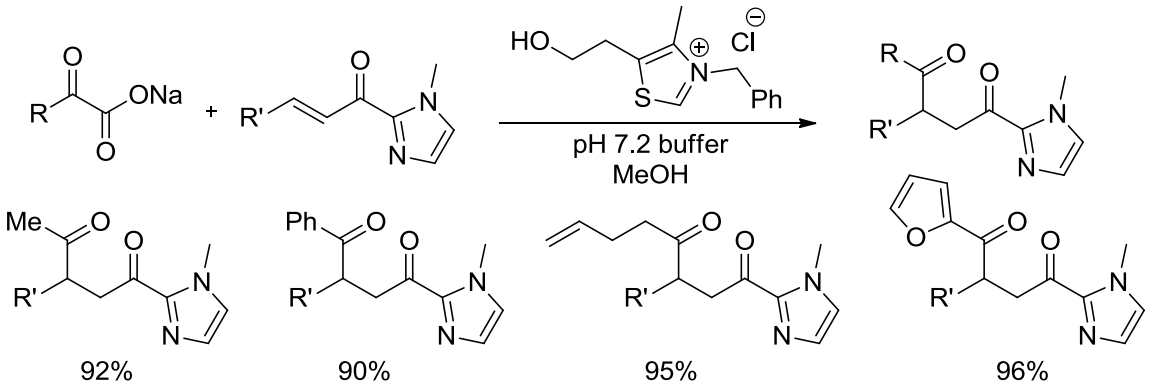


Scheme 40. Mechanism of the oxidative Heck olefination of aryl carboxylic acids.

In the oxidative Heck-type decarboxylative cross-coupling reactions, the costly aryl iodides or bromides are supplanted by inexpensive aryl carboxylic acids.[89] Thus, this new synthetic method provides an effective alternative to the synthesis of arylated olefins. However, the use of stoichiometric amounts of silver salts are required in order to reoxidize the resulting palladium (0) species. In an analogous protocol, Su and his coworkers demonstrated that benzoquinone and molecular oxygen are sufficient to reoxidize the palladium (Scheme 41).[90]

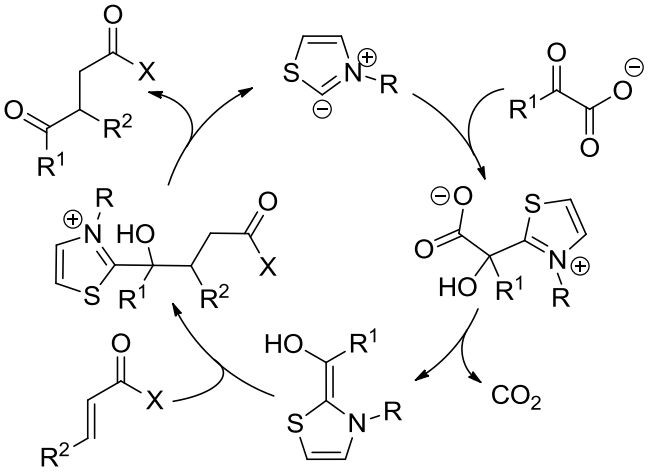
Scheme 41. Pd-catalyzed decarboxylative olefination using BQ or O_2 as oxidant.

In 2005, Scheidt and his coworkers[91] discovered that in the presence of catalytic amount of thiazolium-derived zwitterions, the α-keto carboxylates could be readily converted into reactive carbonyl ainons which undergo conjugate addition to substituted α,β-unsaturated 2-acyl imidazoles in a buffered protic environment. The decarboxylative addition process offers a convenient approach to valuable 1,4-dicarbonyl compounds under mild conditions (Scheme 42).

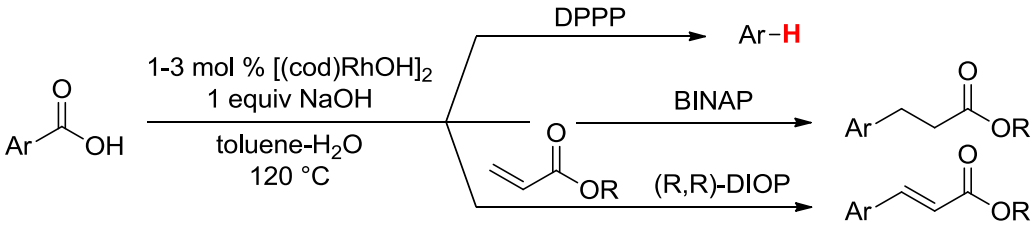


Scheme 42. Conjugate addition α-keto carboxylates to alkenes.

The authors proposed a reaction pathway which is similar to the benzoin-type process involving thiamine-dependent enzymes (Scheme 43). A tetrahedral intermediate is generated through the interaction of a thiazolium ylide with an α-keto carboxylate. The enanamine/carbon nucleophile species is then formed after the loss of CO_2. The electron-rich enamine undergoes conjugate addition to the unsaturated electrophile followed by a deprotonation of the resulting tertiary alcohol, releasing the corresponding ketone and the thiazolium catalyst.



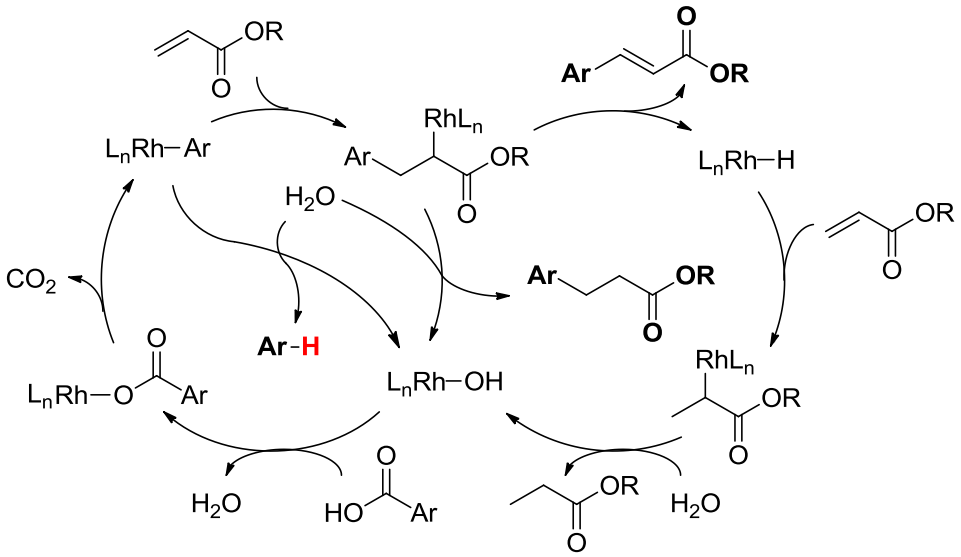
Scheme 43. Proposed reaction pathway for the decarboxylative conjugate addition.



Scheme 44. Rh-catalyzed decarboxylative processes.

Recently, Zhao and his coworkers developed Rh-catalyzed decarboxylative couplings of aromatic carboxylic acids with electron-deficient olefins (Scheme 44).[92] In the presence of Rh catalysts, different decarboxylative processes of aryl carboxylic acids, particularly polyfluorobenzoic acids could be easily achieved by the choice of specific phosphine ligands. For instance, by using the bidentate ligand DPPP, the decarboxylation of aryl carboxylic acids proceeds smoothly, giving the corresponding arenes in high yields. The *in situ* generated aryl rhodium complex resulting from decarboxylation of the aryl carboxylic acid could either undergo β-hydride elimination forming the Heck-Mizoroki product or hydrolysis of the rhodium enolate intermediate, affording the conjugate addition product. The selectivity is highly controlled by the different phosphine ligands, namely BINAP and DIOP. As a

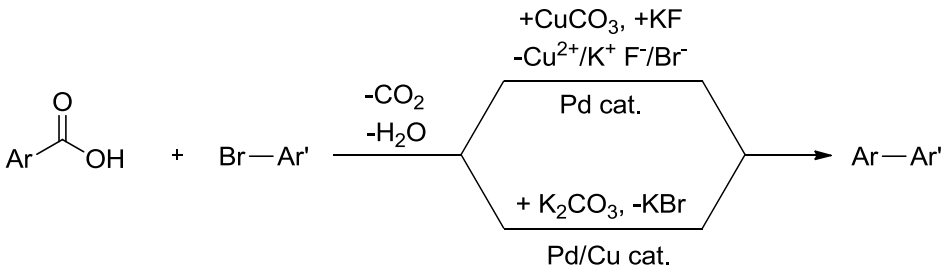
sacrificial hydrogen acceptor, the respective acrylate is required in stoichiometric quantity (Scheme 45).



Scheme 45. Proposed mechanism for the Rh-catalyzed decarboxylative couplings.

1.2.1.2 Cross-coupling of carboxylic acids with organo halides or pseudohalides

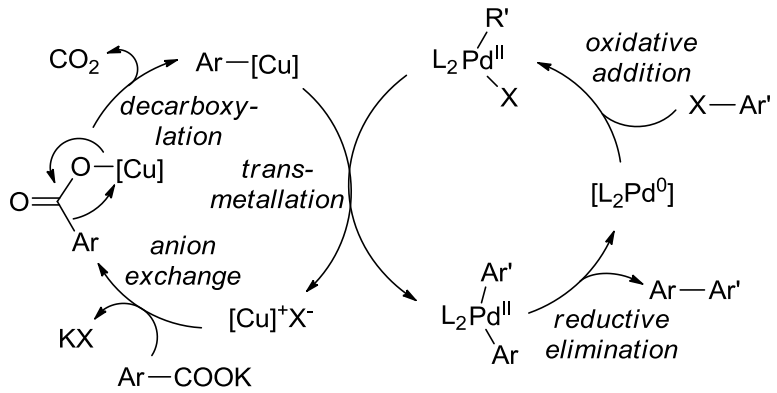
In 2006, Gooßen *et al.* reported the first catalytic biaryl synthesis via the decarboxylative cross-coupling of aromatic carboxylic acids with aryl bromides (Scheme 46).[93] Two complementary protocols were developed for the catalytic transformations. The first catalyst system containing stoichiometric amounts of copper salt allows the decarboxylative coupling of most ortho-substituted aromatic carboxylic acids with aryl bromides to proceed at 120 °C, while the second variant, where both metal catalysts were employed in only catalytic quantities requires a higher reaction temperature of 160 °C and remains limited to 2-nitrobenzoic acids.



Scheme 46. Pd/Cu-catalyzed decarboxylative biaryls synthesis.

The bimetallic catalyst system consists of a copper salt and a palladium precatalyst. As depicted in Scheme 47, the copper salt catalyzes the decarboxylation of aromatic carboxylic acids to generate an aryl copper intermediate. The aryl moiety is then transferred to an aryl

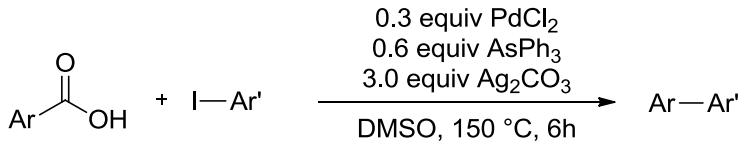
palladium halide complex generated *in situ* from the oxidative addition of aryl halide onto the palladium (0) catalyst, forming an aryl-palladium-aryl species. Reductive elimination releases the biaryl product and regenerates the initial palladium (0) catalyst.



Scheme 47. Mechanism for the decarboxylative cross-couplings.

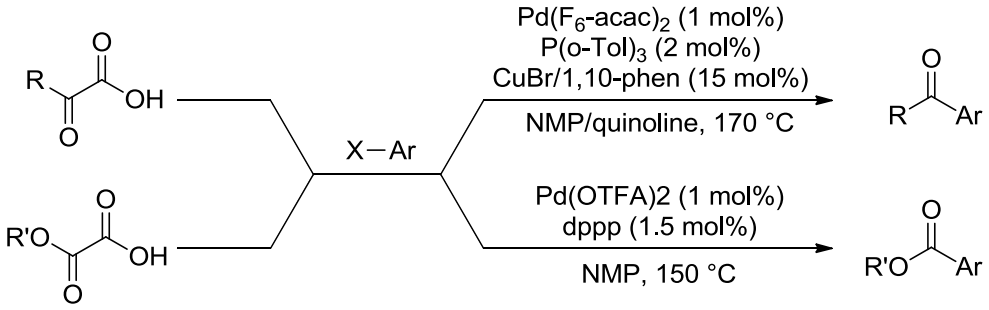
This Pd/Cu-catalyzed decarboxylative biaryl synthesis has been seen as an important milestone in decarboxylative cross-coupling reactions. The traditional transition metal-catalyzed biaryl syntheses such as Kumada-Corriu, Suzuki-Miyaura, Negishi, Stille, Hiyama reactions have inherent disadvantages, namely the requirement of expensive and sensitive organometallic reagents. In contrast, the decarboxylative cross-coupling reactions utilize carboxylic acids as the nucleophilic coupling partners, which are inexpensive, stable in air, and available in wide structural variety. Therefore, the decarboxylative coupling reactions serve as an attractive alternative to the traditional transition metal-catalyzed coupling reactions, providing convenient and efficient methodologies for the C–C and C–heteroatom bond formations.[94]

Another protocol for the decarboxylative cross-coupling of aromatic carboxylic acids with aryl iodides consists of catalytic amounts of $PdCl_2$ and $AsPh_3$ along with excessive silver carbonate (Scheme 48).[95] However, this catalytic transformation is lacking of generality applicability. Moreover, the fact that large quantities of expensive silver salts are required for the transformation limits its synthetic utility and makes the reaction uneconomic.



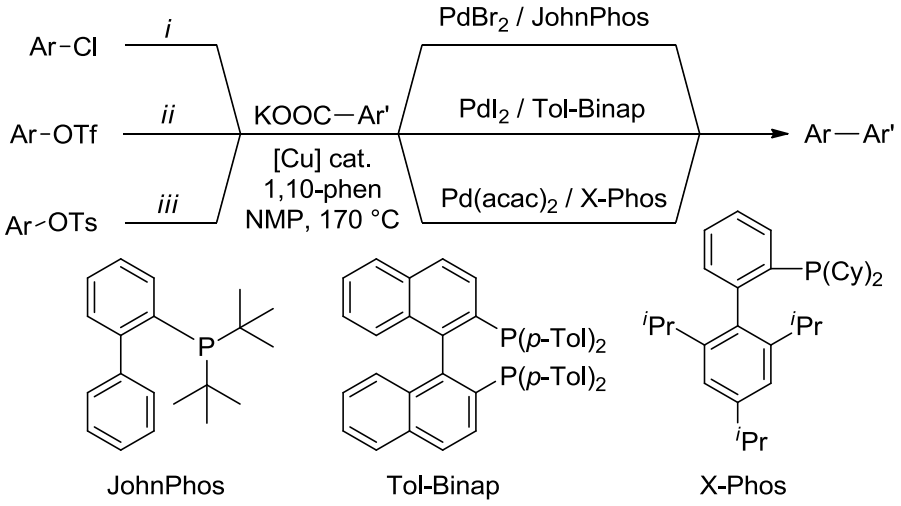
Scheme 48. Pd-catalyzed decarboxylative coupling of aryl iodides using stoichiometric amount of silver salts as additives.

The replacement of aromatic carboxylic acids with α-keto carboxylic acids leads to a straightforward approach to the corresponding ketones[96] and esters[97] via a carbonyl umpolung tactic (Scheme 49). Unlike the conventional Friedel-Crafts acylations, these decarboxylative processes produce regiospecific ketones and esters without using any organometallic reagents.



Scheme 49. Ketone and ester syntheses via carbonyl umpolung.

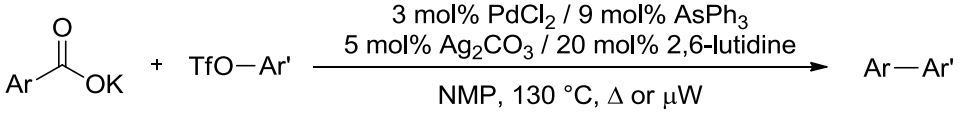
The aryl chlorides have also been demonstrated to be amenable to the decarboxylative cross-coupling reactions (Scheme 50, i).[98] Although the aryl C–Cl bond is much stronger compared to the corresponding C–Br bond,[99] the combination of palladium catalyst and an electron-rich and sterically hindered phosphine ligand JohnPhos allows the success of oxidative addition of palladium onto the aryl chlorides furnishing the decarboxylative coupling process. However, the decarboxylative cross-coupling of aryl bromides and chlorides are both limited to specific carboxylic acids, particularly the ortho-substituted benzoic acids. This is resulted from the competition between halide ions and carboxylates in the coordiantion of the copper catalyst.[100]



Scheme 50. The use of aryl chlorides and sulfonates in decarboxylative couplings.

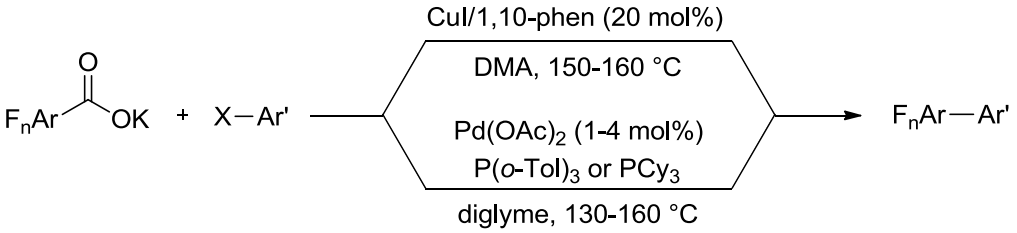
When the aryl halides are superceded by aryl triflates bearing weekly coordinating ions, a much broader range of benzoates is amenable to the decarboxylative cross-coupling reactions (ii).[101] The coupling of aryl tosylates was also realized by using the Buchwald ligand X-Phos (iii). [102] However, the use of less inexpensive and more robust aryl Mesylates as the electrophiles in the decarboxylative coupling is still challenging in this field.

After an intensive investigation of the protodecarboxylation of aromatic carboxylic acids carried out in the Gooßen group,[103] silver has been proved to be an effective decarboxylation catalyst which allows the protodecarboxylation of most benzoic acids already at 120 °C.[104] The combination of palladium and silver catalysts leads to a new protocol for the decarboxylative cross-coupling of aromatic carboxylic acids with aryl triflates at an unprecedentedly low temperature 130 °C (Scheme 51).[105]

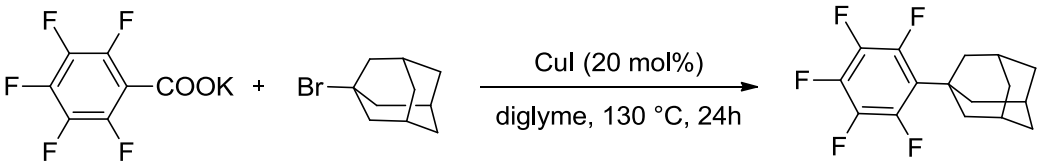


Scheme 51. Pd/Ag-catalyzed decarboxylative coupling.

Polyfluorobenzoic acids are particularly reactive in the presence of several transition metals. Besides Rhodium, copper[106] and palladium[107] catalysts are also demonstrated to be effective for the decarboxylative cross-coupling of fluorinated aromatic carboxylic acids with aryl halides (Scheme 52). DFT calculations showed that the oxidative addition represents the rate-determining step in the Cu-catalyzed decarboxylative coupling, whereas the decarboxylation step is the rate-limiting step in the Pd-catalyzed version.



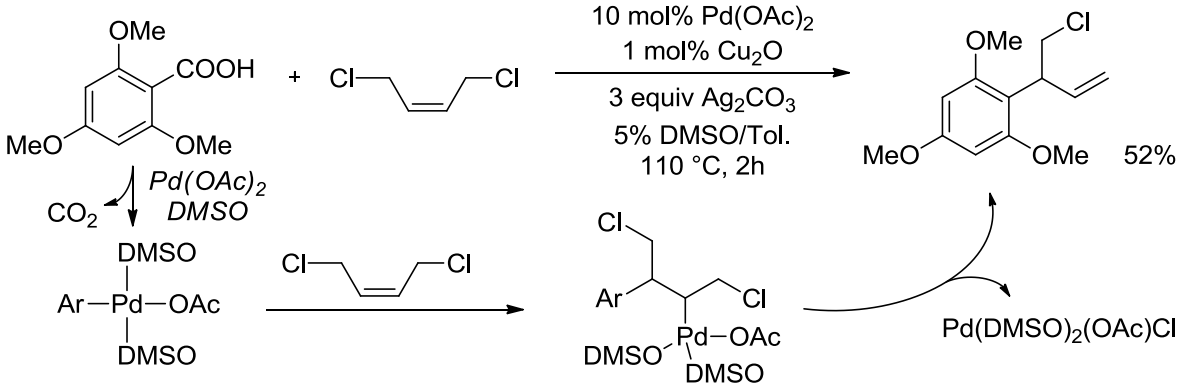
Scheme 52. Polyfluorobenzoates in decarboxylative cross-couplings.



Scheme 53. Decarboxylative coupling of pentafluorobenzoate with 1- bromoadamantane.

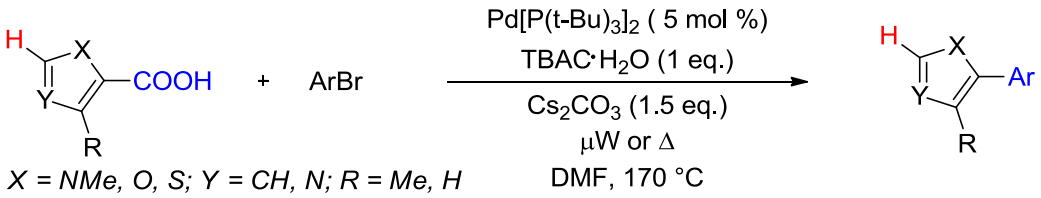
In the presence of a copper catalyst, 1-bromoadamantane could be also coupled with pentafluorobenzoate, affording the corresponding tertiary alkyl arene (Scheme 53).[106]

Allyl arenes could also be easily accessed via the decarboxylative cross-coupling of aromatic carboxylic acids with allylic halides (Scheme 54).[108] The mechanism involves a sequent Heck-type insertion of Ar-PdL$_2$(OAc) into the double bond and β-halide elimination.

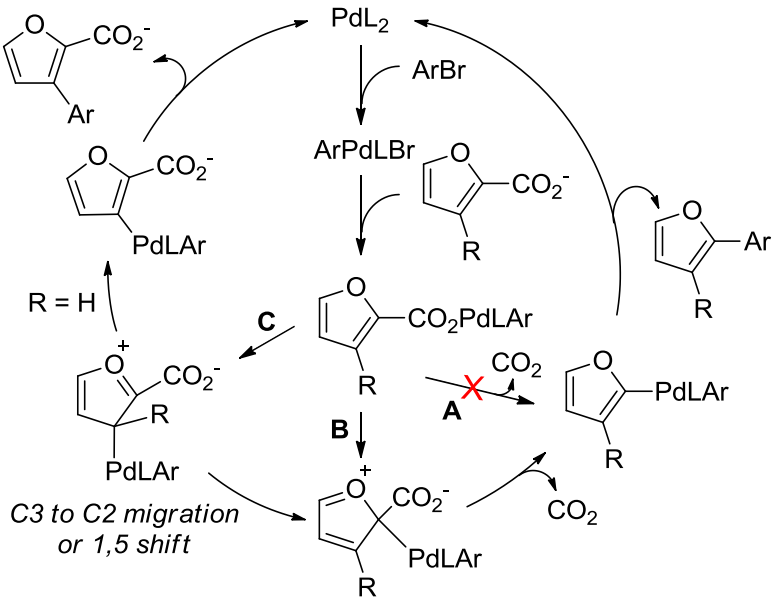


Scheme 54. Decarboxylatvie cross-coupling of aromatic carboxylic acids with allylic halides.

In 2006, Bilodeau and Forgione disclosed the first Pd-catalyzed decarboxylative cross-coupling of five-membered heterocyclic carboxylic acids with aryl halides (Scheme 55).[109]



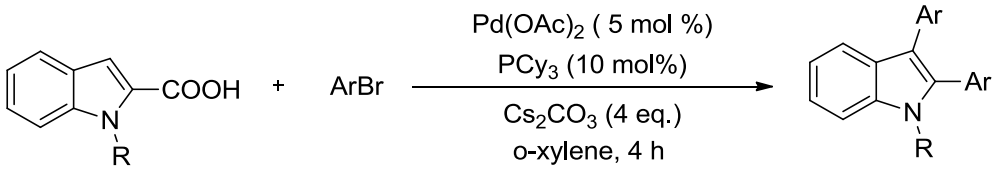
Scheme 55. Decarboxylatvie cross-coupling reaction between heteroaromatic carboxylic acids and aryl halides.



Scheme 56. Proposed mechanism for the decarboxylatvie cross-coupling of heteroaromatic carboxylic acids with aryl halides.

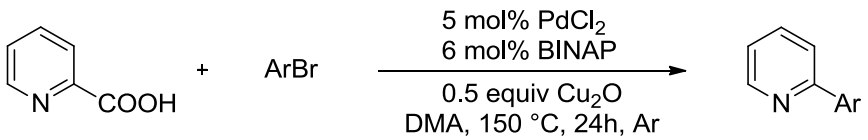
This new transformation possesses obvious advantages over the C–H bond direct arylation, due to the low regioselectivity of the latter reaction system. Unlike for aryl carboxylic acids, the coupling process of heteroaryl surrogates with aryl halides proceeds via electrophilic palladation pathways (Scheme 56, paths B and C) instead of direct decarboxylation, which can be excluded based on the unequivocal observation of 2,3-diarylation byproducts (path A).[110]

The decarboxylative cross-coupling of carboxyindoles with aryl halides has also been elaborated by Miura (Scheme 57).[111] The direct synthesis of 2,3-diarylindoles involves sequential ortho- and ipso-decarboxylative arylation processes.



Scheme 57. Decarboxylatvie cross-coupling of carboxyindoles with aryl halides.

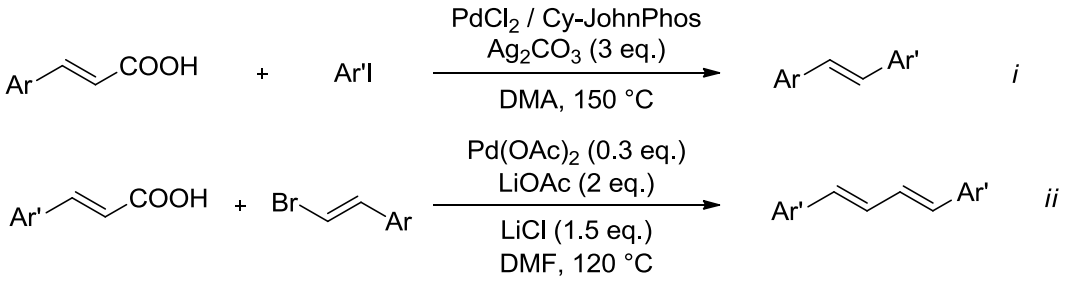
More recently, the use of 2-picolinic acid as a nucleophilic partner in decarboxylative cross-coupling reactions has also been developed by Wu and his coworkers (Scheme 56).[112] 2-Arylpyridines are the one of the most important heterocyclic structural motifs and their syntheses are definitely of great interest for organic chemists. However, due to the instability and the synthetic difficulty of 2-pyridyl organometallics,[113] 2-arylpyridines are hard to access from traditional metal-catalyzed cross-coupling reactions. Therefore this decarboxylative process not only provides an efficient and new route to this important class of substrates, but also has been endowed with highly synthetic utility by using simple and inexpensive 2-picolinic acid as the coupling partner.



Scheme 58. Decarboxylatvie cross-coupling of 2-picolinic acid with aryl halides.

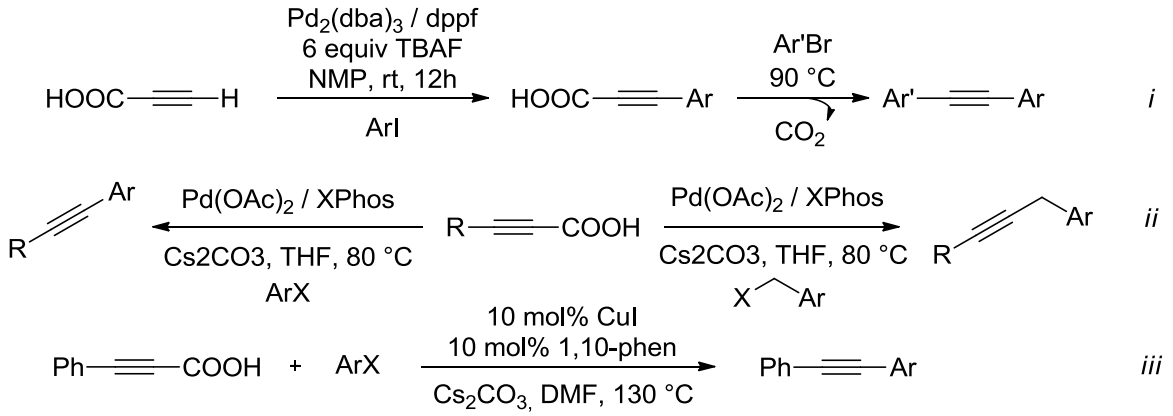
Besides the aromatic and heteroaromatic carboxylic acids, the alkenyl and alkynyl carboxylic acids are also amenable to decarboxylative cross-coupling reactions. In Gooßen's seminal report,[93] cinnamic acid has been successfully coupled with aryl bromides affording stilbenes in almost quantative yields. In Wu's protocol, a broad variety of cinnamic acids was coupled

with various aryl iodides yielding the corresponding 1,2-diaryl olefins in the presence of catalytic amounts of $PdCl_2$ and stoichiometric amounts of Ag_2CO_3 (Scheme 59, i).[114] In 2010, Miura demonstrated the decarboxylative coupling between cinnamic acids and vinyl bromides (Scheme 59, ii).[115]



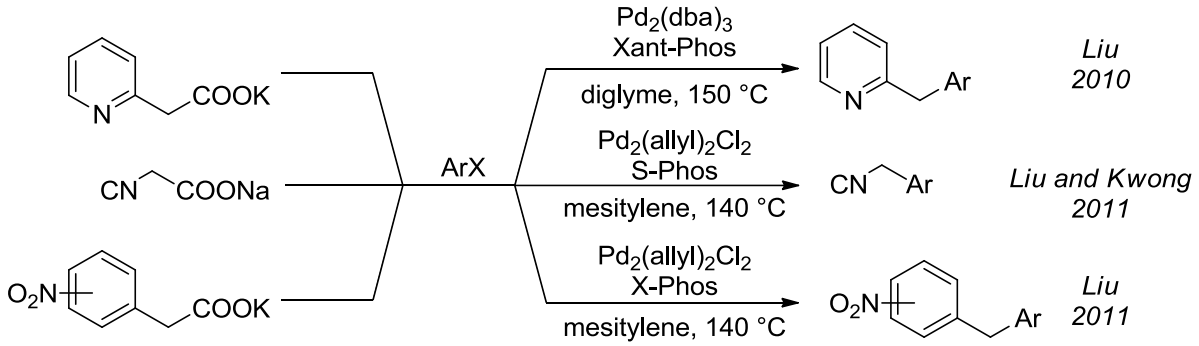
Scheme 59. Decarboxylatvie cross-coupling of cinnamic acids with aryl/alkenyl halides.

In 2008, Lee *et al.* developed a convenient protocol for the synthesis of unsymmetrically substituted diaryl alkynes by applying propiolic acid in the conventional Sonogashira reaction (Scheme 60, i).[116] The carboxylate group remains intact after the Sonogashira coupling and undergoes a subsequent decarboxylative cross-coupling of the arylpropiolic acid with another aryl halide leading to the final diaryl alkynes. In another protocol, Wu and his coworkers demonstrated the palladium-catalyzed decarboxylative cross-coupling of alkynyl carboxylic acids with aryl chlorides and benzyl halides by using X-Phos (Scheme 60, ii).[117] In addition to the palladium catalyst system, the copper-catalyzed decarboxylative cross-coupling of alkynyl carboxylic acids with aryl halides have also been realized (Scheme 60, iii).[118] However, there is controversy over the mechanisms that the transformation is initiated with the formation of the terminal alkynes from the proto-decarboxylation of the substituted propiolic acids followed by the Sonogashira coupling.



Scheme 60. The use of alkynyl carboxylic acids in cross-couplings.

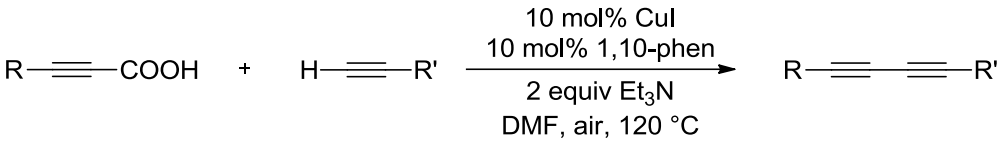
Activated aliphatic carboxylic acids containing electron-withdrawing groups on their α-positions such as cyano,[119] pyridyl,[120] or nitroaryl,[121] could also be used as nucleophiles in decarboxylative cross-coupling reactions. These auxiliary functional groups facilitate the decarboxylation steps (Scheme 61).



Scheme 61. Decarboxylatvie cross-coupling of aliphatic carboxylic acids with aryl halides.

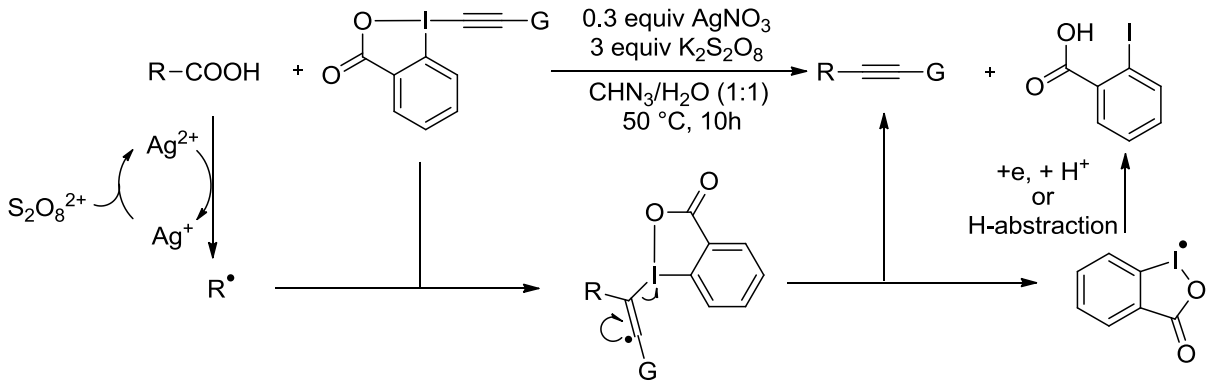
1.2.1.3 Cross-coupling of carboxylic acids with alkynes

In 2010, Jiao and his coworkers described the copper-catalyzed decarboxylative cross-coupling of substituted propiolic acids with terminal alkynes, from which the unsymmetric conjugated diynes are readily approached (Scheme 62).[122] However, the reaction scope is limited to electron-rich substrates, and the yields need to be improved.



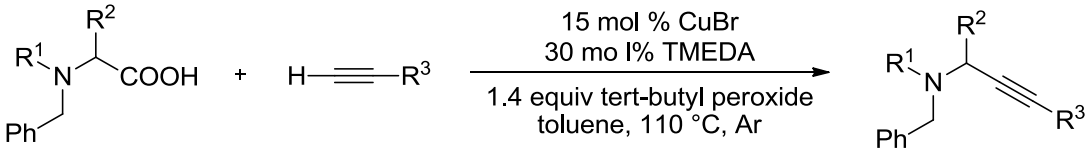
Scheme 62. Decarboxylative cross-coupling between substituted propiolic acids and terminal alkynes.

More recently, Li and his coworkers demonstrated the synthesis of internal alkynes through decarboxylative alkynylation of aliphatic carboxylic acids with the electrophilic alkynylating agents, namely, ethynylbenziodoxolones (Scheme 63).[123] As a typical radical reaction, the mechanism involves an SET (single eletron transfer) process (Scheme 63).



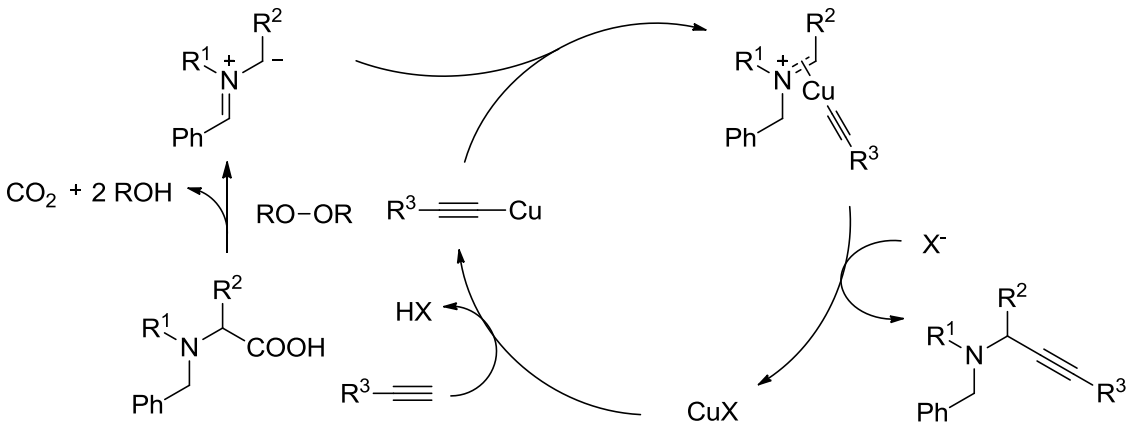
Scheme 63. Decarboxylatvie cross-coupling between aliphatic carboxylic acids and ethynylbenziodoxolones.

In 2009, Li and coworkers developed the copper-catalyzed decarboxylative cross-coupling of α-amino acids with terminal alkynes in the presence of *tert*-butyl peroxide, leading to propargyl amines (Scheme 64).[124] Other activated hydrocarbons such as indoles, nitromethane could also be used in this decarboxylative coupling process, generating indolyl pyrrolidines and piperidines, and β-nitroamines respectively.



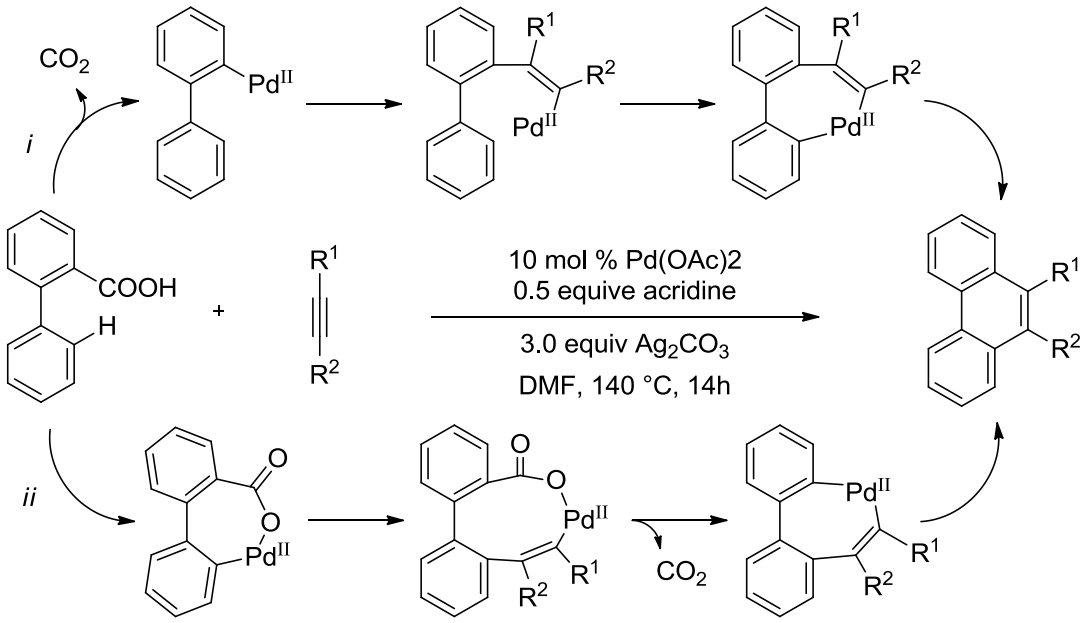
Scheme 64. Decarboxylatvie cross-coupling of α-amino acids with terminal alkynes.

The catalytic transformation starts with the oxidative decarboxylation of α-amino acids to form an imine-type intermediate, which reacts with copper acetylide generating an alkynyl copper imidate. The organocopper species undergoes intramolecular nucleophilic addition to release the desired products and regenerate the copper catalyst (Scheme 65).



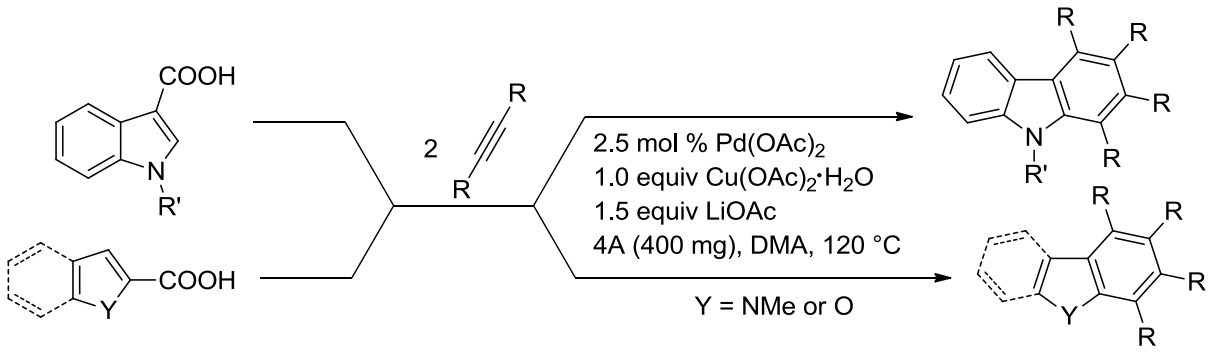
Scheme 65. Mechanism of decarboxylative cross-coupling of α-amino acids.

The decarboxylative cross-coupling of carboxylic acids with internal alkynes has been described recently. For instance, Glorius *et al.* disclosed the palladium-catalyzed intermolecular decarboxylative coupling of 2-phenylbenzoic acids with alkynes (Scheme 66).[125] The reaction could be seen as an intermolecular formal [4+2] annulation yielding the corresponding phenanthrene derivatives. The mechanistic investigation indicated that the reaction initiates with either decarboxylation or carboxylate-directed C–H bond activation. The subsequent carbopalladation of the alkynes leads to a vinyl palladium aryl species, which undergoes reductive elimination to release the product and palladium catalyst.



Scheme 66. Decarboxylative cross-coupling of 2-phenylbenzoic acids with internal alkynes.

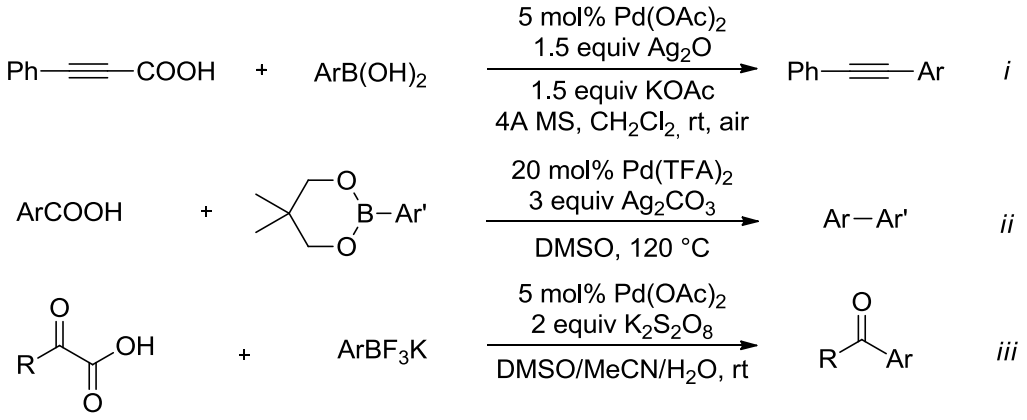
In a related protocol, heteroaryl carboxylic acids such as indole-3-carboxylic acids, pyrrole-, benzofuran-, and furancarboxylic acids were coupled with two molecules of internal alkynes, affording the corresponding condensed heteroaromatic compounds such as carbazoles, indoles, dibenzofuran and benzofuran derivatives are prepared in only on step (Scheme 67).[126]



Scheme 67. Decarboxylative coupling of heteroaromatic carboxylic acids with alkynes.

1.2.1.4 Cross-coupling of carboxylic acids with organometallic reagents

The carboxylate moiety is often used as a nucleophile in cross-coupling reactions, so that an oxidant is essential for the coupling reaction between a carboxylic acid and an organometallic compound. However, most oxidants are scavengers for the decarboxylation steps. As a result, only a few examples of decarboxylative cross-coupling between carboxylic acids and organometallic reagents have been developed up to the present day. Among the oxidants employed, silver salts are most effective, since they not only serve as an efficient oxidant for palladium (0) to palladium (II), but also facilitate the decarboxylation of most of aromatic carboxylic acids. For example, Loh *et al.* reported the palladium-catalyzed decarboxylative cross-coupling of alkynyl carboxylic acids with arylboronic acids, in which Ag_2O was used as an oxidant (Scheme 68, i).[127]



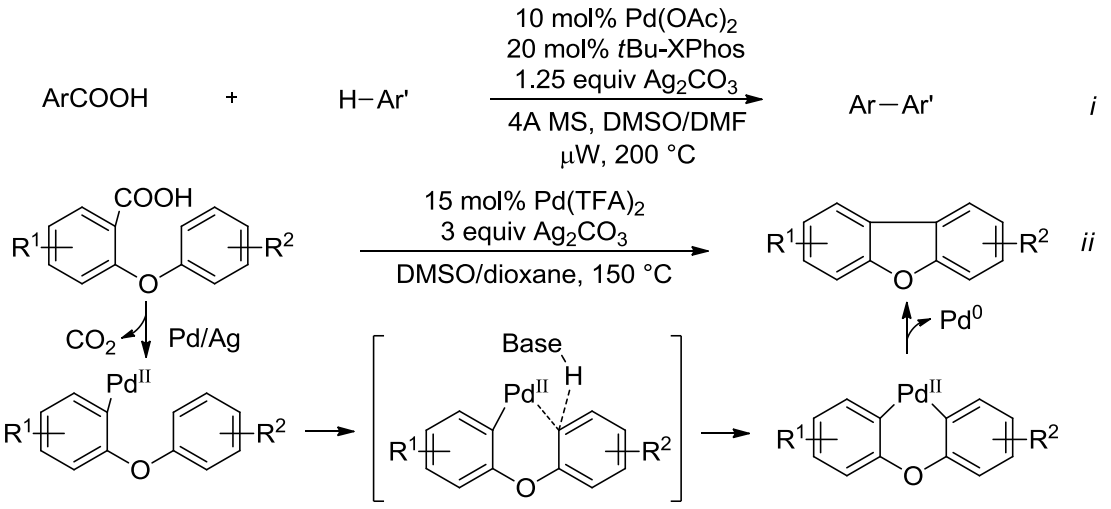
Scheme 68. Decarboxylative cross-coupling between carboxylic acids and arylboron reagents.

Recently, the decarboxylative coupling of aromatic carboxylic acids with arylboronic esters was developed by the group of Liu (Scheme 68, ii).[128] The decarboxylation of α-oxocarboxylic acids occurs readily at room temperature in the presence of $K_2S_2O_8$, to the extent that the combination of palladium catalysts and $K_2S_2O_8$ allows the coupling of oxocarboxylic acids with organoborates (Scheme 68, iii).[129]

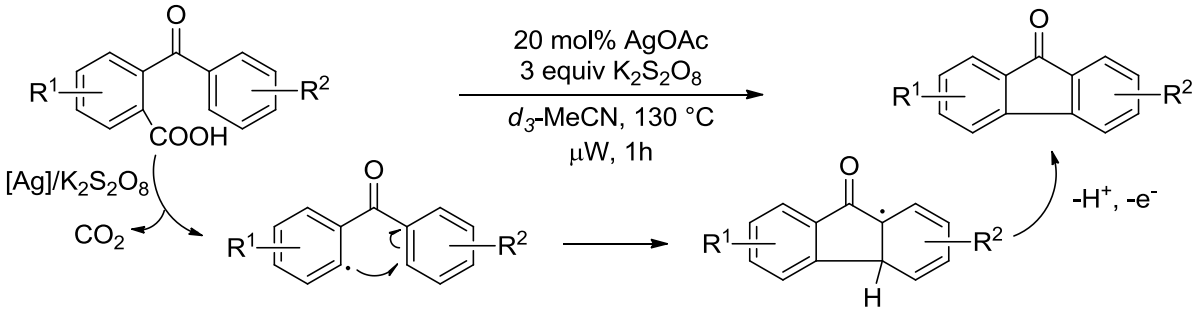
1.2.1.5 Decarboxylative couplings involving C–H bond activation

In the past decades, C–H activation have received much attention from organic chemists and a plethora of new reactions involving this concept have been invented in order to achieve high atom economy. On the view of sustainable organic synthesis, decarboxylative couplings provide an efficient alternative to the traditional metal-catalyzed cross-couplings that require organometallic reagents. Therefore, the combination of C–H activation and decarboxylative couplings becomes an urgent and interesting topic for organic chemists.

In 2009, Crabtree and his coworkers disclosed the first palladium-catalyzed decarboxylative dehydrogenative cross-coupling of aromatic acids with activated arenes by using *t*-Bu-XPhos (Scheme 69, i).[130] An intramolecular variant was later developed by Glorius, in which 2-phenoxybenzoic acids were chosen as the starting materials, affording the corresponding dibenzofurans as products (Scheme 69, ii).[131] The proposed mechanism involves the formation of an aryl-Pd(II) intermediate formed from the decarboxylative metallation, and a palladacycle generated through the intramolecular C–H activation. The reductive elimination of this palladacyle releases the desired product and the palladium (0) catalyst, which is then oxidized to Pd(II).



Scheme 69. Decarboxylative dehydrogenative cross-couplings.

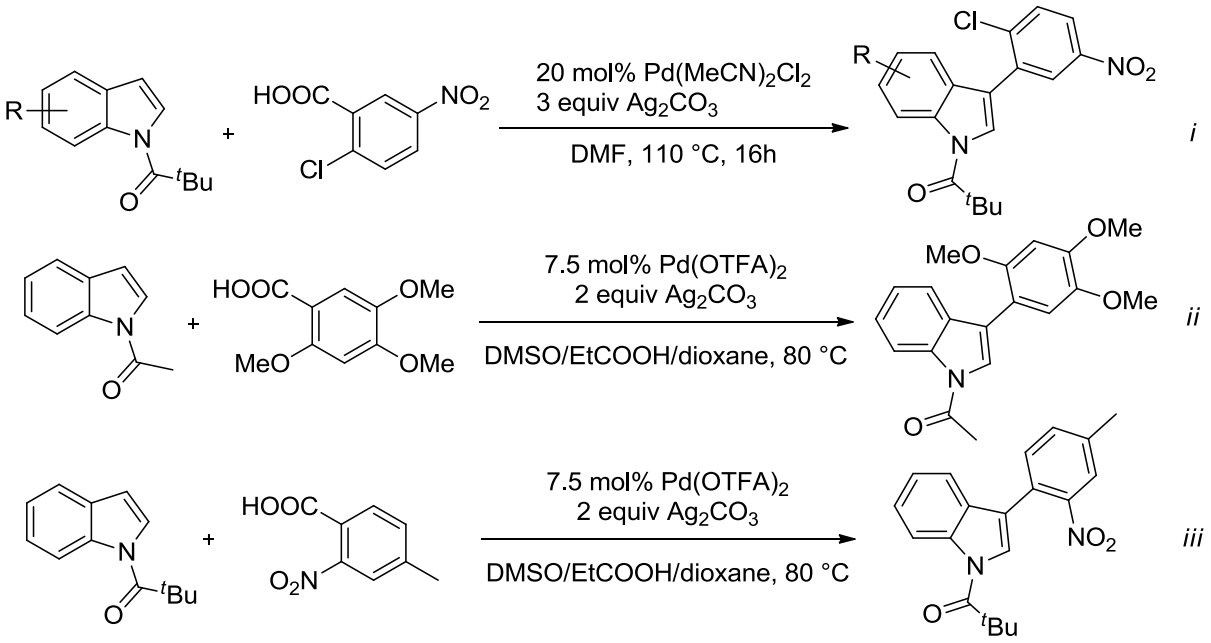


Scheme 70. Decarboxylative fluorenone synthesis.

More recently, Greaney *et al.* reported the silver-catalyzed intramolecular decarboxylative fluorenone synthesis (Scheme 70).[132] In the presence of a silver(I) catalyst and stoichiometric amounts of $K_2S_2O_8$, the aroylbenzoic acid undergoes oxidative decarboxylation to generate an aryl radical, followed by cyclization to afford the fluorenone product.

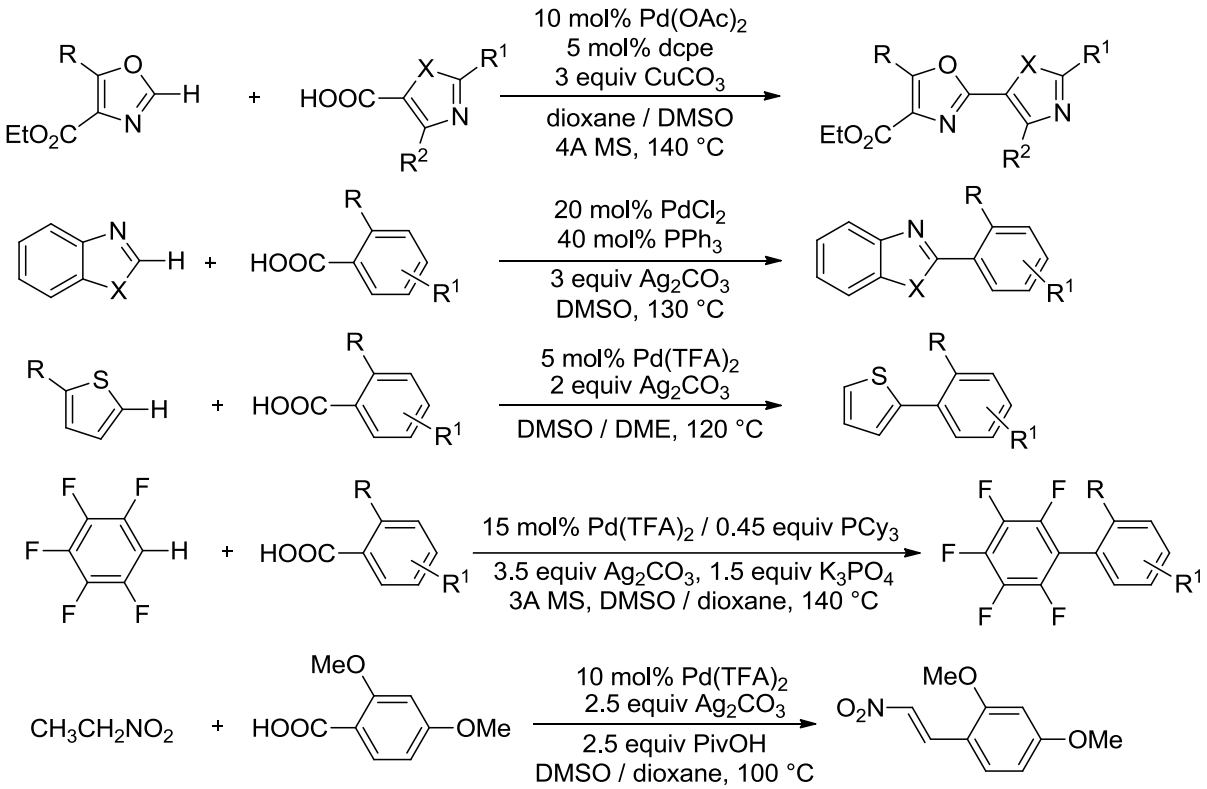
In 2009, Larrosa *et al.* described the palladium-catalyzed intermolecular decarboxylative dehydrogenative cross-couping of electro-deficient aromatic carboxylic acids with substituted

indoles (Scheme 71, i).[133] It is notable that the arylation takes place regioselectively at the C-3 postion of indole. Su and coworkers found that the regioselectivity of the decarboxylative arylation of indoles is highly depended on the electronic nature of the aromatic carboxylic acids. The benzoic acids bearing electron-donating groups give the 2-arylated indoles (Scheme 71, ii),[134] while the electron-poor ones lead to the 3-arylated products (Scheme 71, iii).



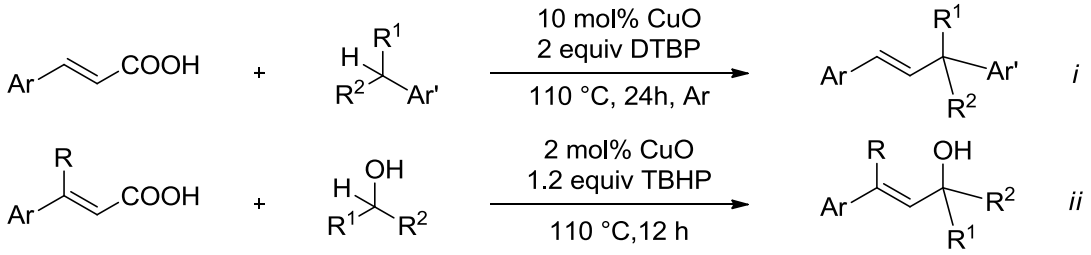
Scheme 71. Regio-selective arylation of indoles by using aromatic carboxylic acids.

The intermolecular decarboxylative cross-couplings between aryl or heteroaryl carboxylic acids and acidic hydrocarbons such as azoles,[135] thiophenes,[136] polyfloruoarenes,[137] and nitroethane[138] have been developed by the groups of Greaney, Tan and Su (Scheme 72).



Scheme 72. Decarboxylative C–H cross-couplings.

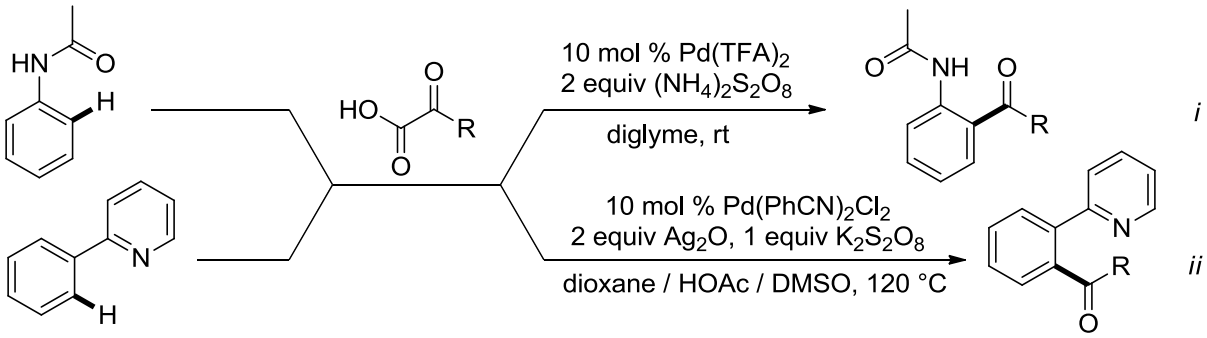
More recently, Mao [139] and Liu [140] independently reported the development of copper-catalyzed oxidative decarboxylative couplings involving an sp^3 C–H bonds activation in the presence of peroxides such as TBHP (Scheme 73, i) or DTBP (ii). These reactions are proposed to proceed via radical addition-elimination of aryl-substituted vinyl carboxylic acids.



Scheme 73. Copper-catalyzed decarboxylative alkenylation of sp^3 C–H bonds with cinnamic acids.

Arenes bearing directing groups such as amide and pyridine are well known to easily undergo C–H activation at the *ortho* position, followed by functionalization in the presence of palladium or other transition metal catalysts. However, the combination of this strategy and decarboxylative processes is problematic, as the decarboxylation of most carboxylic acids is inhibited under oxidative conditions. In 2010, Ge reported the first example of an amide-directing C–H activation and acylation by using α-oxocarboxylic acids as acylating reagents

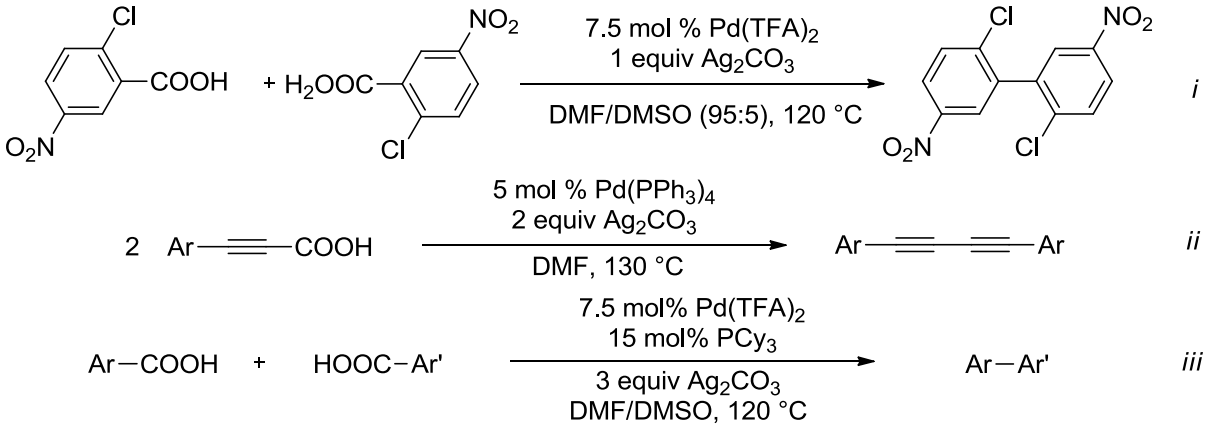
(Scheme 74, i).[141] Unlike aromatic carboxylic acids, the decarboxylation of α-oxocarboxylic acids could be even facilitated by the peroxides employed as oxidants in the protocol. However, changing the directing group to pyridine leads to a high-temperature process (ii),[142] probably due to the higher energy barrier of the C–H activation in the 2-phenyl pyridine systems compared to the acetanilide system.



Scheme 74. Directed C–H activation and decarboxylative couplings.

1.2.1.6 Other decarboxylative couplings forming C–C bonds

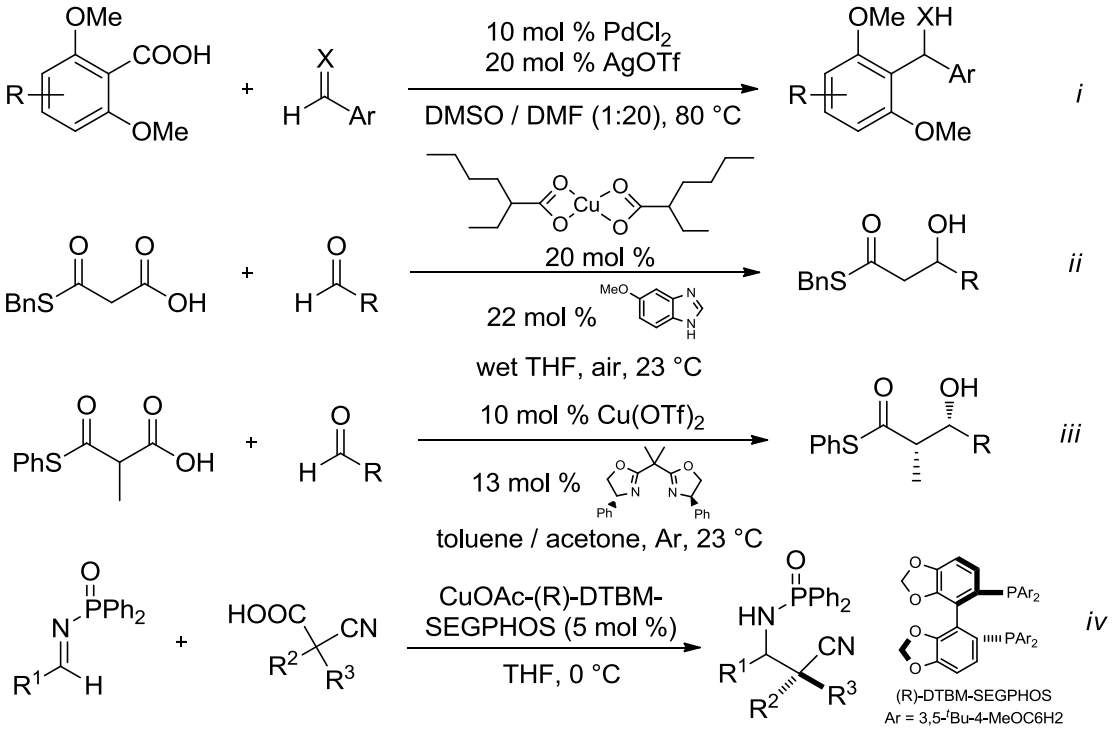
Two identical or different aromatic carboxylic acids could also react with each other, affording symmetric or unsymmetric biaryls, respectively. As a side reaction, the homo-coupling of carboxylic acids is always problematic in the development of decarboxylative coupling reactions.



Scheme 75. Decarboxylative homo- and cross-coupling of two carboxylic acids.

The first full account for the homo-coupling of aromatic carboxylic acids was described by Larrosa in 2008 (Scheme 75, i).[143] Silver salts serve both as decarboxylation catalysts and as oxidants for the *in situ* generated Pd(0) species. Similar to the aromatic carboxylic acids, the homocoupling of alkynyl carboxylic acids has also been disclosed (Scheme 75, ii).[144] More

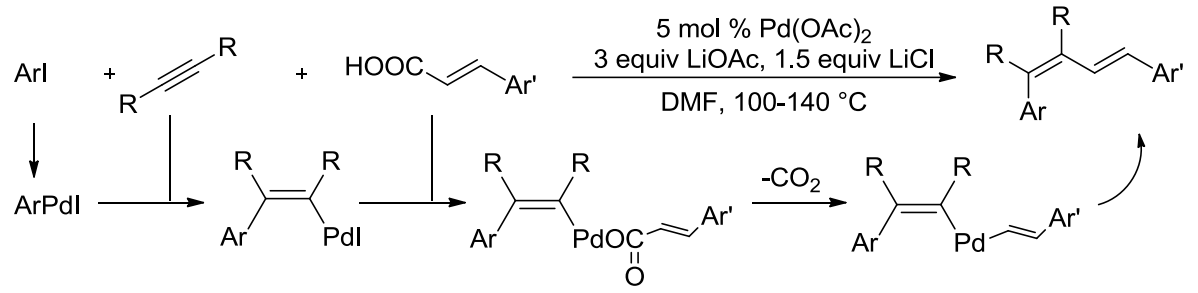
recently, the cross-coupling of two different carboxylic acids was independently developed by the groups of Tan[145] and Su (Scheme 75, iii).[146]



Scheme 76. Decarboxylative addition to aldehydes and imines.

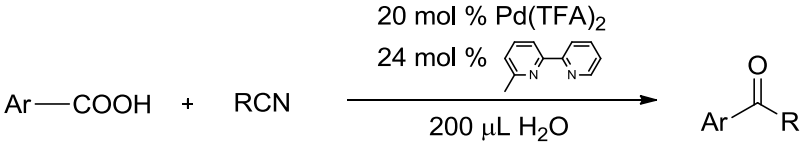
Organometallic species generated via decarboxylation of carboxylic acids can undergo nucleophilic addition to carbon-carbon or carbon-heteroatom multibonds. Such decarboxylative addition reactions of aromatic (Scheme 76, i),[147] aliphatic carboxylic acids[148] (Scheme, ii, iii and iv) to aldehydes and imines have been developed fro specific substrates, but no general method has been reported up to the present day.

Recently, Miura *et al.* described the decarboxylative addition of cinnamic acids to internal alkynes, accompanyed with the coupling of aryl iodides (Scheme 77).[149] The reaction is initiated with the oxidative addition of aryl iodide to a palladium (0) catalyst, forming an aryl halide species which undergoes insertion into the internal alkyne, generating the vinyl palladium halide intermediate. An alkenyl carboxylic acid reacts with this palladium species to form a vinyl palladium carboxylate intermediate, followed by the decarboxylation releasing the final product and the palladium catalyst.



Scheme 77. Decarboxylative addition of aromatic carboxylic acids to alkynes.

In 2010, Larhed *et al.* disclosed the Pd-catalyzed decarboxylative ketone synthesis via the decarboxylative addition of aromatic carboxylic acids to nitriles (Scheme 78).[150] Compared to the aforementioned decarboxylative acylations involving carbonyl unpolungs, this protocol avoids using expensive oxo-carboxylic acids, but requires high catalyst loading.

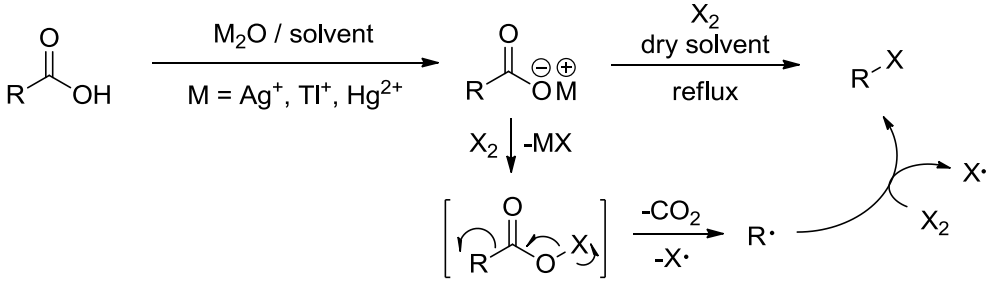


Scheme 78. Decarboxylative addition of aromatic carboxylic acids to nitriles.

1.2.2 Decarboxylative couplings forming C–heteroatom bonds

1.2.2.1 Decarboxylative couplings forming C–halide bonds

When aliphatic and α,β-unsaturated carboxylic acids are treated with bromine in the presence of silver(I)-,[151] thallium(I)-[152] or mercury(II) salts,[153] the corresponding alkyl or vinyl bromides one carbon atom shortened were obtained (Scheme 79). This is so called Hunsdiecker reaction, which is still one of the most useful methods for the synthesis of organohalide compounds.

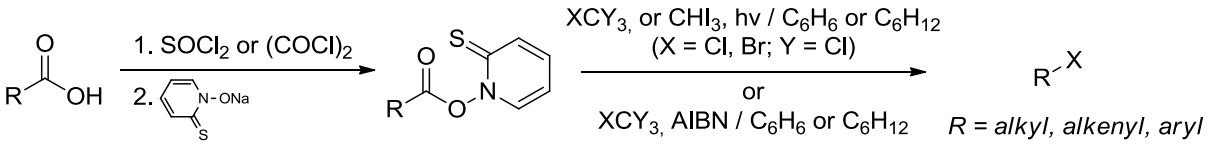


Scheme 79. Hunsdiecker halogenative decarboxylation.

The mechanism involves organic radical intermediates. Taking the decarboxylative bromination as a typical example, the silver carboxylate reacts with bromine to form the acyl

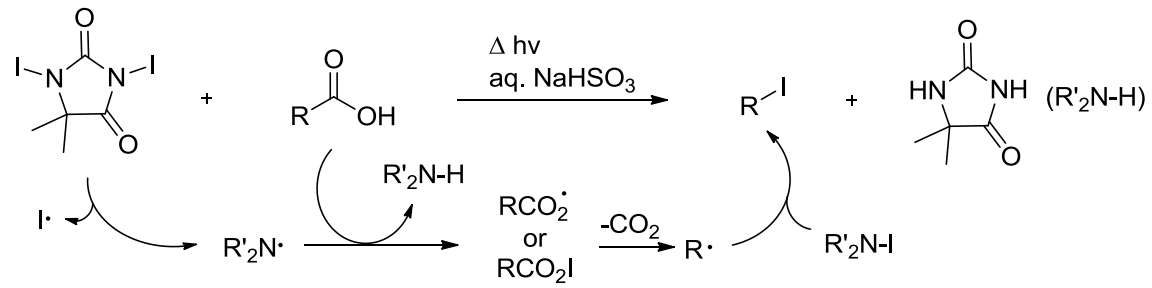
hypohalite, which undergoes fragmentation to generate the carboxylate radical along with a bromo radical. The radical decarboxylation leads to the formation of an alkyl radical which recombines with the bromo radical, affording the terminal bromide.

New decarboxylative halogenating reagents include $PhI(OAc)_2$,[154] *t*-BuOX,[155] XeF_2,[156] and LiX[157] have been explored during the last century in order to avoid the use of heavy metals. In the Barton modifications, the carboxylic acids were first transferred into thiohydroxamates, which can easily undergo halogenative decarboxylation via thermal or photolytic decomposition in halogen donor solvents such as $BrCl_3$, CHI_3, and CCl_4 (Scheme 80).[158]



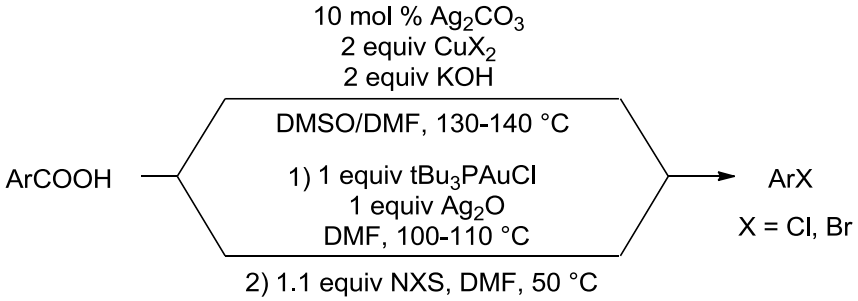
Scheme 80. Barton's conditions for decarboxylative halogenation.

Recently, Gandelman *et al.* reported a metal-free and general iododecarboxylation of both aliphatic and aromatic carboxylic acids (Scheme 81).[159] The key to achieve the full conversions is the use of commercially available 1,3-diiodo-5,5-dimethylhydantoin (DIH) under irradiative conditions. The reaction begins with the homolytic cleavage of the N–I bond in the amide resulting in an *N*-based radical, followed by abstraction of the carboxylic acid hydrogen atom to form an acyloxyl radical. The radical decarboxylation takes place to give the R-radical, which can be iodinated with another molecule of the N-iodoamide.



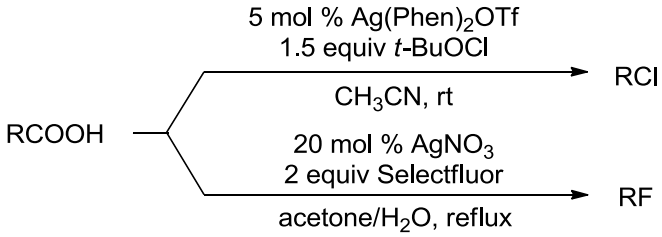
Scheme 81. Gandelman's decarboxylative iodination.

In 2010, Wu and coworkers described the silver-catalyzed decarboxylative chlorination and bromination of aromatic carboxylic acids (Scheme 82, i). The authors used copper(II) halides as the halogen source and silver carbonate as the decarboxylation catalyst. In Larrosa's approach of the same transformation, a stoichiometric amount of silver and gold salts is required in order to generate an aryl gold species, which is halogenated by NXS (ii). Both protocols are limited to electron-deficient benzoic acids.

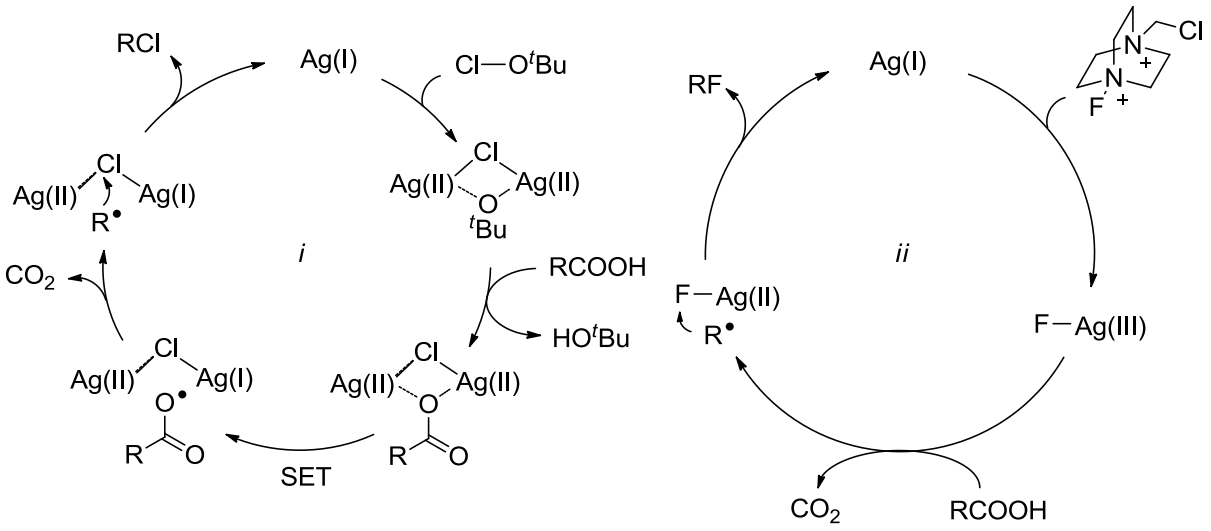


Scheme 82. Transition metal-catalyzed decarboxylative halogenations.

More recently, Li *et al.* demonstrated the silver-catalyzed decarboxylative chlorination and fluorination of aliphatic carboxylic acids by using *t*-butyl hypochlorite and Selectfluor as the halogenating reagents (Scheme 83).



Scheme 83. Silver-catalyzed decarboxylative halogenations.



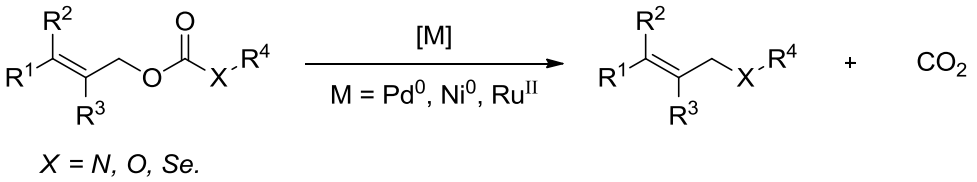
Scheme 84. Proposed mechanisms of silver-catalyzed decarboxylative halogenations.

While the authors proposed that a binuclear chloro-*tert*-butoxy-bridged Ag(II) complex intermediate, the details of the mechanism still seem unclear. According to the authors, a subsequent ligand exchange leads to the formation of the silver carboxylate complex, from which the carboxyl radical is formed. It is supposed to undergo fast decarboxylation to generate the alkyl radical. In the final step, the alkyl chloride is released through the nucleophilic attack at the chloro ligand of the binuclear silver complex (Scheme 84, i). In the

decarboxylative fluorination process, the reaction begins with the formation of an Ag(III)–F intermediate via oxidative addition. A carboxyl radical is then formed through single electron transfer (SET), followed by a fast decarboxylation forming the alkyl radical, which abstracts the fluorine of Ag(II)–F to afford the aryl fluoride product (ii).

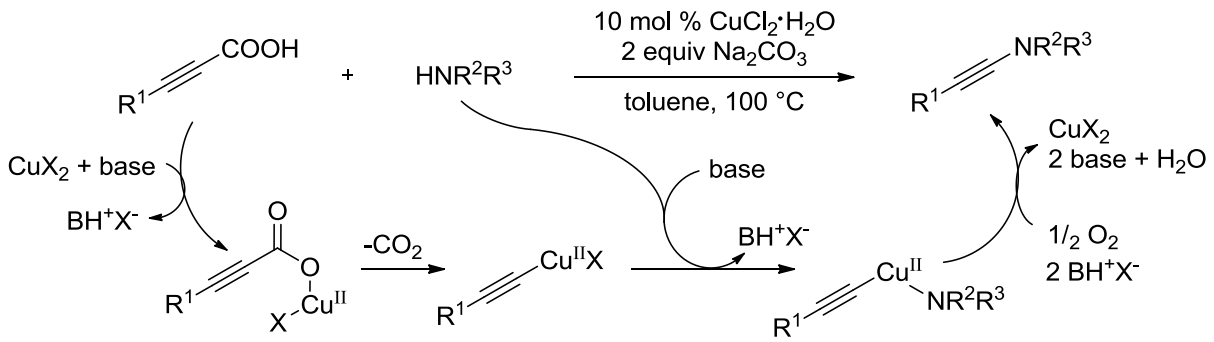
1.2.2.2 Decarboxylative couplings forming C–N and C–O bonds

It is well-known that allylic carbonates and carbamates undergo thermal decarboxylative rearrangement under harsh conditions.[160] While the transition metal-catalyzed regio- and stereospecific decarboxylative allylic etherification and amination have been well documented (Scheme 85),[84] intermolecular decarboxylative C–N and C–O cross-coupling of aryl, alkenyl, and alkynyl carboxylic acids have been rarely reported.



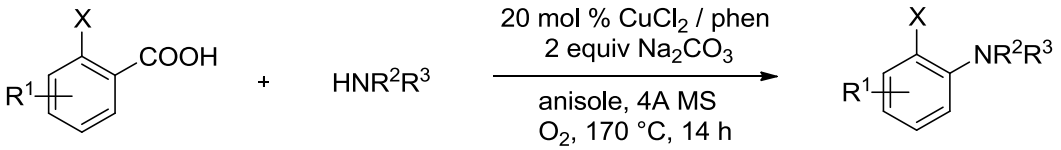
Scheme 85. Metal-catalyzed decarboxylative allylic amination, etherification and selenation.

In 2010, Jiao et al. reported the first Cu-catalyzed decarboxylative amidation of propiolic acids under oxidative conditions (Scheme 86).[161] The reaction condition is rather simple and the use of air as the oxidant advances this catalytic transformation towards being a useful approach to ynamides. In the proposed mechanism, copper(II) carboxylate is firstly formed, followed by a fast decarboxylation, generating an alkynyl copper complex. Nucleophilic attack by an amide affords the alkynyl-Cu-amidate intermediate, which undergoes reductive elimination, releasing the corresponding ynamide. The formed copper(0) catalyst is then reoxidized by oxygen to restart the catalytic cycle.



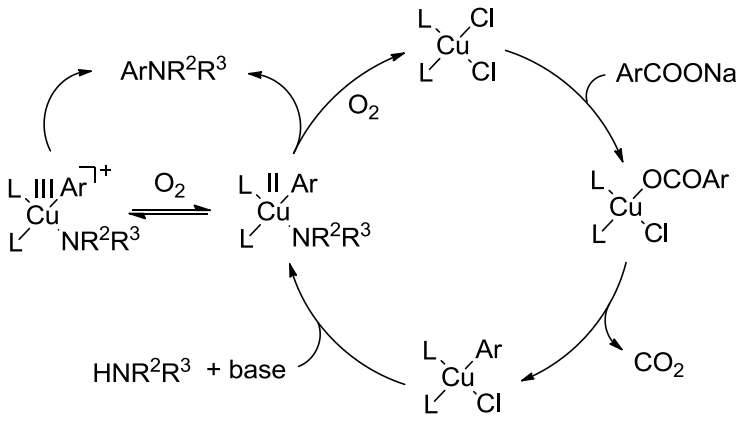
Scheme 86. Proposed methanism of the Cu-catalyzed decarboxylative amidation of propiolic acids.

More recently, Mainolfi *et al.* developed the first decarboxylative cross-coupling between aromatic carboxylic acids and amides (Scheme 87). [162] Using a simple copper(II)-phenanthroline catalyst system, the *ortho*-substituted benzoic acids undergo decarboxylative coupling with various *N*-nucleophiles affording the corresponding *N*-arylated amides.



Scheme 87. Cu-catalyzed decarboxylative amidation of aromatic carboxylic acids.

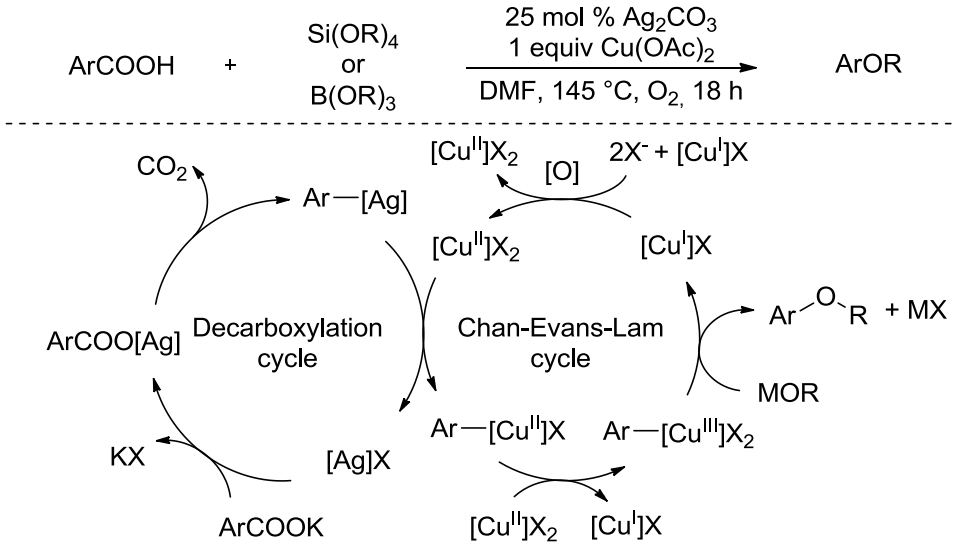
The authors proposed a similar mechanism to the decarboxylative amidation of propiolic acids (Scheme 88). An equilibrium between the Cu(II) and Cu(III) complexes may exist, because the reductive elimination of an aryl Cu(III) intermediate is more favorable. A pathway involving a tandem protodecarboxylation / ortho C–H amidation can be excluded, since the cross-coupling of nitrobenzene and 2-pyrrolidionone does not proceed under the optimized reaction conditions.



Scheme 88. Proposed mechanism of the Cu-catalyzed decarboxylative amidation of aromatic carboxylic acids.

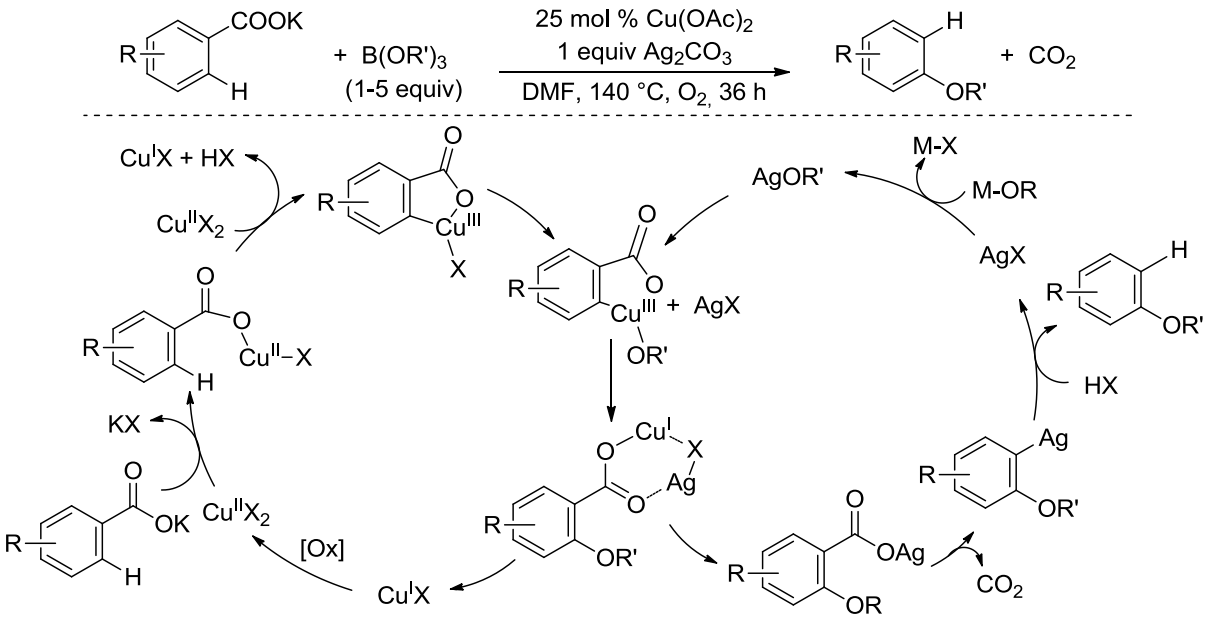
Besides the C–N bond formation, the decarboxylative C–O cross-coupling has been recently established by Gooßen *et al.*[163] As shown in scheme 89, the use of alkyl orthosilicates or aryl borates as the *O*-nucleophiles under aerobic conditions allows the convenient construction of alkyl and aryl diaryl ethers from readily available aromatic carboxylic acids. The bimetallic catalyst system consists of a silver(I) salt and a copper(II) salt, which are responsible for the decarboxylation and Chan-Evans-Lam coupling, [164] respectively. An arylsilver(I) species generated from the decarboxylation cycle undergoes transmetallation with the copper(II) catalyst, forming an an arylcopper species where a standard Chan-Evans-Lam catalytic cycle

is then initiated. This arylcooper(II) intermediate is oxidized to the arylcopper(III) species, followed by a nucleophilic attack of the *O*-nucleophiles affording the ether product and the copper(I) sepcies, which is then oxidized to the initial copper(II) catalyst.

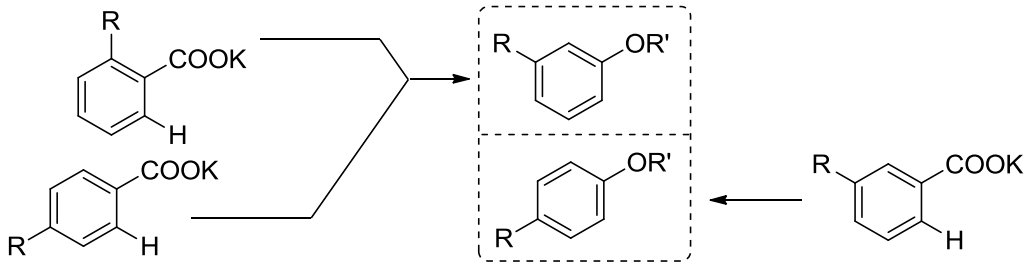


Scheme 89. Ag/Cu-catalyzed decarboxylative etherification.

In addition to the ipso-decarboxylative etherification, a decarboxylative ortho-alkoxylation process was later developed by our group (Scheme 90).[165] This process proceeds via carboxylate-directed *ortho* C–H functionalization followed by protodecarboxylation. Using carboxylate as a traceless directing group, the original substitution pattern is altered in a defined way: *meta*-substituted aryl ethers arise from *para*- and *ortho*-substituted benzoates, and *para*-substituted aryl ethers from *meta*-substituted benzoates (Scheme 91).



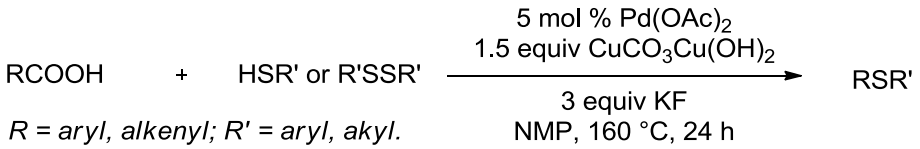
Scheme 90. Carboxylate-directed C–H alkoxylation with concomitant protodecarboxylation.



Scheme 91. Formal *meta*- and *para*-selective direct alkoxylation.

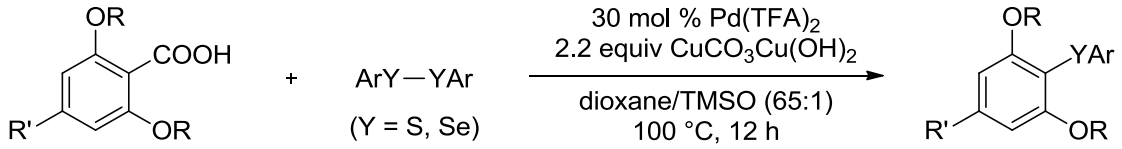
1.2.2.3 Decarboxylative couplings forming C–S, C-Se, and C–P bonds

Carboxylic acids could also be coupled with other heteroatom-nucleophiles forming the corresponding C–S, C-Se, and C–P bonds under oxidative conditions. In 2009, Liu *et al.* demonstrated the first example of a decarboxylative C–S coupling of carboxylic acids with mercaptans and disulfides (Scheme 92).[166] In the presence of a bimetallic Pd(II)/Cu(II) catalyst system, both alkyl and aryl thiols could be coupled with various carboxylic acids affording the corresponding aryl or alkenyl sulfides in good to excellent yields. A stoichiometric amount of $Cu(OH)_2CO_3$ is required for the transformation, because the *in situ* generated Pd(0) species needs to be reoxidized to the initial Pd(II) catalysts by the Cu(II) salt.



Scheme 92. Decarboxylative C–S coupling.

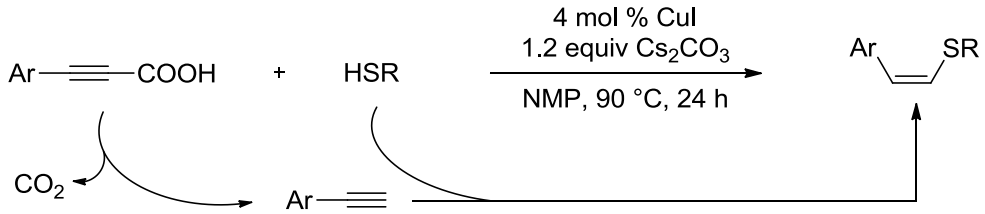
In a related protocol, Becht established the expedient synthesis of diaryl sulfides and selenides from the decarboxylative cross-coupling of 2,6-dialkoxybenzoic acids and diaryl disulfides and diaryl diselenide (Scheme 93).[167] A bimetallic catalyst system consisting of $Pd(TFA)_2$ and Ag_2CO_3 was used at a lower reaction temperature, while the substrates are limited to the *ortho*-disubstituted aryl carboxylic acids.



Scheme 93. Decarboxylative C–S and C–Se coupling.

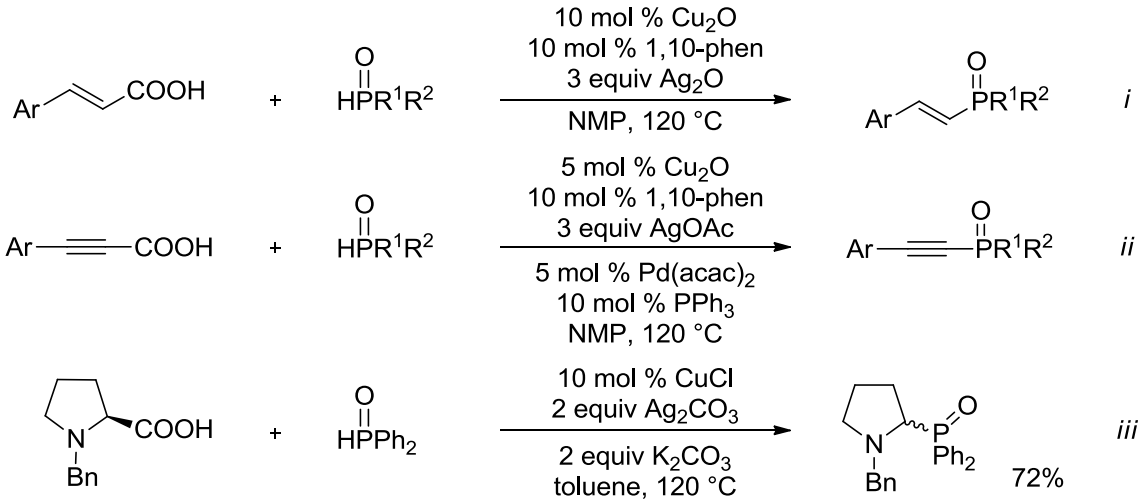
In a subsequent report, Liu *et al.* disclosed the copper-catalyzed decarboxylative cross-coupling of arylpropiolic acids with thiols (Scheme 94).[168] The highly stereospecific *Z*-vinyl sulfides are easily accessed under their optimal conditions. However, the reaction probably

proceeds via a sequential protodecarboxylation and nucleophilic addition of the thiols to aryl alkynes.



Scheme 94. Decarboxylative alkynyl carboxylic acids with thiols.

Decarboxylative C–P couplings of alkenyl and alkynyl carboxylic acids, as well as amino acids with $R^1R^2P(O)H$ compounds were recently developed by the group of Yang (Scheme 95).[169] They presented three complementary protocols, for sp^2-, sp-, and sp^3-C–COOH substrates, from which a number of alkenyl, alkynyl and alkyl phosphine oxides are readily accessed without the need of the corresponding halocarbon precursors.



Scheme 95. Decarboxylative C–P couplings.

In all these three approaches, silver salts serve as decarboxylation catalysts, generating the organonuleophiles for the coupling reactions. The alkenyl and alkyl phosphine oxides are released from the corresponding organo-copper-phosphonyl species generated through the transmetallation from the organosilver species. In the reaction of the alkynyl carboxylic acids, an additional palladium catalyst is required to accomplish the transformation by an intertwined transmetallation from organo-copper and -silver intermediates.

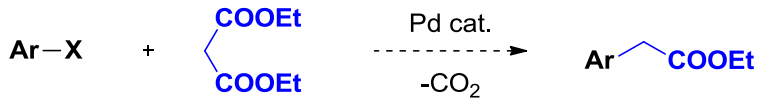
1.3 Outline of the thesis

In the previous subchapters, we have reviewed the most important developments of transition metal-catalyzed cross-coupling reactions, as well as the newly emerged decarboxylative couplings in the past decades. Compared to the well-developed traditional coupling reactions involving the inevitable use of expensive and delicate organometallic reagents, the decarboxylative cross-coupling is still in its infancy. However, the decarboxylative cross-coupling reactions possess both economical and ecological advantages over traditional couplings, since carboxylic acids are inexpensive and commercially available in a large structural diversity. Moreover, they are air stable, easy to handle, and are preparatively accessible by a large number of well-established methods. Notably, decarboxylative couplings generate the new C–C and C–X bonds in incredibly high regioselectivities, because the coupling reactions usually take place only at the positions bearing carboxylic acid groups.

In the past decade, decarboxylative coupling reactions have become powerful methodologies for the C–C and C–heteroatom bond formations. However, there are still many blind spots for the organic chemists to explore. For instance, the reaction temperatures of redox-neutral decarboxylative cross-couplings are still too high, limiting their preparative applications. Another challenge in the field of decarboxylative coupling chemistry is to allow the use of inexpensive and robust carbon electrophiles such organo mesylates and esters.

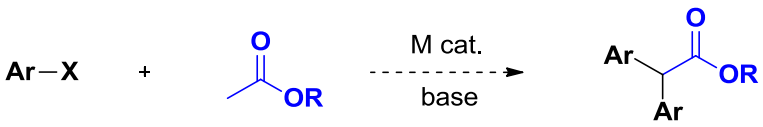
The purpose of this thesis is to investigate the cross-coupling reactions between carboxylic acids and eletrophiles for the regioselective constructions of Csp^3-Csp^2, and Csp^2-Csp^2 bonds. In the following chapters, several important organic building blocks such as aryl acetates, diaryl acetates, imines, ketones, biaryls, styrenes and polysubstituted alkenes are successfully accessed from carboxylic acids and their derivatives by the means of C–H activation and decarboxylative cross-couplings.

In chapter 2, we will describe the synthesis of aryl acetates via palladium-catalyzed dealkoxycarbonylative coupling of malonates with aryl halides (Scheme 96). The goal of this project is to develop an efficient and practical protocol for the synthesis of aryl acetate, especially for sterically demanding arylacetates in an economical and ecologically benign way. Two challenges arouse from this project, namely the effective coupling between malonates and aryl halides and the subsequent decarboxylation leading to the final aryl acetates. We will demonstrate our efforts to solve these problems through deliberately designing and intricate optimization of the coupling reactions.



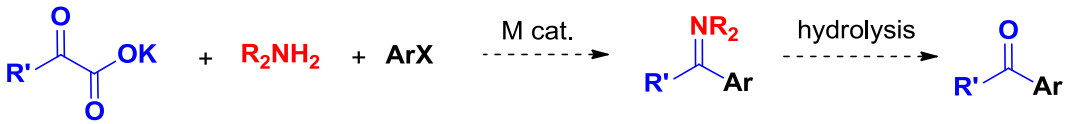
Scheme 96. Synthesis of aryl acetates.

In chapter 3, we will reveal an effective approach to α-diaryl acetates from the cross-coupling of simple acetic acid derivatives and aryl halides (Scheme 97). Although the metal-catalyzed cross-coupling of enolates with aryl halides has been well investigated by many research groups, all the involving protocols require extremely strong bases such as LDA, MHMDS, and MO^{t}Bu (M = Li, K, Na) in order to abstract the hydrogen from the α-position of the carbonyl compounds. However, the use of such expensive and air-sensitive bases dramatically limits the functional tolerance and the preparative applications. A new catalyst system that allows the C–H activation of the α-position of the carbonyl compounds by using mild bases is definitely an emergent task for organic chemists.



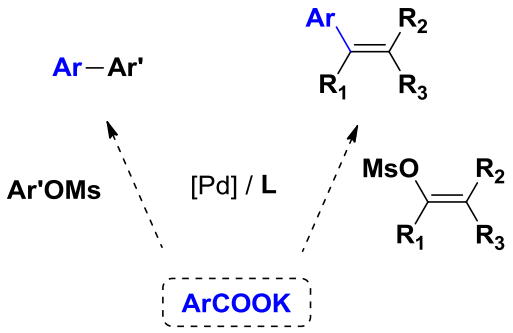
Scheme 97. Synthesis of α-diaryl acetates.

In chapter 4, we describe the one-pot synthesis of azomethines and ketones from oxocarboxylic acids, amines and aryl halides via a low-temperature decarboxylative process (Scheme 98). Our strategy is based on the previously developed method involving the decarboxylative cross-coupling of oxocarboxylic acids and aryl halides from which aryl ketones were obtained. The amines employed will probably undergo fast condensation with the oxocarboxylic acids to form the α-iminocarboxylates, which would be able to undergo decarboxylation at a much lower reaction temperature. Once the imines are formed, they can be readily *in situ* converted into the corresponding ketones by hydrolysis, or amines by reduction. However, the introduction of amines to the previous reaction system may probably lead to several problems such as the interactions between the amines and aryl halides, and the instability of the *in situ* formed α-iminocarboxylates. These challenges will be overcome through systematic investigations.



Scheme 98. Decarboxylative synthesis of azomethines and ketones.

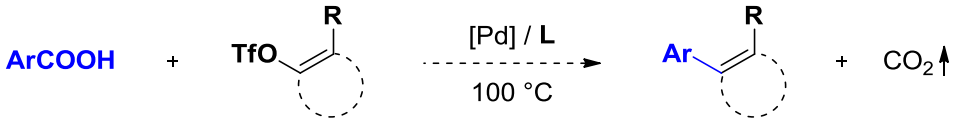
In chapter 5, we will disclose the decarboxylative cross-coupling between aromatic carboxylic acids and simple but extremely robust organo methanesulfonate (Scheme 99). The scope of organo electrophiles in the decarboxylative cross-coupling reaction has covered aryl halides, aryl triflates, and aryl tosylates. However, the use of inexpensive and more robust aryl mesylates as eletrophiles in the decarboxylative coupling reactions is still challenging. The C–O bond in aryl mesylates is particularly strong, so that only a few catalyst systems are capable of activating them. Two commonly used catalyst systems are the Nickel catalysts complexed with trialkylphosphines and palladium catalysts combined with eletron-rich and sterically hindered phosphine ligands. However, due to the incompatibility of nickel catalysts with decarboxylative couplings, we have no other choice to establish a new catalyst system based on palladium and efficient phosphine ligands. In this project, we will break this bottleneck through developing a new class of imidazolyl phosphine ligands. We will also demonstrate that how these unique ligands facilitate the transmetallation from organocopper to palladium catalysts to the extent that the coupling of carboxylic acids with aryl mesylates is smoothly accomplished.



Scheme 99. The use of aryl/alkenyl mesylates in decarboxylative couplings.

In chapter 6, we will describe our efforts against lowering the reaction temperature of the redox-neutral decarboxylative cross-coupling of aromatic carboxylic acids and aryl triflates (Scheme 100). The standard reaction temperature for the Pd/Cu-catalyzed neutral-redox decarboxylative cross-coupling between aryl carboxylic acids and organo eletrophiles is above 170 °C. The employing of a bimetallic Pd/Ag catalyst system allows the coupling of aryl triflates to occur at 130 °C. Our objective of this project is to further reduce the reaction temperature especially for the Pd/Cu catalyst system through developing unique phosphine ligands which are specific for the catalyst system. However, both of decarboxylation and transmetallation steps require elevated temperature to overcome the energy barriers. This project was carried out in the close collaboration with the group of Thiel. In this chapter, we will demonstrate how the Thiel's phosphine ligands influence the decarboxylative coupling

process in such a way that a balance between the decarboxylation and transmetallation is established, so that the reaction could proceed efficiently at a temperature as low as 100 °C.



Scheme 100. Low-temperature decarboxylative cross-couplings.

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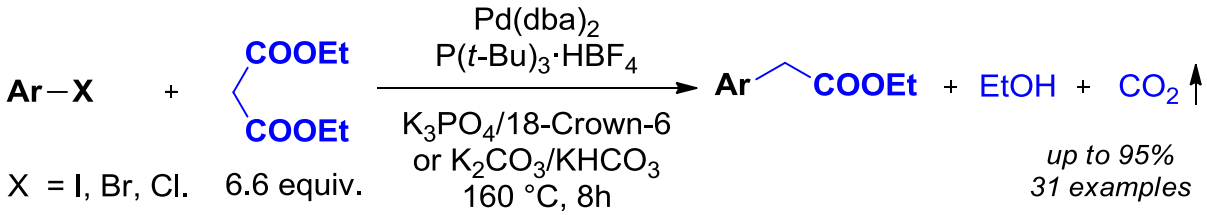
Chapter 2

Practical Synthesis of 2-Arylacetic Acid Esters via Palladium-Catalyzed Dealkoxycarbonylative Coupling of Malonates with Aryl Halides*



*Part of this work has been published: Reproduced in part with permission from [Bingrui Song, Felix Rudolphi, Thomas Himmler, and Lukas J. Gooßen, *Advanced Synthesis & Catalysis*, **2011**, *353*, 1565-1574] Copyright © [2012] Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

2.1 Introduction

Many biologically active compounds belong to the substrate class of aryl and heteroarylacetice acid derivatives. Examples are auxins acting as phytohormonal growth regulators,[1] as well as analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) (Figure 1).[2,3] The development of mild and efficient synthetic methods for the introduction of methylenecarboxyl groups into functionalized molecules is thus of great interest.

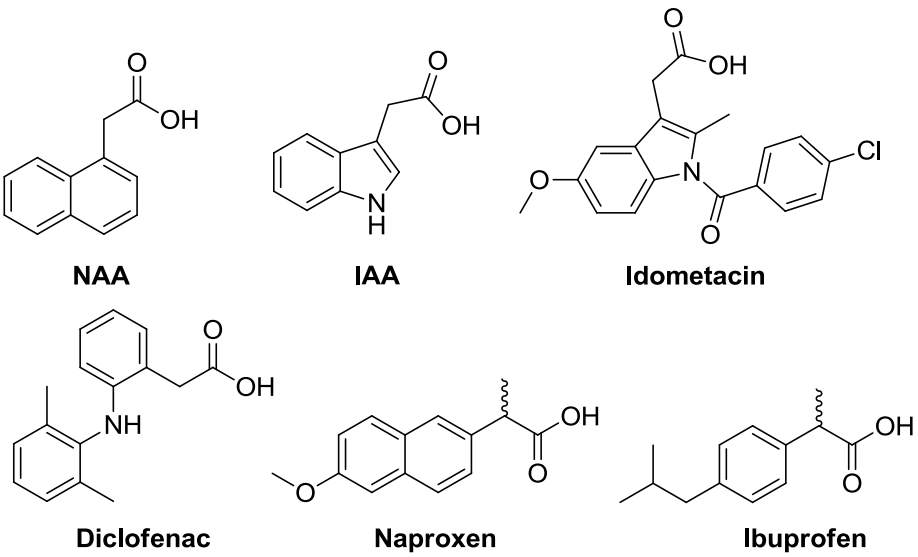
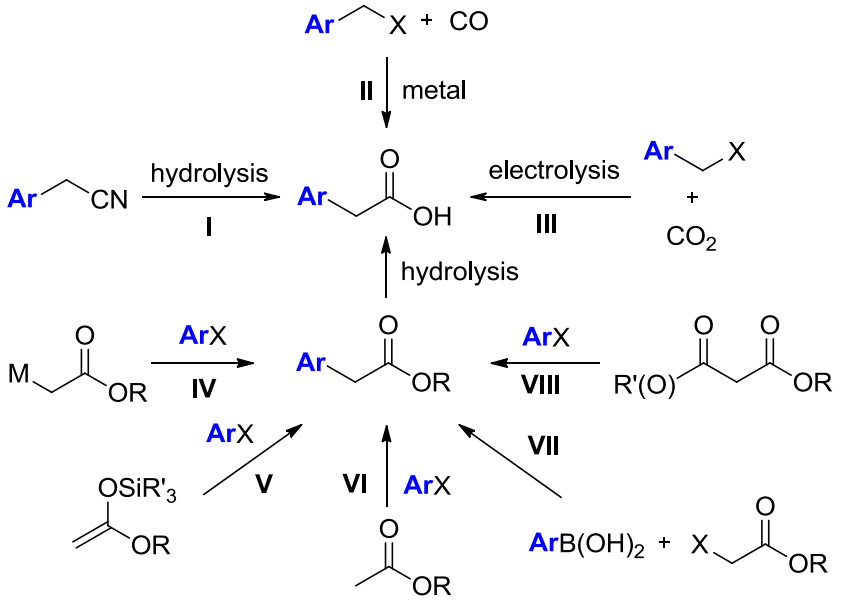


Figure 1. Examples of auxins and nonsteroidal anti-inflammatory drugs.

Traditional methods for the preparation of aryl acetic acids include the hydrolysis of benzyl cyanides (Scheme 1, I),[4] the carbonylation of benzyl halides with metal catalysts (II),[5] and the electrocatalytic carboxylation of benzyl chlorides (III).[6] However, these processes have inherent disadvantages. For example, neither benzyl cyanides nor benzyl halides are available in great structural variety.[7] Moreover, toxic carbon monoxide is required in carbonylation reactions, while electrocatalytic carboxylations require an elaborate reaction setup.

As modern alternatives, transition metal-catalyzed cross-coupling reactions between aryl halides and Reformatsky reagents,[8] tin,[9] copper,[10] and other enolates (IV),[11] or ketene acetals (V) have been developed.[12] Among these reactions, the palladium-catalyzed couplings between aryl halides and enolates developed by Buchwald[13] and Hartwig[14] (VI) are particularly straightforward, but the deprotonation of acetic acid esters requires strong and expensive bases, such as alkali metal hexamethyldisilazides or *tert*-butoxides. A broader range of functional groups is tolerated when using stabilized ketene derivatives or zinc enolates as the coupling partners.[15] The inverse approach, namely the coupling of α-bromoacetic acid derivatives with arylboronic acids (VII) is also compatible with many

functional groups, but not effective for sterically demanding substrates, and requires the use of costly boron reagents.[16]

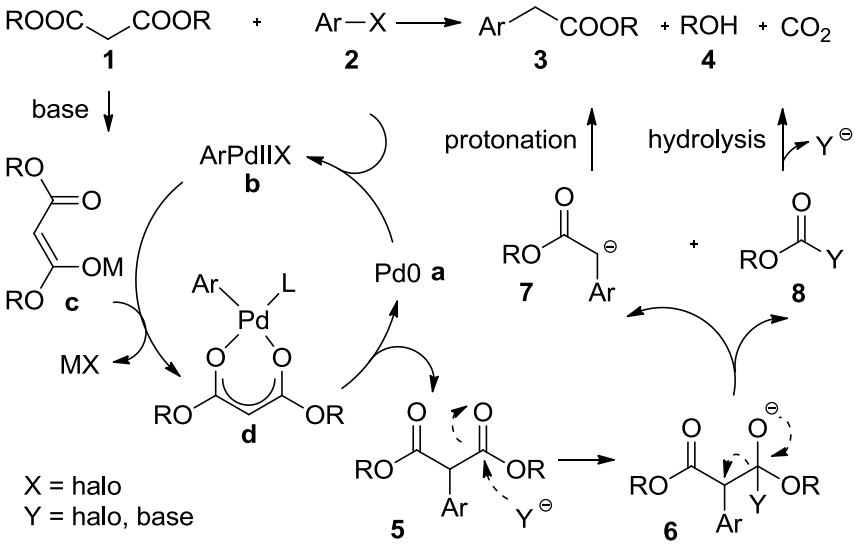


Scheme 1. Traditional and modern syntheses of arylacetic acids.

An interesting but less well-known alternative strategy to obtain 2-arylalkanoic acids consists in an initial cross-coupling of malonates or β-ketoesters with aryl halides, followed by dealkoxycarbonylation or retro-Claisen condensation of the thermally labile intermediates (Scheme 1, VIII).[17] The coupling reaction is mediated by Pd[18] and Cu catalysts.[19] The advantage of this approach is that mild bases suffice to deprotonate the acidic β-dicarbonyl compounds. This synthetic pathway is particularly practical if the dealkoxycarbonylation takes place *in situ* under the conditions of the cross-coupling.

A plausible mechanism for the dealkoxycarbonylative cross-coupling of dialkyl malonates and aryl halides is depicted in Scheme 2.[20] Oxidative addition of the aryl halide (**2**) to the Pd(0) complex (**a**) gives rise to the arylpalladium(II) halide complex (**b**). The halide substituent is then replaced by an enolate nucleophile (**c**) formed via deprotonation of malonate (**1**). Reductive elimination of dialkyl α-aryl malonate (**5**) from the resulting palladium enolate complex (**d**) regenerates the Pd(0) complex, closing the catalytic circle for the palladium. At elevated temperatures, the dialkyl α-aryl malonate (**5**) directly undergoes dealkoxycarbonylation, presumably via a nucleophilic addition-elimination sequence. A base or halide nucleophile adds to one of the ester carbonyl groups with formation of the adduct **6**. In the subsequent elimination step, enolate **7**, which is resonance-stabilized by the newly introduced aryl group, is liberated together with the haloformate **8**. On quenching the reaction mixture with water, hydrolysis of these intermediates leads to the desired arylacetic acid ester

(**3**) along with an alcohol (**4**) and carbon dioxide. This mechanism was supported by observation of the evolution of carbon dioxide (trapped by lime water) and alcohol (detected by proton NMR) during the reaction.



Scheme 2. Proposed mechanism for the palladium-catalyzed dealkoxycarbonylative cross-coupling.

Kondo reported that some aryl iodides and activated aryl bromides can be coupled this way with diethyl malonate in the presence of a Pd-catalyst and 10 equivalents of Cs_2CO_3.[21] However, it takes up to 76 h until the coupling and the subsequent dealkoxycarbonylation reach reasonable conversions. Çetinkaya et al. achieved higher yields within shorter reaction times for a range of aryl halides when employing especially synthesized palladium complexes with customized N-heterocyclic carbene ligands.[22] However, these ligands are not commercially available and accessible only via multistep syntheses. De Koning et al. investigated β-ketoesters as alternative substrates and successively reported a palladium- and a copper-catalyzed protocol for the arylation of acetoacetate esters followed by *in situ* deacetylation.[23] However, these protocols have a rather narrow scope, and the deacetylation step often does not proceed to completion.

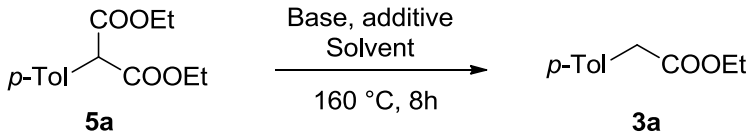
We evaluated all known protocols in the context of the synthesis of *ortho*-substituted aryl acetates, which are important precursors for active substances in crop protection.[24] However, only unsatisfactory yields were achieved in couplings of sterically demanding aryl halides, e.g., 2,6-dimethylphenyl bromide. We thus came to the conclusion that this appealing synthetic approach had not yet reached synthetic maturity. More effective catalyst systems involving commercially available components and inexpensive bases were clearly required to

advance this reaction into a broadly applicable, practical synthetic entry to the important substrate class of arylacetic acids.

2.2 Results and discussion

As a first step towards an effective reaction protocol for a dealkoxycarbonylative coupling of malonates, we investigated the dealkoxycarbonylation reaction of diethyl 4-tolylmalonate (**5a**) at 160 °C under various conditions (Table 1). We found that this compound, which would be the primary product of the desired cross-coupling between an aryl halide and diethyl malonate, is thermally rather unstable. In the presence of cesium carbonate and using polar solvents such as NMP, it rapidly decomposed with formation of multiple products. Only traces of the desired ethyl 4-tolyacetate were detected (entry 1). The selectivity of the dealkoxycarbonylation was substantially higher when using potassium phosphate as the base. However, the desired product was obtained in only 32% yield (entry 2). We next investigated less polar solvents, but did not achieve any higher yields.

Table 1. Dealkoxycarbonylation of diethyl 4-tolylmalonate.



5a **3a**

Entry	Base	Additive	Solvent	Conv. [%]	Yield [%]
1	Cs_2CO_3	—	NMP	100	4
2	K_3PO_4	—	NMP	57	32
3	K_3PO_4	—	DEM[b]	50	40
4	Cs_2CO_3	—	DEM	40	38
5	K_2CO_3	—	DEM	14	12
6	$KHCO_3$	—	DEM	16	11
7	K_2CO_3/$KHCO_3$[c]	—	DEM	18	5
8	**K_3PO_4**	**18-Crown-6**	**DEM**	**99**	**97**
9	—	18-Crown-6	DEM	2	2
10	—	—	DEM	1	1
11	K_3PO_4	18-Crown-6	NMP	42	42

[a] Reaction conditions: **2a** (0.50 mmol), base (1.4 mmol), additive (0.25 mmol), solvent (1.0 mL), 160 °C, 8h. Yields were determined by GC analysis, with *n*-tetradecane as internal standard. [b] Diethyl malonate. [c] K_2CO_3 (1.5 mmol), $KHCO_3$ (1.5 mmol).

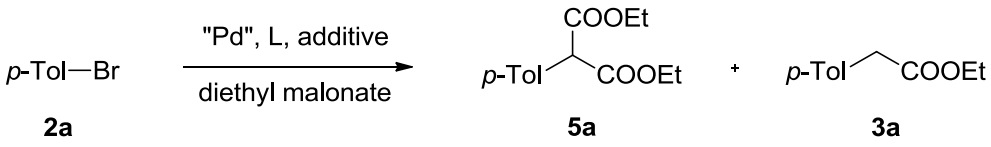
We finally tested the substrate for the desired coupling reaction, diethyl malonate (DEM), as the solvent. This inexpensive, high-boiling compound possesses a moderate polarity, so that it partially dissolves inorganic bases (entries 3-10). We were pleased to see that the selectivity of the dealkoxycarbonylation improved under these conditions (entry 3). Not only the

expensive cesium carbonate (entry 4) but also the much less costly potassium phosphate effectively mediated the reaction (entry 3). In the presence of milder bases such as potassium carbonate (entry 5) or bicarbonate (entry 6), the dealkoxycarbonylation proceeds much more slowly. In an attempt to improve the solubility of potassium phosphate in the reaction solvent, we added catalytic quantities of 18-crown-6. This dramatically increased the efficiency of the dealkoxycarbonylation, and almost quantitative yields of the desired arylacetate **3a** were obtained (entry 8). Control experiments confirmed that the crown ether or DEM solvent alone do not promote the reaction (entries 9 and 10), and that under these conditions, diethyl malonate is a more effective reaction solvent than even NMP (entry 11).

Having thus found optimal conditions for the dealkoxycarbonylation, we next examined the cross-coupling step using the reaction of 4-bromotoluene (**2a**) and diethyl malonate as the model. We employed DEM as both substrate and solvent, and tested various palladium catalyst, ligand systems, and bases (Table 2).

As the initial palladium catalyst, we used a combination of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ in the form of its air-stable, easy-to-handle HBF_4 adduct. This catalyst is known to mediate the cross-coupling of aryl halides and malonates. Even at the elevated temperature of 160 °C, the arylmalonate **5a** remained the major product for most bases tested (Table 2, entries 1-6). Only cesium carbonate gave the dealkoxycarbonylated product **3a** as the main product, albeit in low yield (entry 3). The selectivity changed dramatically when 18-crown-6 was added to the reaction mixture (entry 7). In combination with potassium bases, this additive strongly facilitated the dealkoxycarbonylation, and the arylmalonate was no longer detected. The highest yields of the arylacetate were achieved with potassium phosphate (entries 8 and 9). Control experiments revealed that ammonium salts (entries 11-13) were inferior as phase transfer catalysts, and that DMSO (entry 14), which is known to facilitate decarboxylation reactions,[25] is not effective in this context. The presence of stoichiometric quantities of water has a negative effect on the reaction outcome (entry 15). We next evaluated various palladium precursors and phosphine ligands (entries 16-20). These experiments revealed that several palladium precursors can be employed, but none of them possesses a higher activity than $Pd(dba)_2$. The choice of the phosphine is much more critical, and besides with $P(t\text{-}Bu)_3$, we achieved reasonable yields only with JohnPhos (38%). Under the optimal conditions using $Pd(dba)_2$ (0.5 mol%), $P(t\text{-}Bu)_3 \bullet HBF_4$ (1.1 mol%), K_3PO_4 (2.8 equiv.), and 18-crown-6 (0.5 equiv.) in diethyl malonate (6.6 equiv.) at 160 ^{o}C, ethyl 4-tolylacetate **3a** was formed in 88% yield within only 8 hours (entry 7). Not even traces of the malonate **5a** were detected in the reaction mixture.

Table 2. Optimization of the dealkoxycarbonylative cross-coupling.[a]



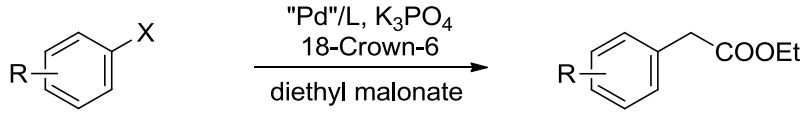
2a **5a** **3a**

entry	"Pd"	Ligand	Base	Additive	Yield [%]	
					5a	**3a**
1[b]	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	$KHCO_3$	—	83	10
2[b]	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	K_2CO_3	—	82	18
3[b]	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	Cs_2CO_3	—	9	20
4[b]	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	Na_3PO_4	—	90	1
5[b]	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	K_3PO_4	—	47	38
6	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	K_3PO_4	—	50	46
7	**$Pd(dba)_2$**	**P(*t*-Bu)$_3$•HBF_4**	**K_3PO_4**	**18-Crown-6**	**0**	**88**
8	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	$KHCO_3$	18-Crown-6	0	80
9	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	K_2CO_3	18-Crown-6	0	75
10	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	Cs_2CO_3	18-Crown-6	0	9
11	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	K_3PO_4	TBAB	29	45
12	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	K_3PO_4	TBAI	20	57
13	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	K_3PO_4	TBAF[c]	17	55
14	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	K_3PO_4	DMSO[d]	70	27
15	$Pd(dba)_2$	P(*t*-Bu)$_3$•HBF_4	K_3PO_4	H_2O[d]	45	19
16	$Pd(OAc)_2$	P(*t*-Bu)$_3$•HBF_4	K_3PO_4	18-Crown-6	0	75
17	$[(allyl)PdCl]_2$	P(*t*-Bu)$_3$•HBF_4	K_3PO_4	18-Crown-6	0	71
18	$Pd(PPh_3)_2Cl_2$	P(*t*-Bu)$_3$•HBF_4	K_3PO_4	18-Crown-6	0	60
19	$Pd(dba)_2$	P(*t*-Bu)$_3$	K_3PO_4	18-Crown-6	0	76
20	$Pd(dba)_2$	JohnPhos	K_3PO_4	18-Crown-6	2	38

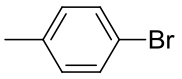
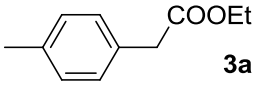
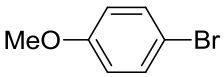
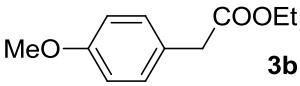
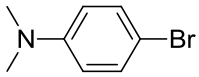
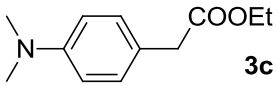
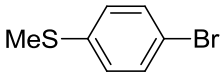
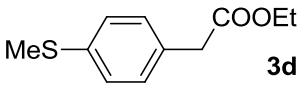
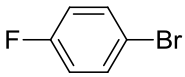
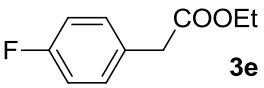
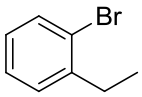
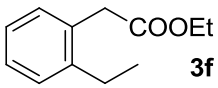
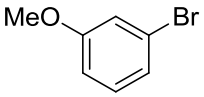
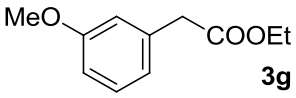
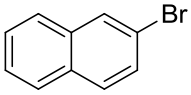
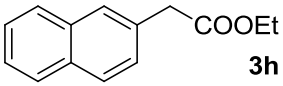
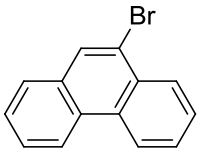
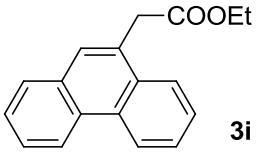
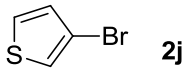
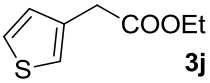
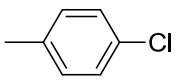
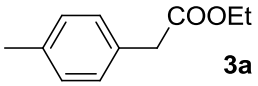
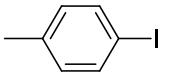
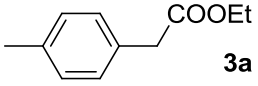
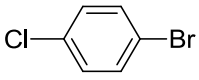
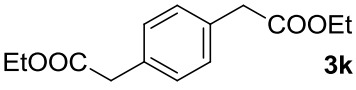
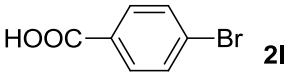
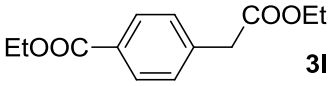
[a] Reaction conditions: **1a** (1.00 mmol), diethyl malonate (6.6 mmol), Pd-source (0.5 mol%), ligand (1.1 mol%), base (2.8 mmol), additive (0.5 mmol); entries 1-6: 150 °C, 16 h; entries 6-20: 160 °C, 8 h. $[allylPdCl]_2$ = allylpalladium(II) chloride dimer; JohnPhos = (2-biphenylyl)di-*tert*-butylphosphine. Yields were determined by GC analysis, with *n*-tetradecane as internal standard. [b] $Pd(dba)_2$ (1.0 mol%), P(*t*-Bu)$_3$•HBF_4 (2.2 mol%), bases (2.3 mmol). [c] Tetrabutylammonium fluoride hydrate. [d] 1.00 mmol.

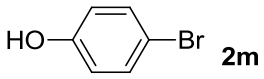
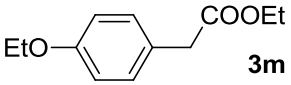
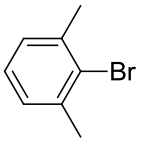
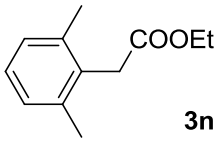
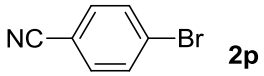
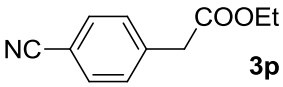
Having thus found an effective and practical protocol to prepare ethyl arylacetates, we next explored its scope by coupling a large variety of aryl halides with diethyl malonate under the previously optimized conditions. As shown in Table 3, the dealkoxycarbonylative cross-coupling reaction proceeded very well for electron-rich aryl halides. In all cases, the dealkoxycarbonylated products were exclusively obtained in high yields. Various functional groups were tolerated in *para*- (**2b**-**e**), *ortho*- (**2f**), and *meta*- (**2g**) positions on the aryl ring.

Table 3. Reaction scope of substituted aryl halides[a]



2a-p (X = Br); **9a** (X = Cl); **10a** (X = I) **3a-p**

Substrate	Product	Yield [%]
 **2a**	 **3a**	87
 **2b**	 **3b**	94[b]
 **2c**	 **3c**	96[b]
 **2d**	 **3d**	95
 **2e**	 **3e**	86
 **2f**	 **3f**	88[c]
 **2g**	 **3g**	93
 **2h**	 **3h**	93
 **2i**	 **3i**	91
 **2j**	 **3j**	94
 **9a**	 **3a**	83[b]
 **10a**	 **3a**	89[b]
 **2k**	 **3k**	68
 **2l**	 **3l**	88

Substrate	Product	Yield [%]
 **2m**	 **3m**	89
 **2n**	 **3n**	15[d,e]
 **2p**	 **3p**	15[d,f]

[a] Reaction conditions A: **1**, **9** or **10** (1.00 mmol), $Pd(dba)_2$ (0.5 mol%), $P(t\text{-}Bu)_3 \bullet HBF_4$ (1.1 mol%), diethyl malonate (6.6 mmol), 18-Crown-6 (0.5 mmol), K_3PO_4 (2.8 mmol), 160 °C, 8 h. Isolated yields. [b] 12 h. [c] 170 °C, 12h. [d] GC yields. [e] 48% of the *m*-xylene was detected. [f] 20 % of benzonitrile was detected.

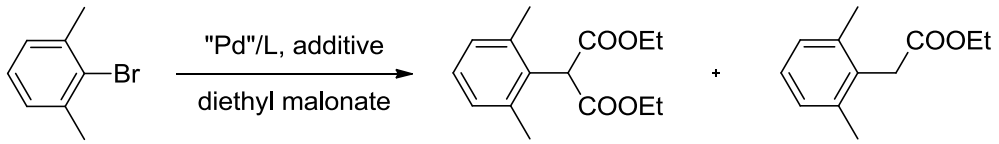
2-Bromonaphthalene (**2h**) and 9-bromophenanthrene (**2i**), as well as 3-bromothiophene as an example of an electron-rich heteroaryl bromide (**2j**), were also converted in excellent yields. The new protocol can be applied also to the coupling of aryl chlorides and iodides (**9a** and **10a**). 4-Chlorophenyl bromide (**2k**) underwent coupling at both halides to give the corresponding diester in good yield within a short time. Due to the good ability of the catalyst to activate aryl chlorides, no differential reaction of the Cl- and Br-groups was observed. Under the reaction conditions, unprotected carboxylic acid groups (**2l**) are converted into the corresponding ethyl esters, presumably via transesterification with the diethyl malonate present in excess, or condensation with the ethanol liberated during the dealkoxycarbonylation step. In analogy, phenolic OH-groups were converted into the ethyl ethers (**2m**).

However, the performance limit of this protocol was reached for sterically hindered substrates such as 2-bromo-*m*-xylene **2n**, and for electron-deficient aryl halides such as 4-bromobenzonitrile **2p**. In both cases, dehalogenation of the aryl halides was the major side reaction, and the products were obtained in unsatisfactory yields.

These results indicate that the reaction protocol is effective mainly for the coupling of electron-rich aryl halides. For these substrates, the dealkoxycarbonylation proceeds slowly compared to the cross-coupling, so that it needs to be facilitated by the most effective mediator, namely the combination of potassium phosphate and 18-crown-6. In contrast, the decarboxylation proceeds more rapidly than the cross-coupling for electron-deficient as well as sterically demanding aryl halides.[26] For these substrates, the bases and conditions must be adjusted such that the cross-coupling step proceeds with optimal selectivity, so as to avoid the undesired dehalogenation reactions.[27]

In order to find an alternative set of conditions which is more favorable for sterically hindered substrates, we used the reaction of 2-bromo-*m*-xylene **2n** with diethyl malonate as a model to reevaluate various reaction conditions. The results are summarized in Table 4. Under none of the conditions tested, the malonate was detected in significant quantities, confirming that in contrast to the previous model reaction of **2a**, the decarboxylation step is not critical for this sterically demanding substrate. Under the previous reaction conditions, the arylacetate **3n** was obtained in low yields, along with large amounts of *m*-xylene resulting from protodehalogenation (entry 1). Without 18-crown-6, the yield was similarly unsatisfactory (entry 2).

Table 4. Optimization for 2-bromo-*m*-xylene.[a]



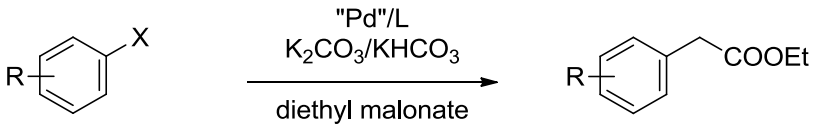
2n **5n** **3n**

Entry	Base [equiv.]	Additive	Yield[%]	
			5n	**3n**
1	K_3PO_4 (2.8)	18-Crown-6	0	15[b]
2	K_3PO_4 (2.8)	—	1	12
3	K_2CO_3 (2.8)	—	1	54[c]
4	Cs_2CO_3 (2.8)	—	0	31
5	$KHCO_3$ (2.8)	—	0	14[d]
6	K_3PO_4 (1.5)/$KHCO_3$ (1.5)	—	0	51
7	**K_2CO_3 (1.5)/$KHCO_3$ (1.5)**	**—**	**0**	**80**
8	Na_2CO_3 (1.5)/$KHCO_3$ (1.5)	—	0	19
9	K_2CO_3 (2.0)/$KHCO_3$ (1.0)	—	0	65
10	K_2CO_3 (1.0)/$KHCO_3$ (2.0)	—	0	54

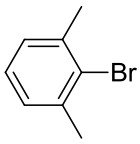
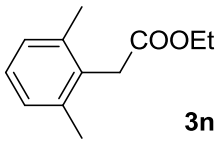
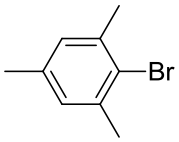
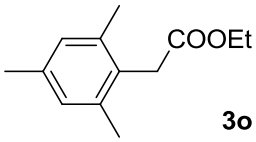
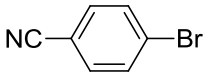
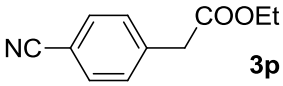
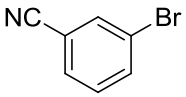
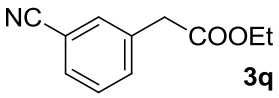
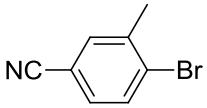
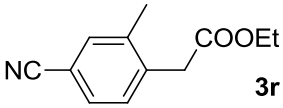
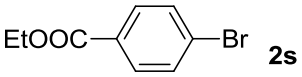
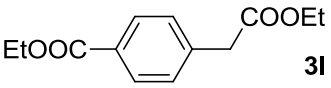
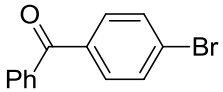
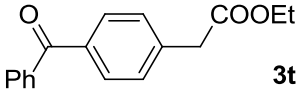
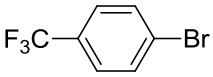
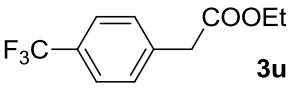
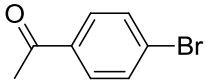
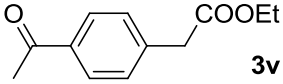
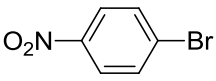
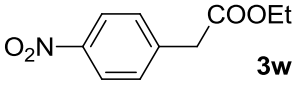
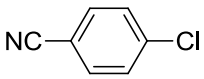
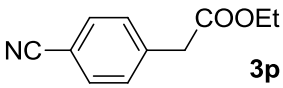
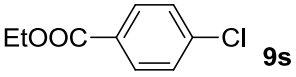
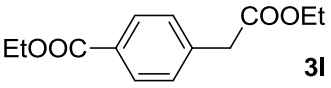
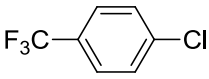
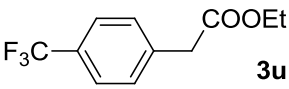
[a] Reaction conditions: **2n** (1.00 mmol), $Pd(dba)_2$ (0.5 mol%), P(*t*-Bu)$_3$•HBF_4 (1.1 mol%), base (2.8-3.0 mmol), additive (0.5 mmol), diethyl malonate (6.6 mmol), 160 °C, 8 h. Yields were determined by GC analysis, with *n*-tetradecane as internal standard. [b] 48 % of *m*-xylene was detected. [c] 32 % of *m*-xylene was detected. [d] 32 % of **2n** and 17% of *m*-xylene were detected.

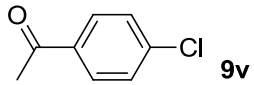
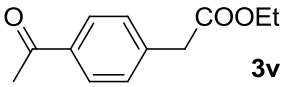
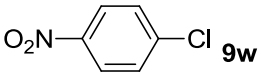
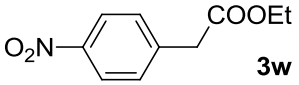
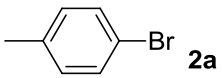
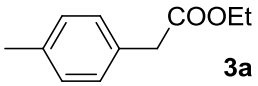
The yields improved substantially when employing carbonate bases (entries 3 and 4). A systematic study revealed that the optimal base consists of a 1:1 mixture of potassium carbonate and bicarbonate. The desired arylacetate **3n** was detected in 80% yield with the adapted conditions (entry 7). Control experiments confirmed that a 1:1 ratio between K_2CO_3 and $KHCO_3$ is crucial for the selectivity of cross-coupling vs. protodehalogenation (entries 9-10). The origin of the cooperative effect of these two bases is still unclear.

Table 5. Reaction scope of sterically hindered and electron-deficient substrates[a]



2n-w (X = Br); **9p**, **9s**, **9u-w** (X = Cl) **3n-w**

Substrate	Product	Yield [%]
 **2n**	 **3n**	81
 **2o**	 **3o**	83
 **2p**	 **3p**	70
 **2q**	 **3q**	77
 **2r**	 **3r**	93
 **2s**	 **3l**	93
 **2t**	 **3t**	95
 **2u**	 **3u**	82
 **2v**	 **3v**	73
 **2w**	 **3w**	60
 **9p**	 **3p**	77
 **9s**	 **3l**	88
 **9u**	 **3u**	73

Substrate	Product	Yield [%]
 **9v**	 **3v**	87
 **9w**	 **3w**	70
 **2a**	 **3a**	16[b,c]

[a] Reaction conditions B: **2** or **9** (1.00 mmol), $Pd(dba)_2$ (0.5 mol%), $P(t\text{-}Bu)_3 \bullet HBF_4$ (1.1 mol%), diethyl malonate (6.6 mmol), K_2CO_3 (1.5 mmol), $KHCO_3$ (1.5 mmol), 160 °C, 8 h. Isolated yields. [b] GC yield. [c] 82 % of malonate product **5a** was detected by GC.

This second protocol was also effective in the coupling of the electron-deficient substrate **2p** (70% yield), which gave only 15% using the protocol optimized for electron-rich compounds. Encouraged by these spot checks, we explored the scope of the new conditions for various aryl halides (Table 5).

The results confirm that the second set of conditions is superior for the coupling of sterically demanding and electron-deficient aryl bromides. The protodehalogenation was largely suppressed, and a good range of arylacetates was obtained in high yields. Common functionalities such as cyano, ester, benzoyl, trifluoromethyl, acetyl, and nitro groups were tolerated (**3p**-**w**). We were delighted to find that the conditions were also suitable for the conversion of aryl chlorides into the corresponding aryl acetates.

Test reactions confirmed that the protocols used in Tables 3 and 5 are complementary to each other. The first, which involves potassium phosphate in combination with 18-crown-6 as the base, is highly effective for the coupling of electron-rich aryl halides but gives low yield for electron-deficient or sterically demanding substrates (Table 3, **3n** and **3p**). In contrast, the second, which is based on a potassium carbonate / bicarbonate mixture, allows the coupling of electron-poor and sterically demanding aryl halides, but is less effective for the coupling of electron-rich substrates (Table 5, **3a**).

2.3 Conclusions

A new palladium catalyst system was developed that allows the convenient synthesis of diversely functionalized arylacetates from readily available aryl halides and diethyl malonate in the presence of mild bases. The reaction proceeds via the arylation of diethyl malonate with formation of diethyl 2-arylmalonates. These intermediates directly undergo a dealkoxycarbonylation to give arylacetic acid esters along with CO_2 and ethanol. The

dealkoxycarbonylation step proceeds rapidly for electron-deficient and sterically demanding derivatives, but is much slower for electron-rich 2-arylmalonates.

Two complementary reaction protocols were necessary to provide a general synthetic entry to alkyl 2-arylacetates. The optimal conditions for the coupling of electron-rich aryl halides involve $Pd(dba)_2$ (0.5%) / $P(t\text{-}Bu)_3 \bullet HBF_4$ (1.1%) as the catalyst and 18-crown-6 (0.5 equiv.) / potassium phosphate (2.8 equiv.) as the base. This base / crown ether combination is essential for a quantitative dealkoxycarbonylation.

In contrast, electron-deficient and sterically demanding aryl halides are best coupled in the absence of crown ether, using a 1:1 potassium carbonate / bicarbonate mixture as the base. This way, the competing protodehalogenation of the aryl halides, otherwise a major side reaction, is effectively suppressed.

Overall, the new protocols, characterized by the use of commercially available, easy-to-handle catalysts and mild bases as well as a high functional group tolerance, have decisively advanced the dealkoxycarbonylative cross-coupling of aryl halides and dialkyl malonates towards being a general and practical synthetic entry to the important substrate class of arylacetic acid derivatives.

2.4 References

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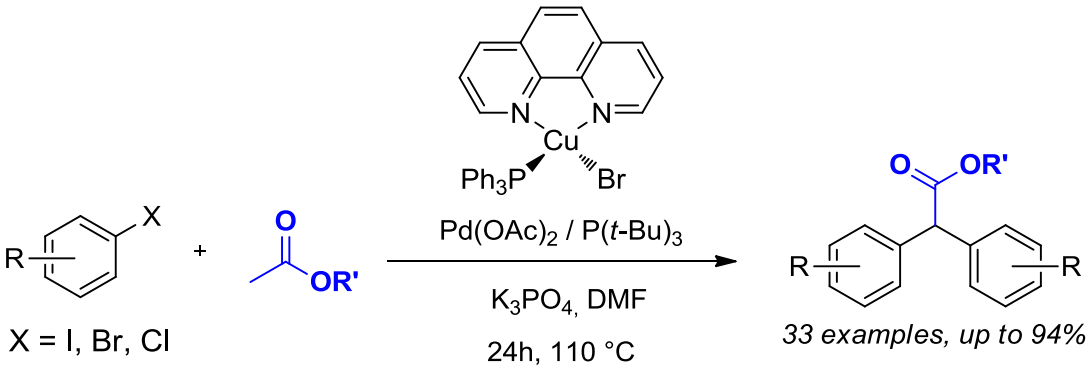
Chapter 3

Palladium/Copper-Catalyzed Di-α-arylation of Acetic Acid Esters*



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3.1 Introduction

The synthesis of diarylacetic acid derivatives is of considerable interest since many of these molecules display unique biological and pharmaceutical activities. For example, adiphenine is a parasympatholytic drug which acts as a smooth muscle relaxant in the treatment of hypermotility and spasms of the genitourinary and gastrointestinal tracts (Figure 1),[1] asimadoline is a potent κ-opioid receptor agonist that has been investigated as a possible treatment for irritable bowel syndrome,[2] and 4-DAMP is a muscarinic acetylcholine receptor antagonist with selectivity for the M_3 and M_5 subtypes.[3]

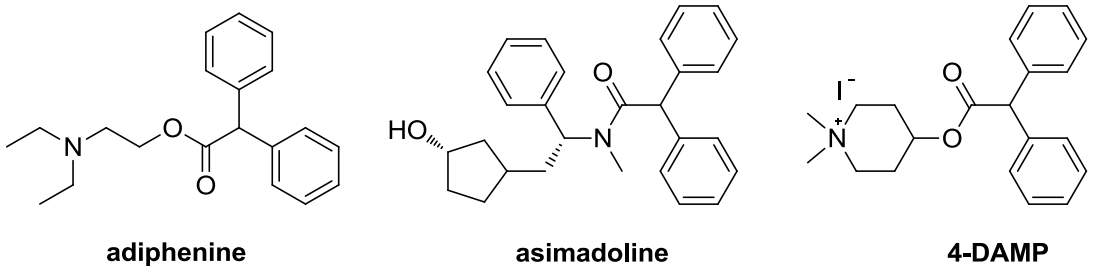
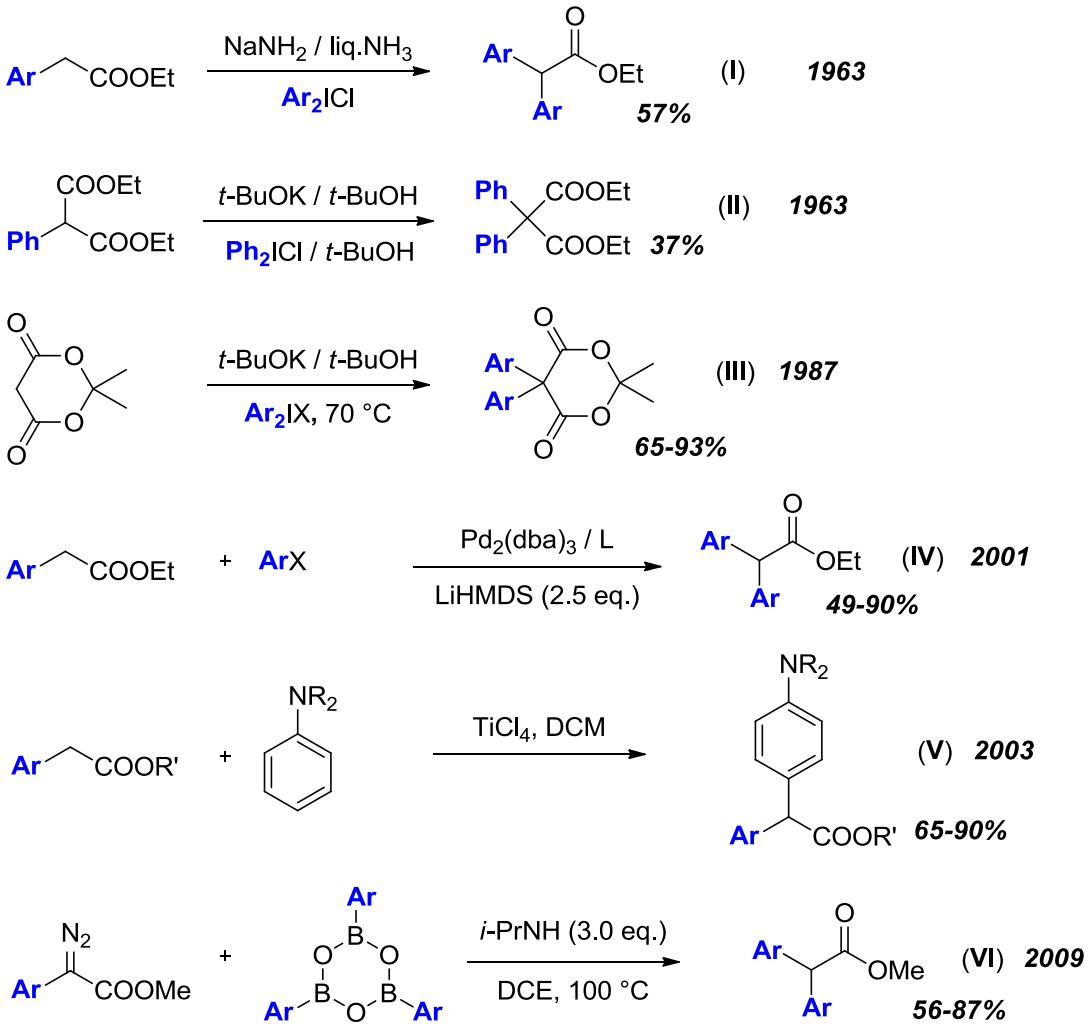


Figure 1. Biologically important diaryl acetic acid derivatives.

A known synthesis of diarylacetic acid derivatives employs diaryliodonium salts as arylating reagents. Carbonanions generated from various carbonyl compounds could be arylated at their α-position with diaryl iodonium salts. In 1963, Forgione[4] disclosed the synthesis of diaryl acetates via the α-arylation of 2-arylacetic esters with diphenyliodonium chloride (Scheme 1, **I** and **II**). Treating Meldrum's acid with stable alkali base and diaryliodonium halides, the corresponding isopropylidene diarylmalonates were also easily prepared (**III**).[5] These methods provided an efficient access to the diarylacetate compounds, whereas they suffer from extremely low atom economy due to the formation of a huge amount of waste.[6]

In the last several decades, the transition metal-catalyzed cross-coupling reactions have emerged as powerful methods for C-C and C-heteroatom bond formations. Under palladium catalysis, aryl acetates could readily react with aryl halides forming the diaryl acetates (**IV**).[7] However, this method required expensive and hard-to-handle bases such as MHDMS. In 2004, Periasamy[8] discovered the titanium-catalyzed arylation of aryl acetates using tertiary arylamines (**V**). Recently, Wang[9] reported the catalysis-free arylation of α-diazocarbonyl compounds with boroxines (**VI**). However, the preparative utility of these strategies is hampered by the limited availability of the required starting materials.

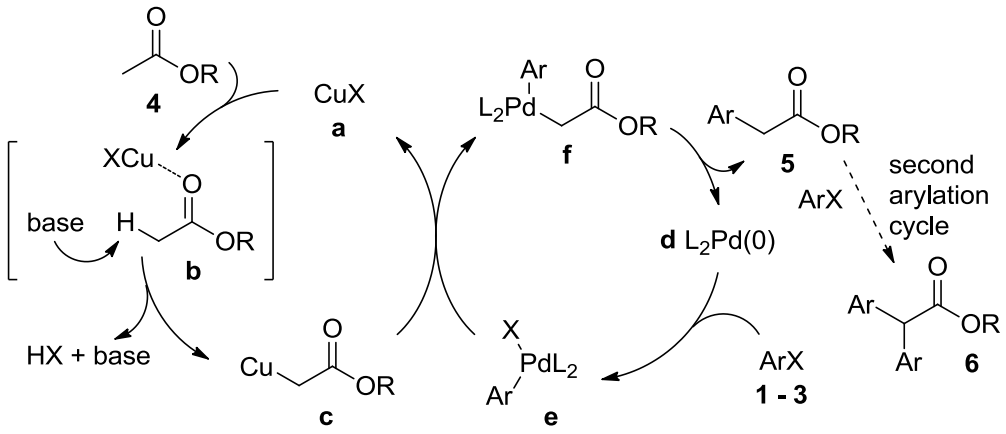


Scheme 1. Previous methods for the synthesis of diaryl acetates.

In this respect, the diarylation of acetic acid esters with aryl halides appeared to be a more attractive approach, as these substrate classes are available in great structural variety at low cost.[10] However, in contrast to 2-arylacetates [2-phenyl acetate: $pK_{a(DMSO)}$ = 22.7] or alkyl ketones [acetone: $pK_{a(DMSO)}$ = 26.5],[11] simple acetic acid esters are much harder to deprotonate [ethyl acetate: $pK_{a(DMSO)}$ = 29.5],[12] so that the use of expensive and hard-to-handle bases such as MHMDS (M = K or Na), LDA, or alkali metal alkoxides seems to be unavoidable in arylation processes of these compounds.[13]

Our strategy to overcome this key limitation, which significantly hampers the preparative applicability of ester arylations, consisted in employing a co-catalyst that allows the deprotonation of simple acetic acid esters by mild bases by stabilizing the resulting enolates. The Sonogashira coupling[14] can be seen as the archetype of a reaction in which a co-catalyst enables the deprotonation of an otherwise relatively inert C-H-bond. Due to the high stability of the intermediate copper acetylides, the Pd/Cu-catalyzed coupling of terminal alkynes with

aryl halides proceeds in the presence of carbonate or amine bases and is thus compatible with most common functional groups.



Scheme 2. Proposed mechanism.

We believed that a similar concept might also work for α-arylation reactions.[15] The proposed mechanism is outlined in Scheme 2. In the first step, the alkyl acetate coordinates to the copper species **a** *via* its carbonyl group. This should acidify the α-protons so that they can be removed with a weak base with formation of a stable copper enolate complex **c**. Under liberation of copper halide species **a**, the enolate moiety is then transferred to arylpalladium(II) complex **e** generated *via* an oxidative addition of the aryl halide to the coordinatively unsaturated palladium complex **d**.

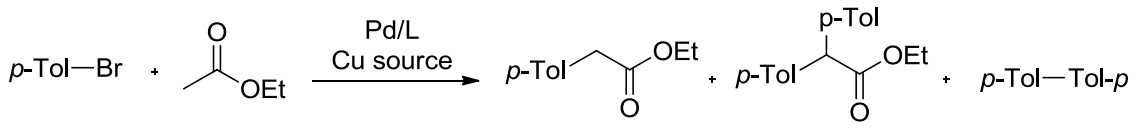
The arylacetate **5** is released from species **f** *via* reductive elimination, regenerating the original palladium species **d**. This initial product should be much more reactive than the starting material [ethyl phenylacetate: $pK_{a(DMSO)}$ = 23.6],[16] so that one would expect it to immediately undergo a second arylation leading to the desired product **6**.

3.2 Results and discussion

In search for a catalyst system that would allow implementing this reaction concept, we evaluated the arylation of ethyl acetate with 4-bromotoluene in the presence of a palladium / *tert*-butyl phosphine catalyst system (Table 1, entries 1-3). We chose this Pd catalyst as the starting point on the basis that it has successfully been employed in α-arylations of enolates.

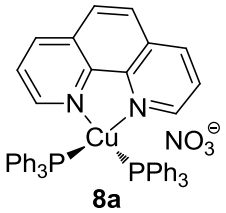
No arylation product was observed in the presence of simple carbonate or phosphate bases, which was expected as they are less basic than ester enolates by several orders of magnitude (pK_a of HCO_3^- = 10.3, pK_a of HPO_4^{2-} = 12.3).[17] Instead, solely homo-coupling product **7aa** of the aryl bromide was formed. However, as soon as catalytic amounts of copper halides were introduced into the reaction system, arylated products were formed (entries 4-6).

Table 1. Optimization of reaction conditions.[a]

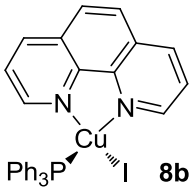


1a **4a** **5aa** **6aa** **7aa**

Entry	Cu source	Base	Solvent	Yield (%)[b]		
				5aa	**6aa**	**7aa**
1	—	Cs_2CO_3	DMF	0	0	9
2	—	K_2CO_3	DMF	0	0	8
3	—	K_3PO_4	DMF	0	0	34
4	CuI	K_3PO_4	DMF	1	13	19
5	CuBr	K_3PO_4	DMF	0	10	29
6	CuCl	K_3PO_4	DMF	1	8	29
7	CuI/Phen[c]	K_3PO_4	DMF	2	28	1
8	CuBr/Phen[c]	K_3PO_4	DMF	0	35	2
9	CuCl/Phen[c]	K_3PO_4	DMF	2	19	1
10	**8a**	K_3PO_4	DMF	3	49	2
11	**8b**	K_3PO_4	DMF	1	45	3
12	**8c**	K_3PO_4	DMF	2	66	3
13	**8d**	K_3PO_4	DMF	1	60	4
14	**8e**	K_3PO_4	DMF	1	32	26
15	**8f**	K_3PO_4	DMF	0	24	28
16	**8g**	K_3PO_4	DMF	0	55	2
17	**8h**	K_3PO_4	DMF	0	63	4
18	**8i**	K_3PO_4	DMF	2	35	2
19	**8c**	K_3PO_4	DMA	1	61	0
20	**8c**	K_3PO_4	NMP	10	17	3
21	**8c**	K_3PO_4	Toluene	0	1	0
22	**8c**	Cs_2CO_3	DMF	11	23	0
23	**8c**	K_2CO_3	DMF	0	0	0
24	**8c**[d]	K_3PO_4	DMF	39	11	0
25[e]	**8c**	K_3PO_4	DMF	0	54	12
26[f]	**8c**	K_3PO_4	DMF	**2**	**86**	**2**
27[g]	**8c**	K_3PO_4	DMF	7	43	8
28[h]	**8c**	K_3PO_4	DMF	0	0	0



8a



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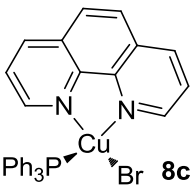

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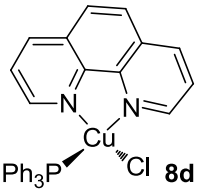

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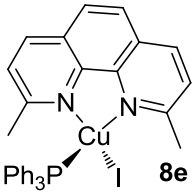

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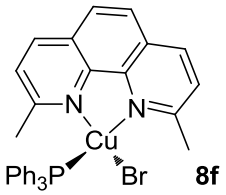

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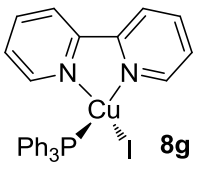

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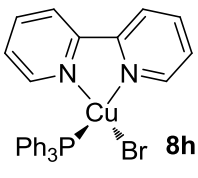

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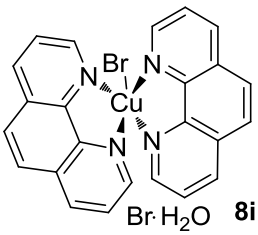


8i

[a] Reaction conditions: 4-bromotoluene (0.5 mmol), ethyl acetate (2.5 mmol), $Pd(OAc)_2$ (1.0 mol%), P(*t*-Bu)$_3$•HBF_4 (2.2 mol%), Cu source (1.2 mol%), base (1.5 mmol), solvent (2.0 mL), 110 °C, 24 h. [b] Yields were determined by GC analysis, with *n*-tetradecane as internal standard. [c] 1,10-Phenanthroline (2.4 mol%). [d] 3.6 mol%. [e] $Pd(OAc)_2$

(3.0 mol%), P(*t*-Bu)$_3$•HBF$_4$ (3.6 mol%). [f] Pd(OAc)$_2$ (2.0 mol%), P(*t*-Bu)$_3$•HBF$_4$ (2.4 mol%), **8c** (2.4 mol%). [g] Without P(*t*-Bu)$_3$•HBF$_4$. [h] Without Pd(OAc)$_2$ and P(*t*-Bu)$_3$•HBF$_4$.

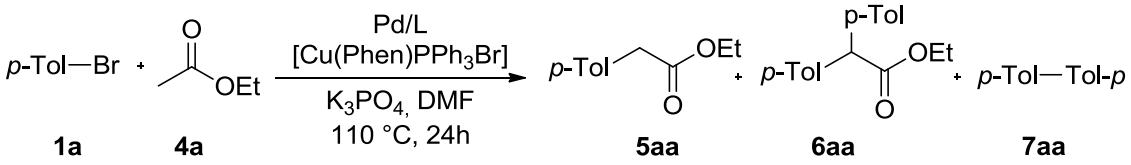
The selectivity of the reaction dramatically increased when 1,10-phenanthroline was added to the copper catalyst, but the conversion still remained unsatisfactory (entries 7-9). This was substantially improved by introducing the copper(I) phenanthroline phosphine complex **8a** as the co-catalyst. We then synthesized various related copper complexes (**8b-h**) and tested their catalytic activities (entries 11-17).[18] This study revealed that copper(I) complexes (entries 10-17) are more effective than copper(II) complex (entry 18), particularly when they contain a bromide counterion. Mixed PPh$_3$-phenanthroline and PPh$_3$-bipyridine ligands were similarly effective, whereas phosphine-free complexes did not give good results. The highest yields were thus obtained with [Cu(phen)PPh$_3$Br] **8c** (entry 12). We next screened various bases and solvents and found that amides such as DMF and DMA are particularly effective reaction solvents (entries 12 and 19-21). Among the bases tested, potassium phosphate gave the best results. The less basic cesium carbonate led to the desired products with low conversion and selectivity (entry 22), and potassium carbonate was almost ineffective (entry 23).

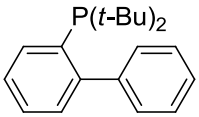
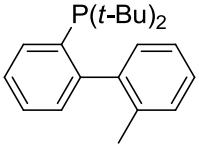
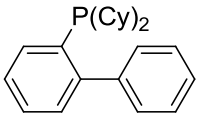
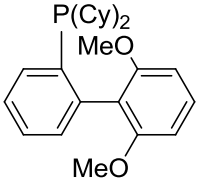
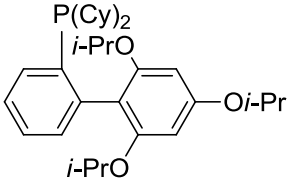
The ratio between copper and palladium catalysts has a strong influence on the ratio between mono- and diarylated products. The best results are obtained at a 1/1.2 ratio. Increasing the Cu/Pd ratio leads to the monoarylated acetate **5aa** as the major product (entry 24), whereas at lower Cu/Pd ratio larger amounts of the homo-coupling byproducts were formed (entry 25).

Control experiments confirmed that the palladium is indispensable (entries 27 and 28) in this transformation[19] and that *t*-butylphosphine is the most effective ligand for the palladium catalyst (Table 2). Under optimal reaction conditions (2.0 mol% of Pd(OAc)$_2$, 2.2 mol% of P(*t*-Bu)$_3$•HBF$_4$, and 2.4 mol% of [Cu(phen)PPh$_3$Br], 3.0 equiv. of K$_3$PO$_4$, DMF, 110 ^{o}C), the desired diarylation product was finally obtained in 86% yield along with only trace quantities of the monoarylated product **5aa** and the homocoupling product **7aa** (entry 26).

We next explored the scope of the new protocol (Table 3). We thus treated *n*-butyl acetate and ethyl acetate with various aryl halides. In all cases, the diarylacetates were obtained in good to excellent yields. Electron-rich and electron-poor aryl bromides were successfully coupled, and many functional groups were tolerated, including esters, ethers, thioethers, nitriles, and amines. Under the mild reaction conditions, 4-bromochlorotoluene reacted exclusively at the bromine atom leaving the chloro-substituent intact (**6ag**).

Table 2. Screening of palladium source and ligands.[a]

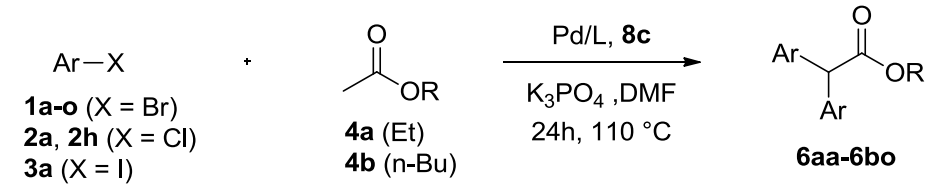


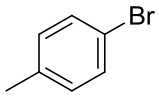
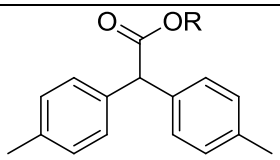
Entry	Pd source	Ligand	Yield (%)[b]		
			5aa	**6aa**	**7aa**
1	$Pd(OAc)_2$	$P(t\text{-}Bu)_3 \bullet HBF_4$	2	66	3
2	$Pd(OTFA)_2$	$P(t\text{-}Bu)_3 \bullet HBF_4$	2	56	5
3	$Pd(acac)_2$	$P(t\text{-}Bu)_3 \bullet HBF_4$	14	50	0
4	$Pd(dba)_2$	$P(t\text{-}Bu)_3 \bullet HBF_4$	13	2	0
5	$PdBr_2$	$P(t\text{-}Bu)_3 \bullet HBF_4$	5	62	0
6	$Pd(OAc)_2$	PPh_3	22	16	0
7	$Pd(OAc)_2$	$P(n\text{-}Bu)_3 \bullet HBF_4$	17	10	0
8	$Pd(OAc)_2$		20	17	3
9	$Pd(OAc)_2$		13	12	5
10	$Pd(OAc)_2$		5	56	5
11	$Pd(OAc)_2$		3	43	4
12	$Pd(OAc)_2$		10	13	5

[a] Reaction conditions: 4-bromotoluene (0.5 mmol), ethyl acetate (2.5 mmol), Pd source (1 mol%), ligand (2.2 mol%), [Cu(Phen)PPh_3Br] (1.2 mol%), base (1.5 mmol), solvent (2.0 mL), 110 °C, 24 h. [b] Yields were determined by GC analysis, with *n*-tetradecane as internal standard.

The successful conversion of 3-bromopyridine demonstrates that *N*-heterocycles are also compatible with this reaction (**6ao**). Sterically hindered aryl bromides were found to be less reactive but gave high yields at slightly increased catalyst loadings and extended reaction times (**6al**).

Table 3. Pd/Cu-catalyzed diarylation of acetate esters[a]



Substrate	Product	R		Yield (%)[b]
		Et	**6aa**	86
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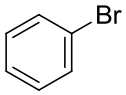	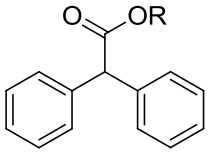	Et	**6ab**	90
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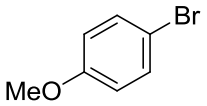	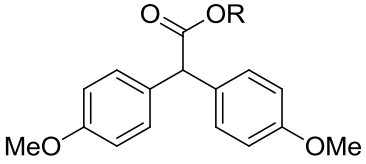	Et	**6ac**	93
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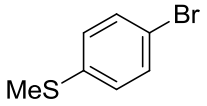	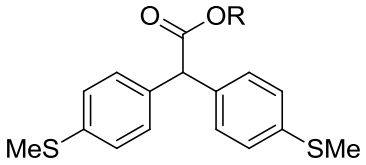	Et	**6ad**	84
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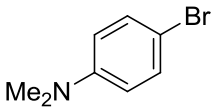	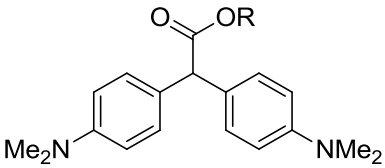	Et	**6ae**	74
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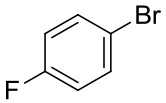	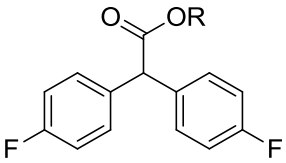	Et	**6af**	94
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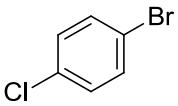	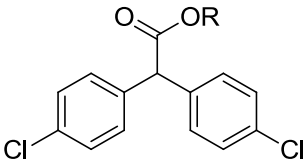	Et	**6ag**	65
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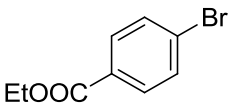	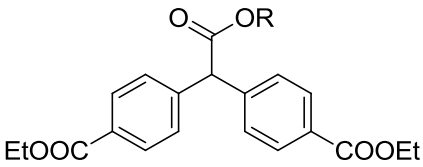	Et	**6ah**	87
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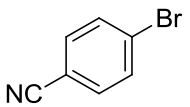	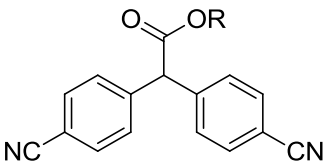	Et	**6ai**	55
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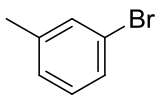
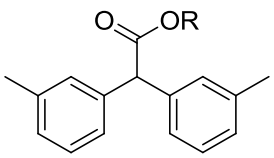
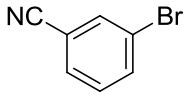
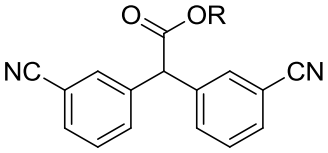
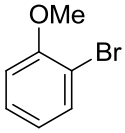
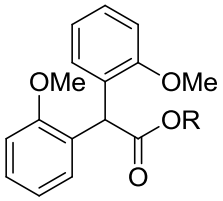
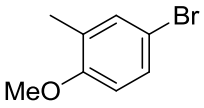
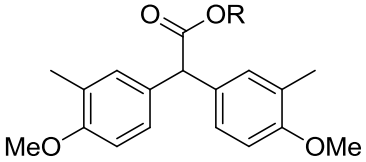
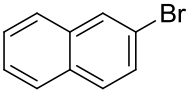
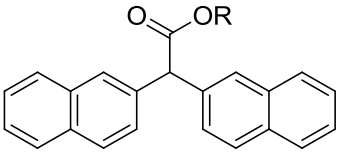
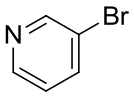
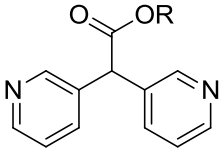
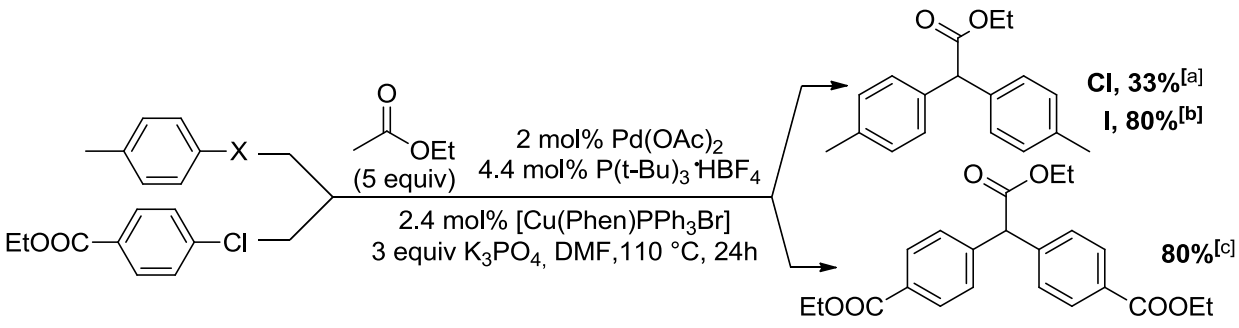
		Et	**6aj**	90
		n-Bu	**6bj**	91

Substrate	Product	R		Yield (%)[b]
		Et	**6ak**	69
		Et	**6al**	70[c,d]
		Et	**6am**	82
		n-Bu	**6bm**	73
		Et	**6an**	82
		n-Bu	**6bn**	81
		Et	**6ao**	74
		n-Bu	**6bo**	75

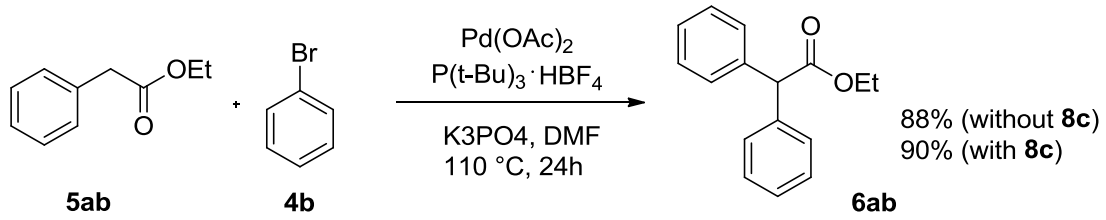
[a] Reaction conditions: Aryl halide **1-3** (1.00 mmol), ester **2** (5.00 mmol), $Pd(OAc)_2$ (2 mol%), P(*t*-Bu)$_3$•HBF_4 (4.4 mol%), **8c** (2.4 mol%), K_3PO_4 (3.00 mmol), DMF (4.0 mL), 110 °C, 24 h. [b] Isolated yields. [c] 48 h. [d] $Pd(OAc)_2$ (3 mol%), P(*t*-Bu)$_3$•HBF_4 (6.6 mol%), **8c** (3.6 mol%).

This method was not restricted to aryl bromides. Aryl chlorides and iodides also reacted smoothly with ethyl acetate affording the corresponding diarylated products in moderate to good yields (Scheme 3). In the reaction of the electron-deficient aryl chlorides such as **2h**, the monoarylated product **5ah** was not detected. However, for the electron-rich 4-chlorotoluene (**2a**), the diarylation product was obtained in only 33% yield, accompanied by a large amount of monoarylated product **5aa**. For this type of electrophiles, a selective monoarylation process might be feasible.



Scheme 3. Cross-ouplng of ethyl acetate with aryl chlorides and iodides. [a] 33 % of monoarylated product was detected. [b] 20 % of starting material was detected. [c] K_3PO_4 (4.00 mmol).

In order to shed some light on the reaction mechanism, we performed a control experiment in which ethyl 2-arylacetate, the expected intermediate in this reaction, was treated with phenyl bromide in the presence of the catalyst system (Scheme 4). The second arylation proceeded cleanly within a short time, and the product was even formed in good yield in the absence of the copper co-catalyst. In contrast, the first arylation step does not proceed without the copper co-catalyst (Table 1, entries 1-3). This experiment confirms that the second arylation step proceeds more readily than the first. Even under forcing conditions and using a large excess of aryl bromides, we never observed more than trace quantities of triarylated compounds. This can be explained with the steric bulk of the corresponding enolates, which appears to hinder their coordination to the palladium complex.



Scheme 4. Pd-Catalyzed arylation of ethyl α-phenyl acetate.

3.3 Conclusions

A bimetallic palladium/copper catalyst system was found to effectively promote the diarylation of alkyl acetates with aryl halides under unprecedentedly mild conditions. The new diarylation method represents a convenient and generally applicable synthesis of alkyl diarylacetates. The discovery that the ester α-proton could be activated by catalytic amounts of copper species to the extent that it can be removed by a relatively weak base potentially opens up new opportunities for the design of various related coupling reactions with C-H functionalization. Further insights into the mechanism, reaction scope, and the transfer to other substrate classes are still desirable.

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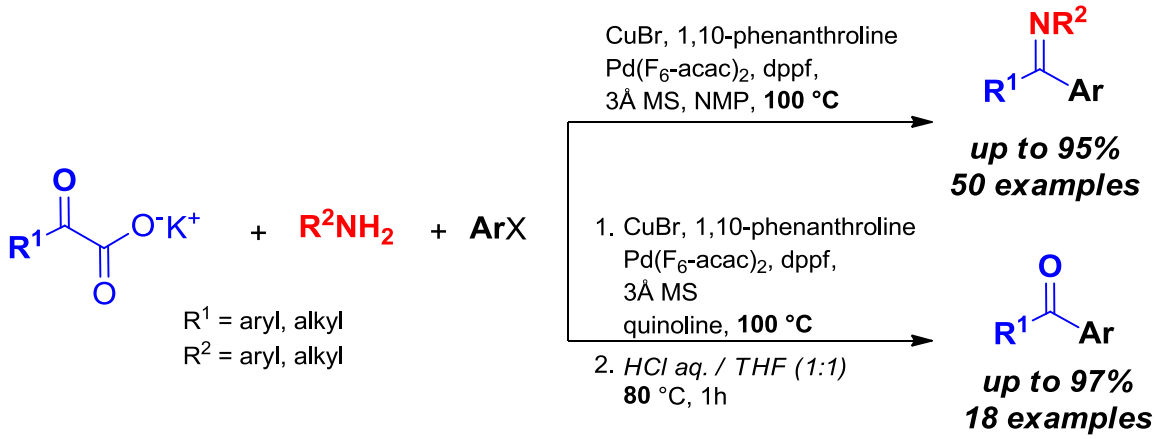
Chapter 4

Development of Decarboxylative Coupling Processes for the Synthesis of Azomethines and Ketones*



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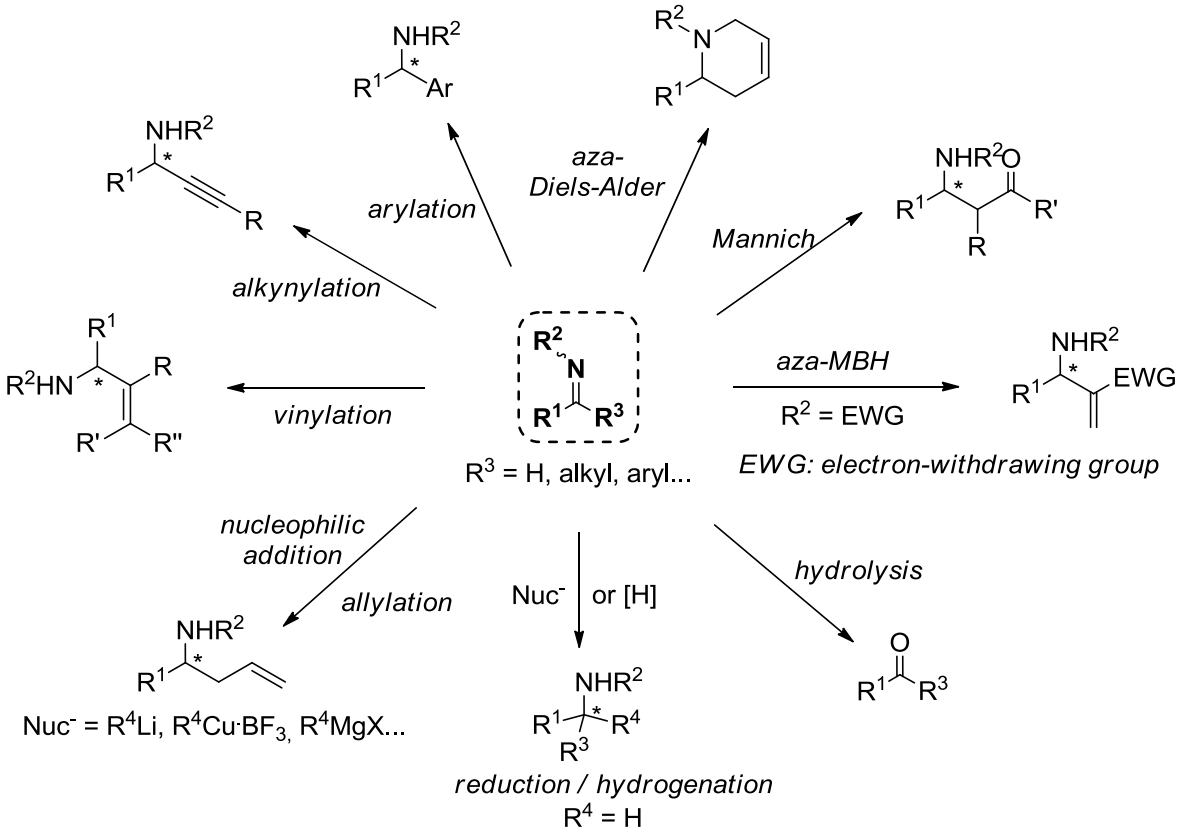
4.1 Introduction

Azomethines are valuable intermediates in organic syntheses. As illustrated in Scheme 1, a wide range of amines[1] and other nitrogen-containing molecules[2] can be synthesized from azomethines. The reduction of imines is one of the most widely used strategies for the preparation of amines.[3] α-Branched amines (e.g. allylic, propargylic, α-alkylated and arylated amines) can be obtained by addition of organometallic nucleophiles such as organolithium, -copper, -zinc, or -magnesium reagents to the imine moiety.[4]

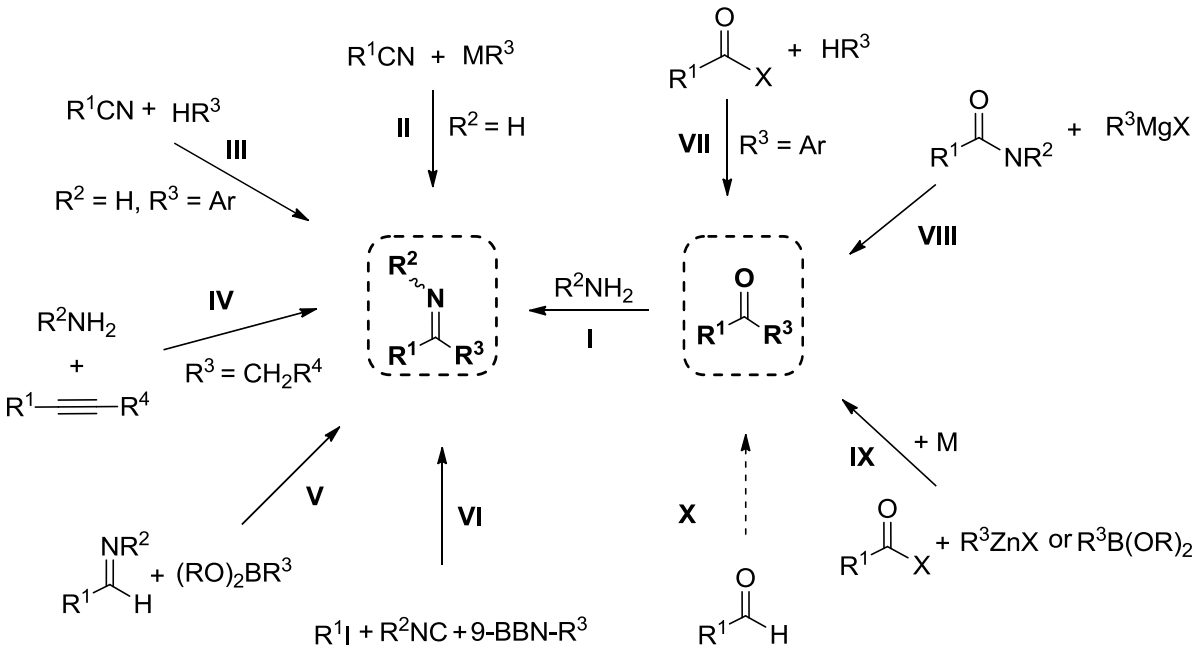


Scheme 1. Products accessible from imine synthons.

Azomethines can also be used as substrates for aza-Diels-Alder,[4e] Mannich[5] and aza-Morita-Baylis-Hillman (aza-MBH) reactions.[6] Their hydrolysis leads to the formation of ketones.[7] Moreover, imino groups can serve as directing groups in C-H activation reactions.[8] In addition, azomethines are used as ligands, e.g., for Fe-based olefin polymerization catalysts.[9] A direct, yet modular access to this class of intermediates based on easily available reagents, in which all three substituents could independently be varied, is thus of high interest.

As depicted in Scheme 2, various methods for the synthesis of azomethines have been reported. Traditionally, they are prepared by the condensation of a carbonyl functionality with a primary amine (Scheme 2, pathway **I**),[10] the addition of organometallic reagents to nitriles

(**II**),[11] or the arylation of nitriles under Friedel-Crafts conditions (**III**).[12] Examples of modern transition metal-catalyzed syntheses include the hydroamination of alkynes catalyzed by Ru, Rh, Au or Ti (**IV**),[13] the ruthenium-catalyzed oxidative coupling of aldimines and boronates (**V**),[14] the palladium-catalyzed addition of arenes or boronic acids to nitriles (**II** or **III**)[15] and the dehydrogenative coupling of alcohols and amines.[16] However, none of these syntheses is fully modular since the products result from combinations of only two reagents. The benefit of multicomponent reactions is that they allow the generation of greater molecular diversity in a single step.[17] However, to the best of our knowledge, the Pd-catalyzed cross-coupling of aryl halides, isonitriles, and organometallic reagents is the only known synthesis that allows an independent variation of all three substituents of the azomethine (Scheme 2, **VI**).[18] Unfortunately, the low availability, toxicity and bad odour of the isonitriles limit the practical utility of this synthetic strategy.

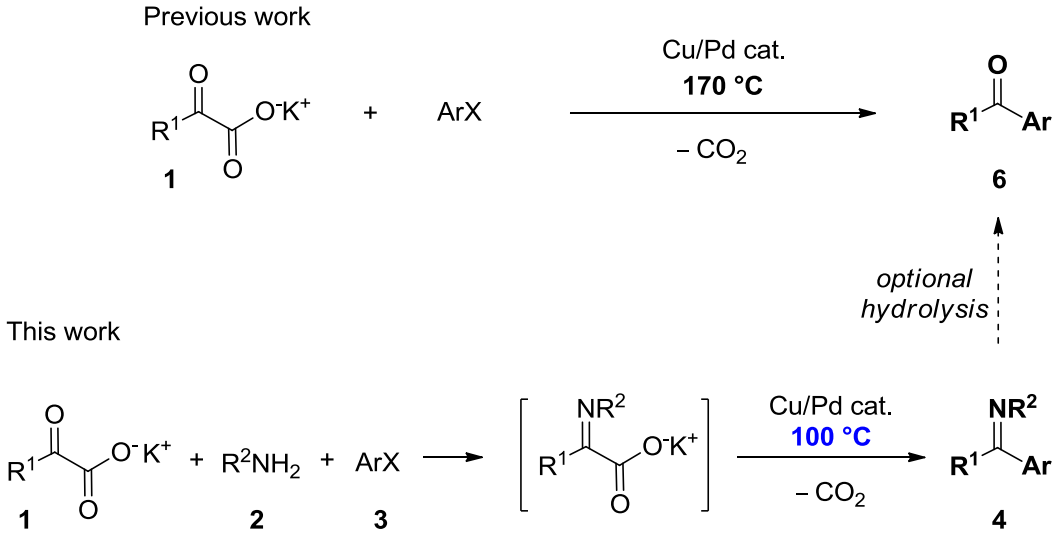


Scheme 2. Synthetic entries to azomethines.

In the most widely-used azomethine synthesis, the condensation of amines with ketones, two of the three substituents of the final product originate from the ketone building block. Ketones are usually assembled via Friedel-Crafts acylation of arenes (**VII**),[19] couplings of organometallic species with carboxylic acid derivatives, e.g., Weinreb amides (**VIII**)[20] or acid chlorides (**IX**),[21] or carboxylic acids activated *in situ* with anhydrides[22] or coupling reagents.[23] Further synthetic entries to ketones include the coupling of acyl anion equivalents (**X**), e.g. cyanohydrins,[24] acetals,[25] dithianes or hydrazones,[26] with carbon electrophiles, as well as the

insertion of C-C multiple bonds into the aldehyde C-H bonds. However, all these approaches to the aryl ketones are not effective sufficient for the preparative applications.

In the context of our work on decarboxylative cross-coupling reactions, we have recently communicated an alternative aryl ketones synthesis. It involves the generation of acyl nucleophiles via the decarboxylation of α-oxocarboxylates at a copper catalyst and their *in situ* coupling with aryl halides at a palladium co-catalyst. (Scheme 3, top).[27] The key advantage of this and related decarboxylative couplings,[28] which have successfully been used e.g. in the synthesis of biaryls,[29,30] vinyl arenes,[31] allyl derivatives,[32] esters,[33] and aryl ketones,[34] is that they draw on easily available carboxylic derivatives rather than sensitive organometallic reagents as sources of carbon nucleophiles.

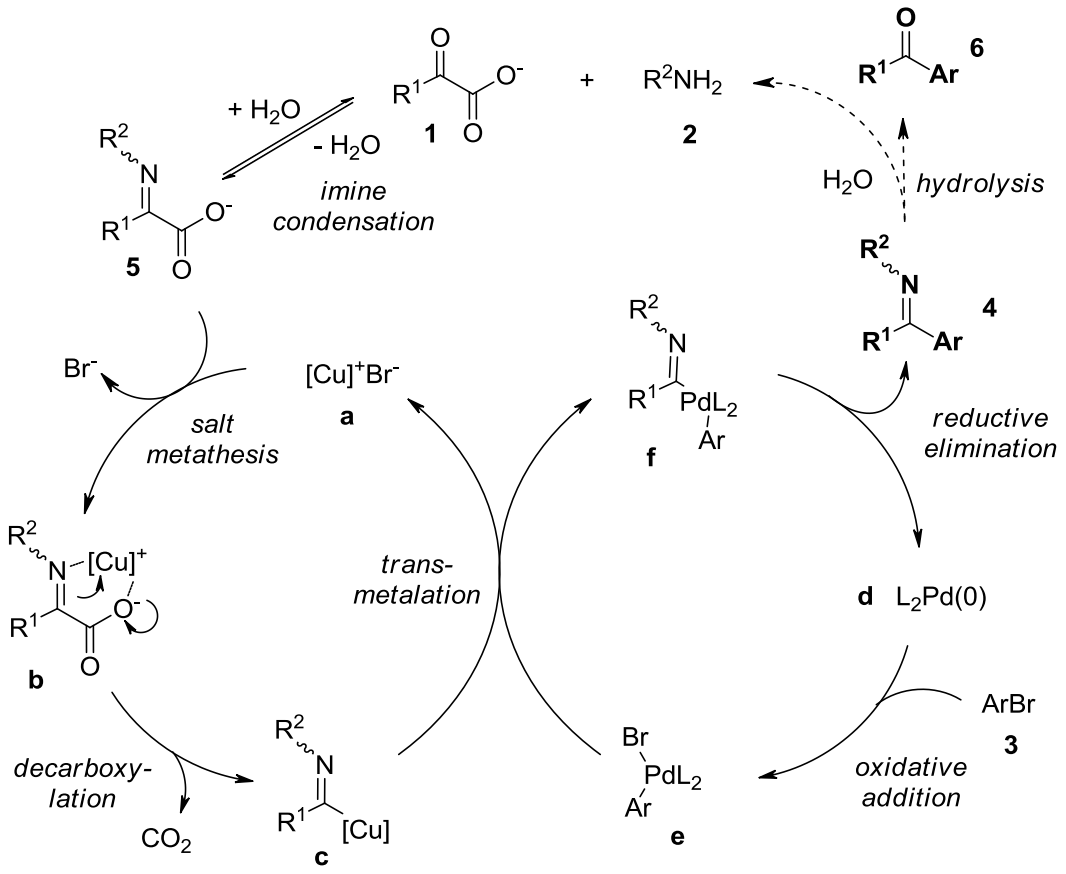


Scheme 3. Decarboxylative synthesis of ketones and azomethines.

We envisioned that a mechanistically related decarboxylative cross-coupling between α-iminocarboxylates and aryl halides should also be possible (Scheme 3, bottom). If the α-iminocarboxylates could be generated directly in the reaction mixture from α-oxocarboxylates salts and primary amines, this would represent a highly modular one-pot azomethine synthesis starting from three independently variable, broadly available and easy-to-handle components.

The mechanistic basis for our desired decarboxylative azomethine synthesis is outlined in Scheme 4. We reasoned that upon mixing the α-oxocarboxylate **1** with the primary amine **2**, at least a fraction of the molecules might condense via the hemiaminal to the α-iminocarboxylate **5**. Once inside the coordination sphere of the copper catalyst, either of these carboxylates should lose CO_2 more readily than the α-oxocarboxylate due to the higher stability of imidoyl over acyl anions.[35,36] At a reaction temperature well below that required for the decarboxylation of copper α-oxocarboxylates, the α-iminocarboxylate complex **b**

should already extrude CO_2 resulting in the selective formation of the imidoyl copper complex **c**. In the transmetallation step, the imidoyl residue should be transferred onto the arylpalladium halide **e**, regenerating the initial copper halide species **a**. The arylpalladium species **e** itself arises from the oxidative addition of the aryl halide **3** to the second catalyst component, the low-valent palladium(0) species **d**. The desired azomethine product **4** would be liberated from complex **f** via reductive elimination, regenerating the original palladium species **d** and closing the catalytic cycle.



Scheme 4. Mechanistic outline of the targeted imine / ketone synthesis.

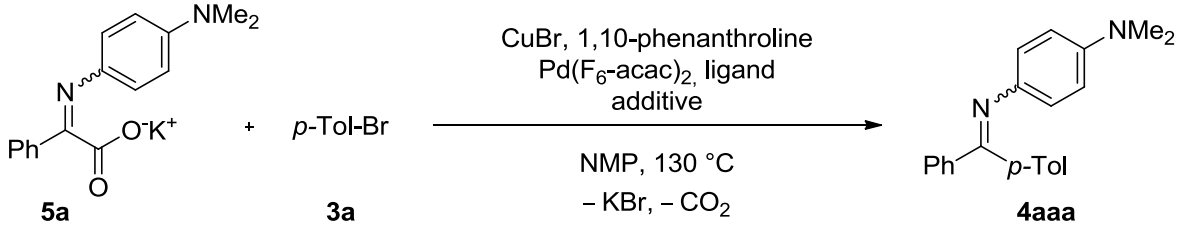
The Pd/Cu-catalyzed decarboxylative coupling of α-oxocarboxylates with aryl bromides requires very forcing conditions, i.e. 170 °C for 16h.[37] If the above decarboxylative synthesis of azomethines indeed proceeded at substantially reduced temperatures, it would be useful also for the synthesis of aryl ketones **6**. Rather than decarboxylative coupling α-oxocarboxylates **1** themselves, they could be converted *in situ* into more reactive α-iminocarboxylates **5** using an inexpensive amine **2**, then react to the azomethines **4**, and finally be hydrolyzed to the ketones **6** (Scheme 4, dotted arrow). Overall, the role of the amine would be that of a recyclable "organocatalyst" that would help reducing the activation barrier of the decarboxylation step.[38]

4.2 Results and discussion

4.2.1 Decarboxylative coupling of α-imino carboxylates and aryl bromides

The first step towards the desired azomethine synthesis was to study the decarboxylative coupling of preformed α-iminocarboxylates with aryl halides. We attempted to synthesize α-iminocarboxylate salts by stirring α-oxocarboxylic acids with amines in methanol and, once the reaction was complete, deprotonated the resulting α-iminoacids with potassium *tert*-butoxide. However, the condensation step did not go to completion for aliphatic amines, and most of the products did not crystallize.

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



Entry	Ligand	Additive	Yield (%)[b]
1	P(*o*-Tol)$_3$	—	5
2	P(*o*-Tol)$_3$	Mg(OTf)$_2$	62
3	P(*o*-Tol)$_3$	3Å MS	27
4	dppf	3Å MS	40
5	dppf	Mg(OTf)$_2$	68
6	dppf	Mg(OTf)$_2$, 3Å MS	85

[a] Reaction conditions: 1.2 mmol **5a**, 1.0 mmol **3a**, 15 mol% CuBr, 15 mol% 1,10-phenanthroline, 1 mol% Pd(F$_6$-acac)$_2$, 0.5 mol% dppf or 1 mol% P(*o*-Tol)$_3$, 5 mol% Mg(OTf)$_2$ when applicable, 200 mg 3Å molecular sieves (MS), 2 mL NMP, 130 °C, 16 h. dppf = 1,1'-bis(diphenylphosphinyl)ferrocene. [b] Yields determined by GC analysis using *n*-tetradecane as the internal standard.

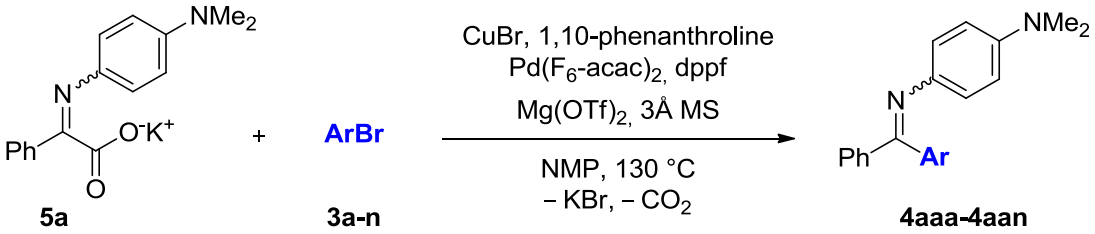
In contrast, (*N*-[4-(dimethylamino)phenyl]imino)phenylacetate (**5a**) was directly obtained in high yields and crystalline form. Thus, we chose the reaction of **5a** with 4-bromotoluene (**3a**) as a model for optimizing the decarboxylative cross-coupling step, using the solvent and catalyst system optimized for the decarboxylative ketone synthesis, i.e. 1 mol% Pd(F$_6$-acac)$_2$, 2 mol% P(*o*-Tol)$_3$, 15 mol% CuBr, and 15 mol% 1,10-phenanthroline.[27] After stirring the reaction mixture for 16 h at 170 °C in *N*-methylpyrrolidinone (NMP)/quinoline, the desired azomethine **4aaa** was isolated in an almost quantitative yield as a mixture of stereoisomers. Encouraged by this finding, we lowered the reaction temperature to 130 °C and studied the reaction systematically (Table 1). Control experiments confirmed that at this low reaction

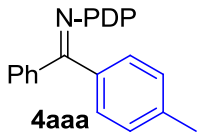
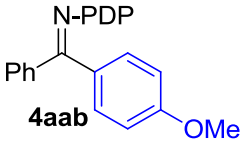
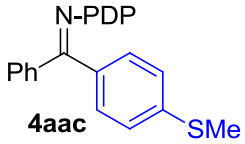
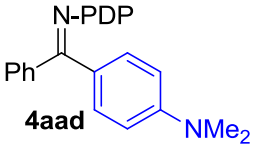
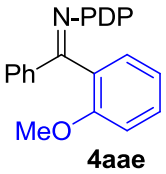
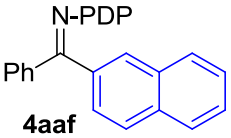
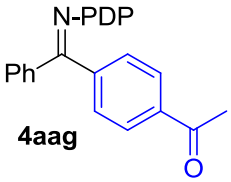
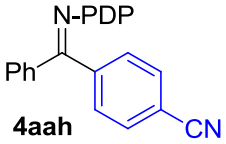
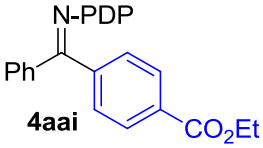
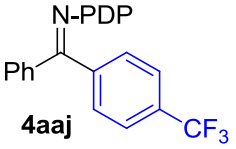
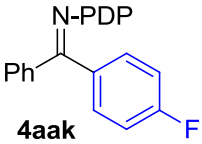
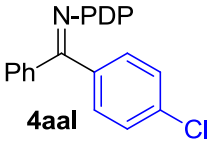
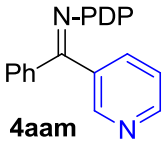
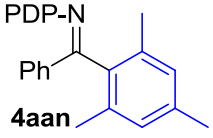
temperature, the decarboxylative coupling between α-oxocarboxylates and aryl halides does not proceed at all. In contrast, the azomethine product **4aaa** was formed in detectable amounts at this temperature (entry 1).

The addition of Lewis acids, and of $Mg(OTf)_2$ in particular, was found to strongly facilitate the reaction (entry 2). This finding can be rationalized by a coordination of Lewis acid to the nitrogen atom of the iminocarboxylate, thereby reducing the electron-density in the α-position to the carboxylate group, and thus, enhancing the decarboxylation rate. The beneficial effect of molecular sieves (entry 3) can be attributed to their Lewis acidity, but may also result from their ability to remove trace amount of water from the reaction mixture, thereby precluding a hydrolysis of the starting material. Among the ligands tested, bis(diphenylphosphinyl)ferrocene (dppf) gave the best results (entries 4 and 5). In combination with $Mg(OTf)_2$ and molecular sieves as additives, the azomethine product **4aaa** was formed in 85 % yield (entry 6). The only side reaction observed was a protodecarboxylation of the iminocarboxylate **5a,** leading to the aldimine. Control experiments revealed that under the above reaction conditions, this aldimine does not react with the aryl bromide **3a** with formation of azomethine **4aaa**, which confirms that the product is indeed formed via a decarboxylative coupling rather than via protodecarboxylation followed by Heck-type reaction.

We next examined the scope of this optimized protocol with regard to the electrophilic coupling partner by treating iminocarboxylate **5a** with various aryl bromides **3** (Table 2). In all cases, the azomethines **4** were obtained in moderate to good yields. Both electron-rich (**3a-f**) and electron-poor (**3g-j**) aryl bromides were successfully coupled, and many functional groups were tolerated, including amino, keto, cyano, ester and trifluoromethyl residues. Under the mild reaction conditions, 1-bromo-4-chlorobenzene (**3l**) reacted exclusively at the bromine atom while leaving the chlorine intact. The successful conversion of 3-bromopyridine (**3m**) demonstrates that nitrogen heterocycles are also compatible with this reaction. Only for the sterically crowded aryl bromide **3n** an unsatisfactory yield was obtained.

Table 2. Scope of the imine synthesis from preformed α-iminocarboxylate **5a**.[a]



Product	Yield (%)[b]	Product	Yield (%)[b]
 **4aaa**	85	 **4aab**	82
 **4aac**	64	 **4aad**	50
 **4aae**	58	 **4aaf**	53
 **4aag**	57	 **4aah**	77
 **4aai**	70	 **4aaj**	82
 **4aak**	75	 **4aal**	86
 **4aam**	84	 **4aan**	10

[a] Reaction conditions: 1.2 mmol **5a**, 1.0 mmol aryl bromide **3**, 15 mol% CuBr, 15 mol% 1,10-phenanthroline, 1 mol% $Pd(F_6\text{-acac})_2$, 1 mol% dppf, 5 mol% $Mg(OTf)_2$, 200 mg 3Å molecular sieves, 2 mL NMP, 130 °C, 16 h. PDP = 4-(dimethylamino)phenyl. [b] Isolated yields.

4.2.2 Development of a one-pot azomethine synthesis

With optimized conditions for the decarboxylative cross-coupling in hand, we focused on the development of a one-pot protocol for the synthesis of azomethines from α-oxocarboxylates **1**, amines **2** and aryl halides **3** without prior isolation of the α-iminocarboxylates **5**. The key challenge was that the condensation step would now have to proceed under non-acidic conditions. This implies that the amine has to react with a carbonyl atom adjacent to a negatively charged carboxylate group. An NMR experiment revealed that when heating potassium phenyloxoacetate (**1a**), cyclohexylamine (**2b**) and molecular sieves in methanol for several hours, appreciable amounts (80%) of the iminocarboxylate **5b** are formed, but still, 20% of potassium phenyloxoacetate (**1a**) remain present (Figure 1).

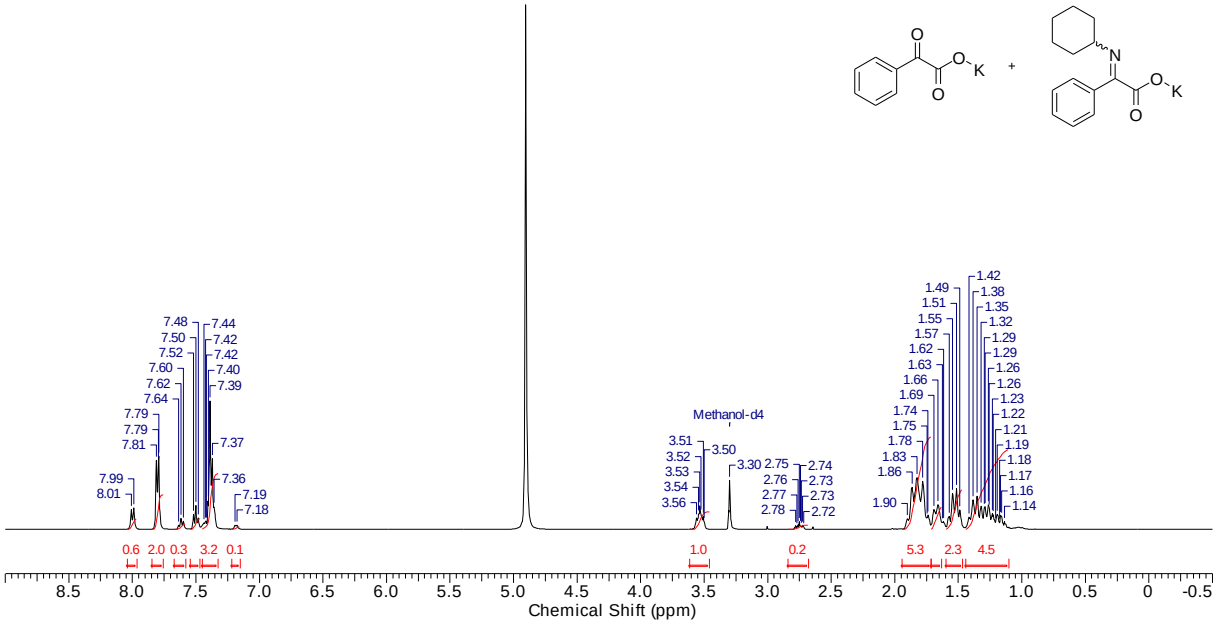
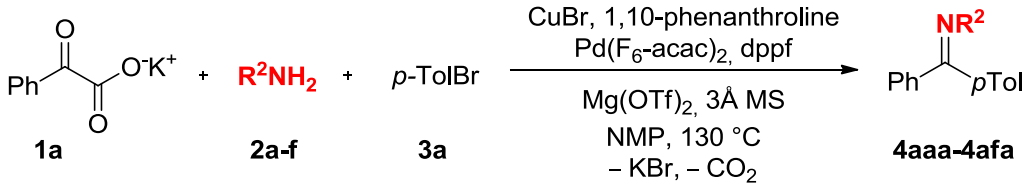


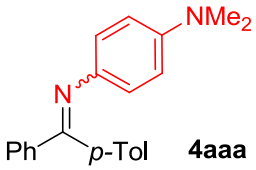
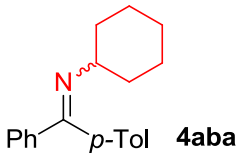
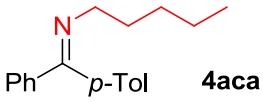
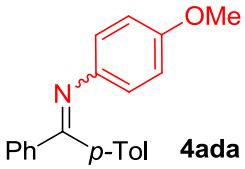
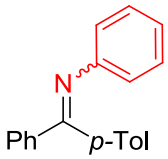
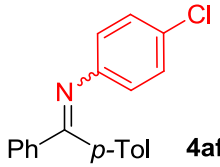
Figure 1. Mixture of α-oxocarboxylate, cyclohexylamine and molecular sieves in methanol-d_4 (resulting in 20% of α-oxocarboxylate and 80% of α-iminocarboxylate)

This confirms that the condensation step is rather slow. For a successful one-pot azomethine synthesis, the water released in the imine condensation step would have to be continuously trapped, and the reaction would have to be performed at a temperature too low for decarboxylation of the α-oxocarboxylate salts present in the reaction mixture. This way, it should be possible to avoid the competing protodecarboxylation and the formation of aryl ketones. Indeed, when we heated a mixture of potassium phenyloxoacetate (**1a**), 4-(dimethylamino)aniline (**2a**) and 4-bromotoluene (**3a**) in the presence of molecular sieves and the previously optimized catalyst system for 16 h to 130 °C, the desired azomethine product **4aaa** was detected in 60% yield. We next evaluated whether the reaction would also work with those amines, whose α-iminocarboxylates we had been unable to isolate, and found that

they gave even better results (Table 3). For cyclohexylamine (**2b**), the corresponding azomethine **4aba** was formed in almost quantitative yield.

Table 3. Evaluation of primary amines in the three-component coupling.[a]



Product	Yield (%)[b]	Product	Yield (%)[b]
 **4aaa**	60	 **4aba**	96
 **4aca**	87	 **4ada**	70
 **4aea**	62	 **4afa**	75

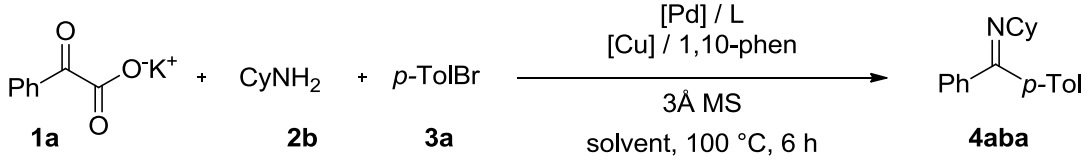
[a] Reaction conditions: 0.6 mmol **1a**, 0.6 mmol amine **2**, 0.5 mmol **3a**, 15 mol% CuBr, 15 mol% 1,10-phenanthroline, 1 mol% $Pd(F_6\text{-acac})_2$, 1 mol% dppf, 5 mol% $Mg(OTf)_2$, 100 mg 3Å molecular sieves, 1 mL NMP, 130 °C, 16 h. [b] Isolated yields.

Based on these findings, we decreased the reaction temperature to 100 °C, shortened the reaction time to 6 h, and re-optimized the catalyst system using cyclohexylamine (**2b**) as the amine component.

Upon mixing all reaction components in the presence of molecular sieves, the desired azomethine product **4a** was obtained in moderate yields already after 6 h at 100 °C (Table 4, entry 1). The main side reaction was a protodecarboxylation under formation of the aldimine. Control experiments revealed that both palladium and copper are essential for this reaction (entries 2-4). In an attempt to optimize the yield, we first varied the copper and palladium catalysts. Copper(I) bromide was found to be the most effective copper source, with other copper salts lower yields were obtained (entries 5-10). The presence of 1,10-phenanthroline as a ligand for the copper is beneficial (entries 11-12). The choice of the palladium precursor was found to have only a limited effect on the reaction outcome (entries 13-20). The key towards achieving higher yields was the choice of the phosphine ligand. Moderately electron-

rich triarylphosphines such as tri(*p*-methoxyphenyl)phosphine (entry 22), and chelating phosphines with a large bite angle such as 1,1'-diphenylphosphinoferrocene (dppf, entry 24), gave best results. Trialkylphosphines and less electron-rich triarylphosphines were less effective (entries 25-27). Among the solvents tested, the polar aprotic *N*-methylpyrrolidone (NMP) was found to be optimal. Using quinoline as the solvent, even higher yields were detected, but the separation of the azomethine product from the basic amine proved to be laborious (entry 28). Similarly high yields were achieved with NMP after increasing the reaction time to 16 h (entry 31). The presence of molecular sieves was crucial for achieving high yields, but for this substrate combination, Lewis acids were no longer required (entries 32-33). With the optimized catalyst system (1 mol% $Pd(F_6\text{-acac})_2$, 1 mol% dppf, 15 mol% CuBr, 15 mol% 1,10-phenanthroline, 3 Å molecular sieves, NMP), azomethine **4aba** was formed in 92% yield at 100 °C as a mixture of stereoisomers.

Table 4. Optimization of the one-pot three-component azomethine synthesis.[a]



1a **2b** **3a** **4aba**

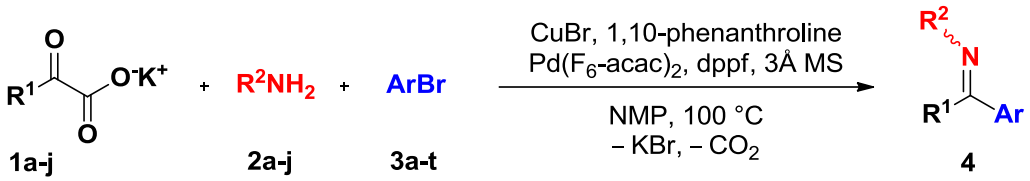
Entry	Cu source	Pd source	Ligand	Solvent	Yield (%)[b]
1	CuBr	$Pd(F_6\text{-acac})_2$	P(*o*-Tol)$_3$	NMP	49
2	—	$Pd(F_6\text{-acac})_2$	P(*o*-Tol)$_3$	NMP	0
3	—	$Pd(F_6\text{-acac})_2$	dppf	NMP	0
4	CuBr	—	—	NMP	0
5	CuI	$Pd(F_6\text{-acac})_2$	P(*o*-Tol)$_3$	NMP	43
6	Cu_2O	$Pd(F_6\text{-acac})_2$	P(*o*-Tol)$_3$	NMP	5
7	$CuCl_2$	$Pd(F_6\text{-acac})_2$	P(*o*-Tol)$_3$	NMP	20
8	CuI	$Pd(F_6\text{-acac})_2$	dppf	NMP	59
9	Cu_2O	$Pd(F_6\text{-acac})_2$	dppf	NMP	6
10	$CuCl_2$	$Pd(F_6\text{-acac})_2$	dppf	NMP	31
11	CuBr	$Pd(F_6\text{-acac})_2$	P(*o*-Tol)$_3$	NMP	14[c]
12	CuBr	$Pd(F_6\text{-acac})_2$	dppf	NMP	36[c]
13	CuBr	$PdCl_2$	P(*o*-Tol)$_3$	NMP	51
14	CuBr	$Pd(OAc)_2$	P(*o*-Tol)$_3$	NMP	38
15	CuBr	$Pd(acac)_2$	P(*o*-Tol)$_3$	NMP	42
16	CuBr	$Pd(dba)_2$	P(*o*-Tol)$_3$	NMP	48
17	CuBr	$PdCl_2$	dppf	NMP	75

Entry	Cu source	Pd source	Ligand	Solvent	Yield (%)[b]
18	CuBr	$Pd(OAc)_2$	dppf	NMP	54
19	CuBr	$Pd(acac)_2$	dppf	NMP	68
20	CuBr	$Pd(dba)_2$	dppf	NMP	68
21	CuBr	$Pd(F_6\text{-acac})_2$	—	NMP	27
22	CuBr	$Pd(F_6\text{-acac})_2$	$P(p\text{-}MeOC_6H_4)_3$	NMP	38/82[d]
23	CuBr	$Pd(F_6\text{-acac})_2$	binap	NMP	69
24	**CuBr**	**$Pd(F_6\text{-acac})_2$**	**dppf**	**NMP**	**81**
25	CuBr	$Pd(F_6\text{-acac})_2$	dppb	NMP	77
26	CuBr	$Pd(F_6\text{-acac})_2$	PCy_3	NMP	37
27	CuBr	$Pd(F_6\text{-acac})_2$	PPh_3	NMP	43
28	CuBr	$Pd(F_6\text{-acac})_2$	dppf	quinoline	93
29	CuBr	$Pd(F_6\text{-acac})_2$	dppf	DMF	43
30	CuBr	$Pd(F_6\text{-acac})_2$	dppf	DMPU	5
31	CuBr	$Pd(F_6\text{-acac})_2$	dppf	NMP	92[d]
32	CuBr	$Pd(F_6\text{-acac})_2$	dppf	NMP	75[e]
33	CuBr	$Pd(F_6\text{-acac})_2$	dppf	NMP	25[f]

[a] Reaction conditions: 1.2 mmol **1a**, 1.2 mmol **2b**, 1.0 mmol **3a**, 15 mol% Cu cat., 15 mol% 1,10-phenanthroline, 1 mol% Pd cat., 2 mol% ligand (1 mol% for bidentate ligands), 200 mg 3Å molecular sieves, 2 mL NMP, 100 °C, 6 h. dba = dibenzylideneacetone, binap = 2,2'-bis(diphenylphosphinyl)-1,1'-binaphthyl, dppf = 1,1'-bis(diphenylphosphinyl) ferrocene, dppb = 1,4-bis(diphenylphosphinyl)butane. [b] Yields were determined by GC analysis using *n*-tetradecane as the internal standard. [c] without 1,10-phenanthroline. [d] 16 h. [e] $Mg(OTf)_2$ (5 mol %) was used as Lewis acid. [f] 3Å molecular sieves is replaced by $Mg(OTf)_2$ (5 mol %).

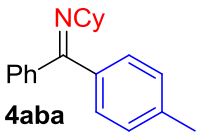
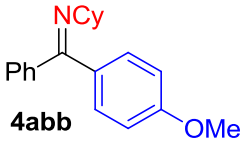
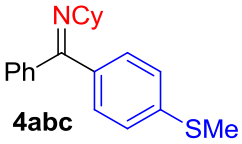
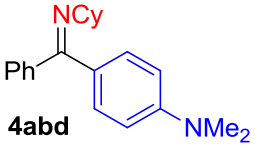
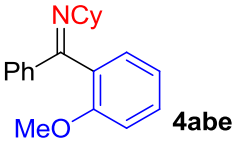
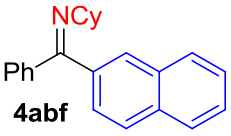
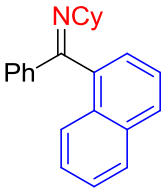
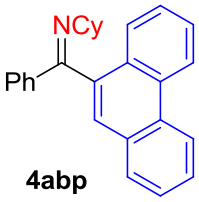
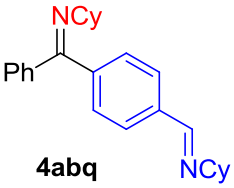
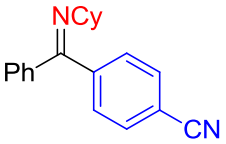
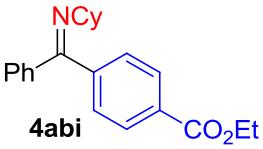
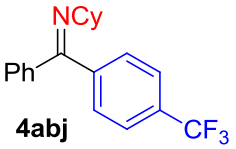
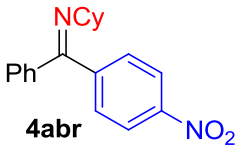
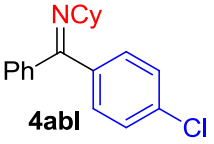
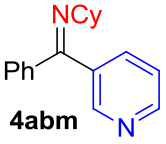
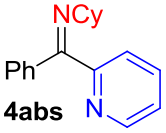
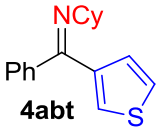
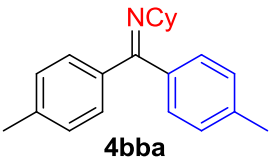
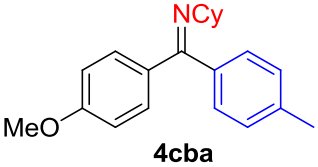
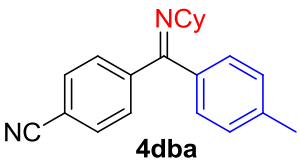
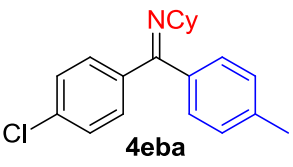
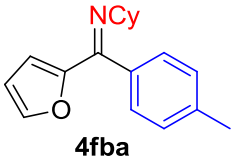
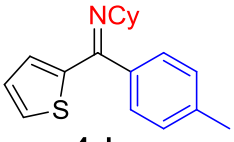
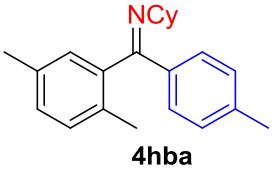
We next explored the scope of the one-pot reaction under the optimized conditions (1 mol% $Pd(F_6\text{-acac})_2$, 1 mol% dppf, 15 mol% CuBr, 15 mol% 1,10-phenanthroline, 3Å molecular sieves, NMP, 100 °C, 16 h). As can be seen in Table 5, various aryl bromides **3** were successfully coupled with potassium aryl- or alkyl-α-oxoacetates **1** and primary amines **2**. Electron-rich (**3a-e**) and electron-deficient substrates bearing cyano (**3h**), ester (**3i**), trifluoromethyl (**3j**) or nitro (**3r**) groups gave similarly high yields. Heteroaryl bromides such as 3-bromopyridine (**3m**) and 3-bromothiophene (**3t**) also gave good results. When starting from 4-bromobenzaldehyde (**3q**), the aldehyde group reacted with the amine to the corresponding imine. Thus, 2.2 equivalents of the primary amine were employed, and the product was isolated in the form of the corresponding imine **4abq**.

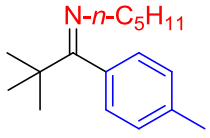
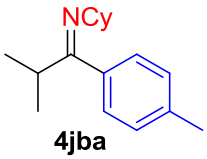
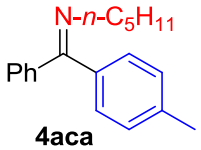
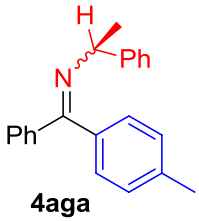
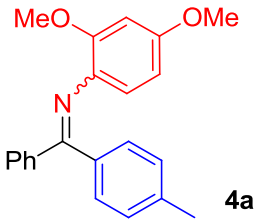
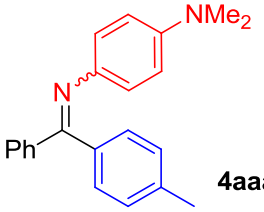
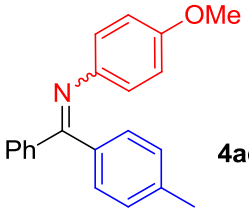
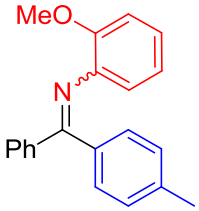
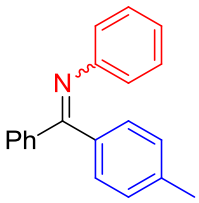
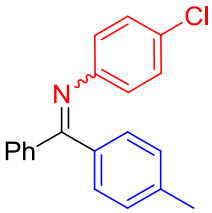
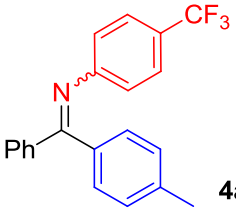
Table 5. Substrate scope of the one-pot three-component imine synthesis.[a]



1a-j 2a-j 3a-t 4

R^1 = aryl, heteroaryl, alkyl; R^2 = aryl, alkyl.

Product	Yield (%)[b]	Product	Yield (%)[b]	Product	Yield (%)[b]
 4aba	91 (61)[c]	 4abb	90	 4abc	92
 4abd	85	 4abe	86	 4abf	93
 4abo	58	 4abp	66	 4abq	54[d]
	95	 4abi	83	 4abj	65
 4abr	57	 4abl	94	 4abm	91
 4abs	46	 4abt	85	 4bba	62
 4cba	34	 4dba	94	 4eba	89
 4fba	71	 4gba	53	 4hba	66

Product	Yield (%)[b]	Product	Yield (%)[b]	Product	Yield (%)[b]
 **4ica**	45[e]	 **4jba**	(46)[e,g]	 **4aca**	87
 **4aga**	64	 **4aha**	94[f]	 **4aaa**	60[f]
 **4ada**	66[f]	 **4aia**	73[f]	 **4aea**	53[f]
 **4afa**	75[f]	 **4aja**	(16)[f,g]		

[a] Reaction conditions: 1.2 mmol α-oxocarboxylate **1**, 1.2 mmol primary amine **2**, 1.0 mmol aryl bromide **3**, 15 mol% CuBr, 15 mol% 1,10-phenanthroline, 1 mol% Pd(F_6-acac)$_2$, 1 mol% dppf, 200 mg 3Å molecular sieves, 2 mL NMP, 100 °C, 16 h. [b] Isolated yields. [c] From 4-chlorotoluene. [d] 2.2 equiv. of amine. [e] 36 h. [f] 130 °C. [g] Yield determined by GC analysis using *n*-tetradecane as the internal standard.

The use of the electron-rich, sterically demanding phosphine 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl instead of dppf allows extending the reaction from aryl bromides to aryl chlorides. This is exemplified by the synthesis of **4aba** from 4-chlorotoluene.

Variation of the α-oxocarboxylate substrate **1** showed that aryl- α-oxocarboxylates with electron-rich (**1b**,**c**,**h**) or electron-poor ring substituents (**1d**,**e**) as well as heteroarenecarboxylates (**1f**,**g**) were all smoothly converted. For the aliphatic α-oxocarboxylate **1i**, longer reaction times were required. The synthesis of enolizable azomethines is also possible (**4jba**) but their isolation in pure form via distillation proved to be troublesome. For such compounds, a different workup procedure has to be developed, or they have to be used without further purification.

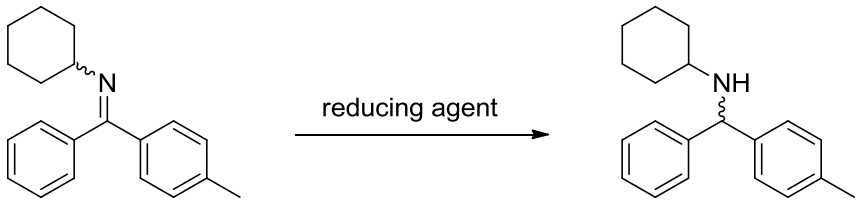
The amine component is also variable (**2a-i**). For both linear and branched aliphatic amines, good yields were obtained. In order to convert electron-rich anilines (**2a**,**d**,**h**,**i**), the reaction temperatures had to be increased to 130 °C. The performance limit of the current system is

reached with the electron-deficient aniline **2j**. For even less electron-rich anilines, no conversion was observed, which may be due to their low reactivity in imine condensation reactions.

4.2.3 Reduction of the azomethine into the corresponding amine

Considering that the reduction of azomethines to secondary amines is an important synthetic application, we investigated this reaction using compound **4aba**, a typical example of the products accessible by our new synthetic method. We tested various reaction conditions (Table 6) and found that the highest yields of the amine **7a** are obtained when the azomethine is treated either with a 3:1 mixture of sodium borohydride and aluminium chloride (entry 4), or with lithium aluminium hydride (entry 5) in THF.

Table 6. Optimization of the reduction step.[a]



4aba **7a**

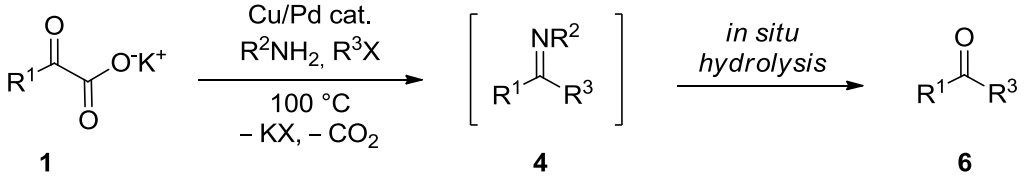
Entry	Reducing agent	Solvent	T (°C)	Yield (%)[b]
1	$LiAlH_4$	THF	40	0
2	$LiAlH_4/AlCl_3$	THF	40	66
3	$NaBH_4$	THF	60	4
4	$NaBH_4/AlCl_3$	THF	60	97
5	$LiAlH_4$	THF	60	100
6	H_2/ Pt/C	EtOH	80	44
7	H_2/ Pd/C	EtOH	80	0[c]

[a] Reaction conditions: 1 mmol **4aba**, 2 mL solvent, 16 h. [b] Yields determined by GC analysis using *n*-tetradecane as the internal standard. [c] the deaminated product was obtained in 91 % yield.

Due to the steric hindrance and low polarity of the C=N bond in the ketimine group, a reaction temperature of 60 °C is required. Hydrogenation over a heterogeneous platinum catalyst (10 bar H_2, 5 mol% Pt/C, EtOH, 80 °C) was less effective, and with palladium catalysts, deaminated product was obtained predominantly.

4.2.4 Application of the decarboxylative α-imino carboxylate coupling to the synthesis of aryl ketones

Since the synthesis of azomethines was found to proceed in such high yields at temperatures well below those required for the synthesis of ketones via decarboxylative coupling of α-oxocarboxylates **1**, we decided to develop a one-pot synthesis of ketones via intermediate formation of azomethines (Scheme 5). In this process, the α-oxocarboxylate salts **1** would need to be converted into α-iminocarboxylates **5**, these would have to be coupled under decarboxylation with aryl halides **3**, and the resulting azomethines **4** would have to be hydrolyzed to the ketones **6**. By lowering the decarboxylation barrier with added amine, the reaction temperatures might be dramatically reduced, thus minimizing thermal degradation of sensitive substrates.



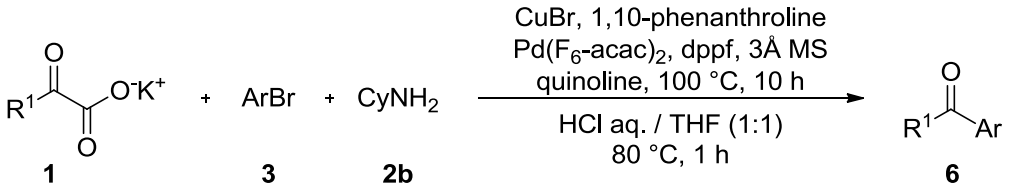
Scheme 5. Decarboxylative synthesis of ketones and azomethines.

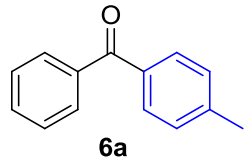
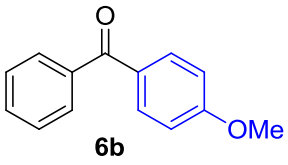
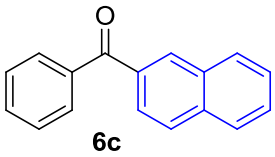
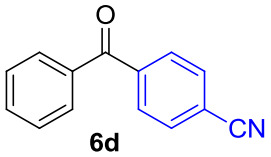
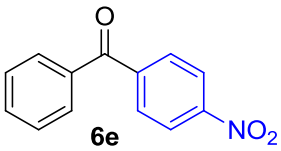
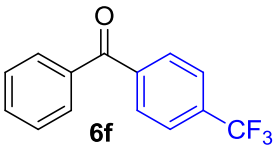
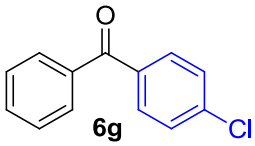
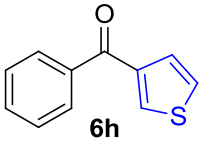
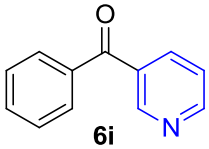
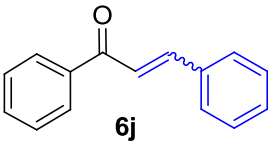
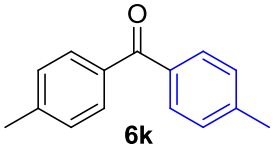
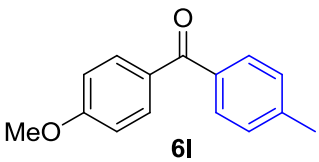
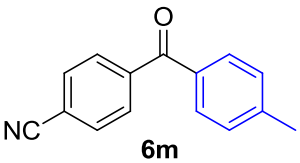
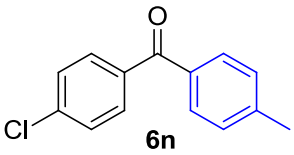
Since the basic azomethines **4** would no longer need to be separated from the reaction medium, it should now be possible to use quinoline as the solvent (Table 4, entry 4). In addition to its beneficial effect on the reaction rate, it should easily be removed along with the amine mediator in an acidic work-up. We used cyclohexylamine (**2b**) as the amine mediator, as it is inexpensive and the corresponding α-iminocarboxylates had proven to be particularly reactive towards decarboxylation. After stirring a mixture of potassium phenyloxoacetate (**1a**), cyclohexylamine (**2b**), and 4-bromotoluene (**3a**) in the presence of molecular sieves and the previously optimized catalyst system (1 mol% $Pd(F_6\text{-acac})_2$, 1 mol% dppf, 15 mol% CuBr, 15 mol% 1,10-phenanthroline, 3Å molecular sieves) in quinoline at 100 °C for 10 h, GC-analysis revealed that the azomethine intermediate **4aba** had formed in quantitative yield. The reaction was allowed to cool slightly, a mixture of 2M HCl and THF (1:1, 3 mL) was added, and the reaction was stirred for one hour at 80 °C to completely hydrolyze the azomethine intermediate. After acidic work-up, ketone **6a** was isolated in 97% overall yield.

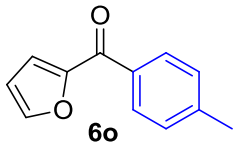
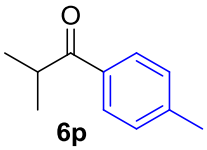
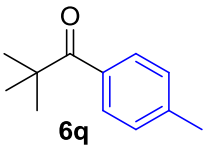
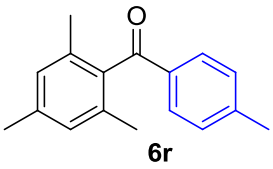
Having thus identified an effective protocol for the synthesis of ketones, we next investigated its scope. As can be seen from the examples in Table 7, a wide range of diversely substituted aryl ketones are accessible in good to excellent yields. The reaction works equally well for aryl bromides bearing electron-donating and -withdrawing groups. In all cases, better

conversions are achieved using the new amine-mediated protocol than the previously reported direct decarboxylative coupling of α-oxocarboxylate salts.[27] The mild reaction conditions even allowed synthesizing 4-nitrobenzophenone (**6e**) in 65% yield, a compound that was obtained only in traces using the previous protocol.[27]

Table 7. Substrate scope of the one-pot ketone synthesis.[a]



Product	Yield (%)[b]	Product	Yield (%)[b]
 **6a**	97	 **6b**	87
 **6c**	95	 **6d**	94
 **6e**	65	 **6f**	88
 **6g**	92	 **6h**	97
 **6i**	91	 **6j**	42
 **6k**	55	 **6l**	71
 **6m**	60	 **6n**	30

Product	Yield (%)[b]	Product	Yield (%)[b]
 **6o**	73	 **6p**	85[c]
 **6q**	44[c]	 **6r**	7[d]

[a] Reaction conditions: 1.2 mmol α-oxocarboxylate **1**, 1.2 mmol primary amine **2**, 1.0 mmol aryl bromide **3**, 15 mol% CuBr, 15 mol% 1,10-phenanthroline, 1 mol% $Pd(F_6\text{-acac})_2$, 1 mol% dppf, 200 mg 3Å molecular sieves, 2 mL quinoline, 100 °C, 10 h; quenching with 3 mL of 2 M HCl / THF (1:1), 80 °C, 1 h. [b] Isolated yields. [c] 36 h. [d] Yield determined by GC analysis using *n*-tetradecane as the internal standard.

The advantages of the new protocol are visible for heterocyclic derivatives: in the coupling of both 3-bromothiophene and 3-bromopyridine, the corresponding aryl ketones **6h** and **6i** were now isolated in 97% and 91% rather than 50% and 57%, respectively. Moreover, the new protocol for the first time allows the decarboxylative coupling of vinyl halides, as demonstrated by the synthesis of **6j**.

The reaction is also broadly applicable to the α-oxocarboxylate substrates. Aryl α-oxocarboxylates with electron-rich and electron-poor substituents were smoothly converted, and even heterocyclic derivatives gave high yields. The conversion of aliphatic α-oxocarboxylates is also possible, but requires longer reaction times. Even the enolizable ketone **6p** was obtained in 85% yield after 36 h. The limit of the current catalyst system was reached with the sterically crowded substrate 2,4,6-trimethylphenyloxoacetate.

4.3 Conclusions

In summary, we have developed a highly modular, one-pot three-component protocol for the synthesis of diversely substituted azomethines via decarboxylative coupling, starting from simple potassium α-oxocarboxylates, primary amines and various aryl halides. This new procedure, which is mediated by a bimetallic copper/palladium catalyst, shows a remarkable substrate scope and excellent functional group tolerance. All three substituents in the azomethine products can be individually varied. A wide range of valuable imines is thus accessible in high yields at 100 °C, an unprecedentedly low temperature for redox-neutral decarboxylative cross-couplings. In combination with an *in situ* hydrolysis of the azomethines, the new reaction can be used also for the synthesis of ketones from α-oxocarboxylate salts and aryl halides in the presence of cyclohexylamine. In this process, the inexpensive amine

mediator serves to reduce the reaction temperature of the decarboxylation step by intermediate imine condensation. The concept of lowering the temperature of decarboxylative couplings of α-oxocarboxylates by performing them in the presence of amines should open up new opportunities also for related decarboxylation transformations of α-oxocarboxylates, e.g., 1,2- and 1,4-additions, allylations or arylations with C-H activation.

4.4 References

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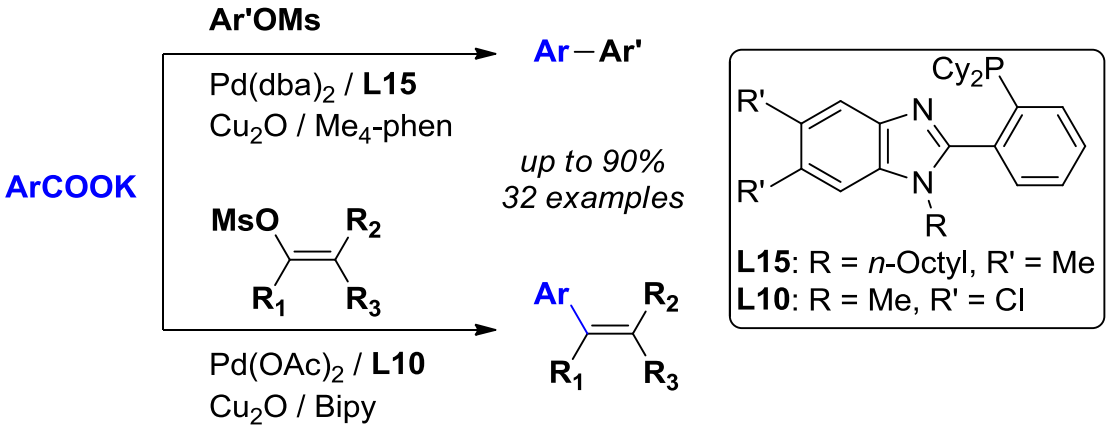
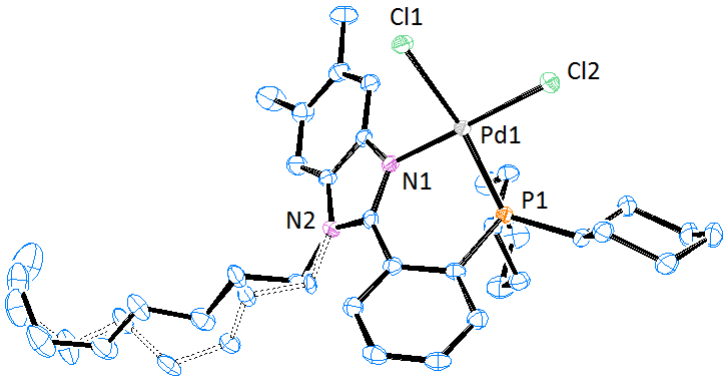
Chapter 5

Decarboxylative Cross-Coupling of Mesylates Catalyzed by Copper/Palladium Systems with Customized Imidazolyl Phosphine Ligands*





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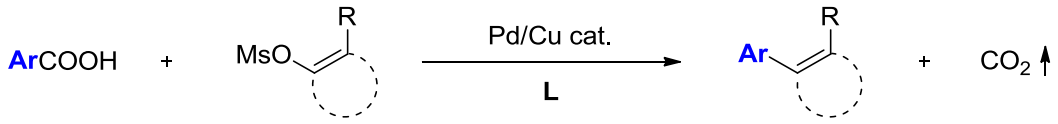
5.1 Introduction

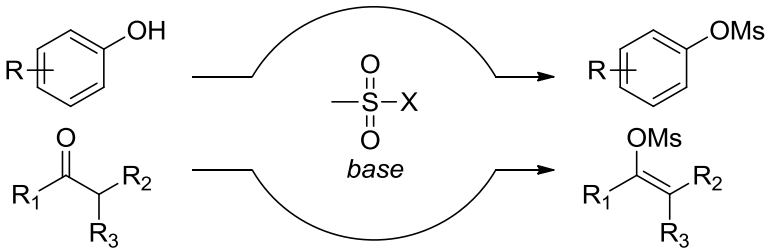
Redox-neutral decarboxylative cross-couplings mediated by Cu/Pd or Ag/Pd bimetallic catalyst systems proved to have a particularly broad scope with regards to both carboxylates and carbon electrophiles. In this reaction variant, the decarboxylation step is mediated by a Cu(I) [1] or Ag(I) catalyst, [2] while a Pd-complex catalyzes the coupling with a carbon electrophile. Whereas aryl bromides and iodides can be converted with very simple ligand systems, [3] the activation of aryl chlorides, [4] triflates [5] and tosylates [6] requires the use of sophisticated catalyst systems containing electron-rich, bulky phosphine ligands. However, all attempts to develop decarboxylative couplings of the notoriously hard-to-activate methanesulfonates (mesylates) as carbon electrophiles have failed so far (Scheme 1).



Scheme 1. Decarboxylative cross-coupling of aryl/alkenyl mesylates.

5.1.1 Activation of aryl and alkenyl mesylates

Aryl and alkenyl mesylates are particularly attractive carbon electrophiles for preparative- or industrial-scale syntheses, since they have the lowest molecular weight of all sulfonate leaving groups. They are easily accessible by esterification of broadly available phenols or enolates with inexpensive mesyl chloride or anhydride (Scheme 2), often in substitution patterns different to related organohalides.[7] Aryl and alkenyl mesylates are comparably stable against air and moisture, which makes them easy to store and handle. Their use in cross-coupling reactions is, therefore, desirable from economical, ecological and practical standpoints.



Scheme 2. Accesses to aryl/alkenyl mesylates.

However, the higher basicity of mesylates in comparison with e.g., triflates or even tosylates results in a particularly stable C–O bond (Figure 1)[8] that can only be cleaved with only a few extremely active cross-coupling catalysts.

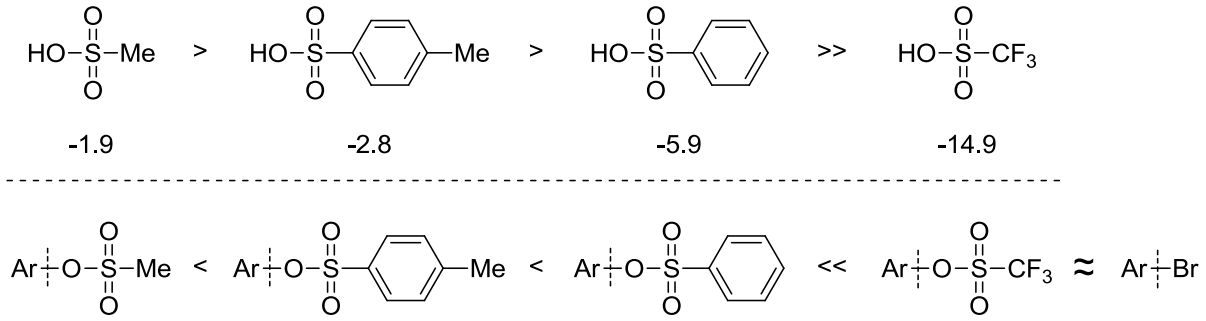
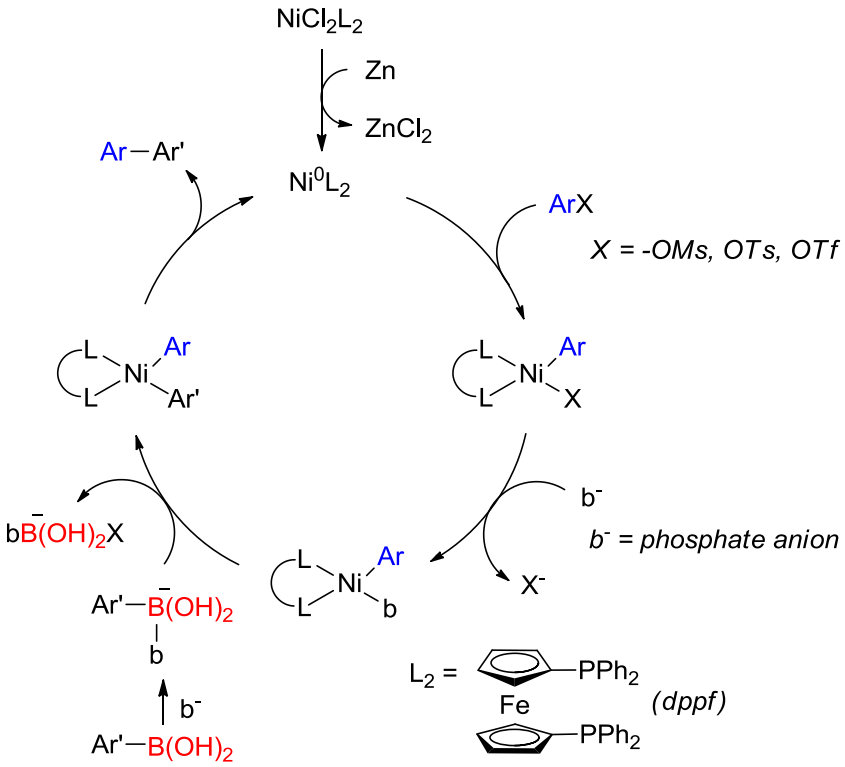


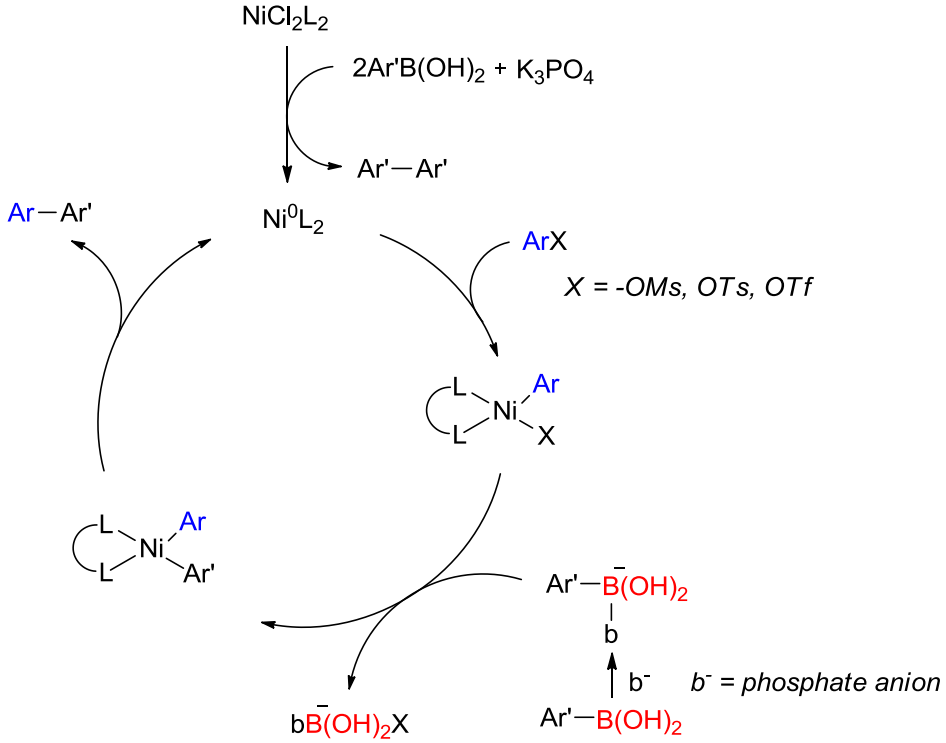
Figure 1. A comparison on the leaving-group activity of commonly used sulfonate groups, based on the pKa value of their conjugate acids.



Scheme 3. Ni-catalyzed Suzuki-Miyaura reaction of aryl mesylates using Zn as reductant.

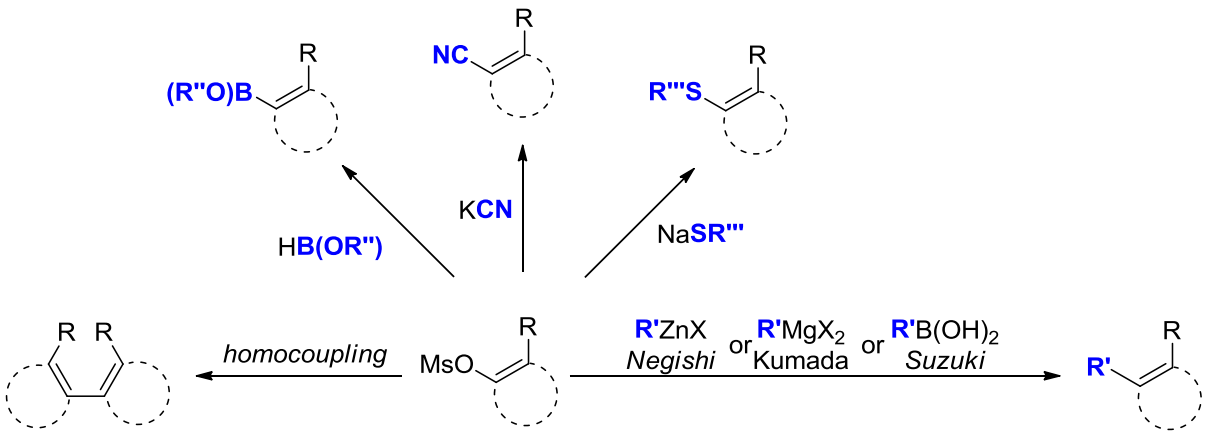
In 1995, Percec[9] reported the first example of cross-coupling of arylboronic acids with aryl mesylates, employing nickel or palladium catalysis. Using nickel complexes as the catalysts, the activated aryl mesylates were converted to the corresponding biaryls in high yields, whereas the Pd-catalyzed coupling of aryl mesylates could not give comparable results even when employing $Pd(dppf)_2Cl_2$ and $Pd(PPh_3)_4$, which were the most effective catalysts for Suzuki-Miyaura reactions at that time. As a stronger nucleophile compared to Pd(0), Ni(0) is sufficiently nucleophilic to undergo oxidative addition with aryl mesylates, especially when

the catalyst is supported by electron-rich phosphines ligands such as dppf or PCy_3. However, these protocols often require stoichiometric amounts of zinc or other reductants such as *n*-BuLi[10] and NaH[11] for the generation of Ni(0) (Scheme 3). Recent developments have allowed the coupling of aryl mesylates in Suzuki-Miyaura cross-coupling reactions in the absence of reducing agents, using a high excess of of phosphine ligands (normally 4 equivalents) (Scheme 4).



Scheme 4. Ni-catalyzed reductant-free Suzuki-Miyaura reaction of aryl mesylates.

In the past two decades, aryl sulfonates have been successfully used as carbon electrophiles in a array of Ni-catalyzed cross-coupling reactions, including homocoupling, Kumada-coupling, Negishi-coupling, Suzuki-coupling, C–S coupling, borylation, and cyanation (Scheme 5).[12]



Scheme 5. Ni-catalyzed cross-couplings of aryl/alkenyl mesylates.

Although the Ni-catalyzed cross-coupling reaction of aryl mesylates has been established and elaborated since the mid-1990s, the same coupling reactions with the use of palladium catalyst had not been discovered until early 2000s due to the difficulty in the oxidative addition of aryl mesylates onto palladium catalysts. The breakthrough was recently achieved by the development of electron rich and sterically demanding phosphine ligands. Many research groups including Fu,[13] Hartwig,[14] Buchwald,[15] Beller,[16] Verkade,[17] and Kwong,[18] have made substantial contributions to the new generation of effective ligands capable of activating unreactive carbon electrophiles (Figure 2).

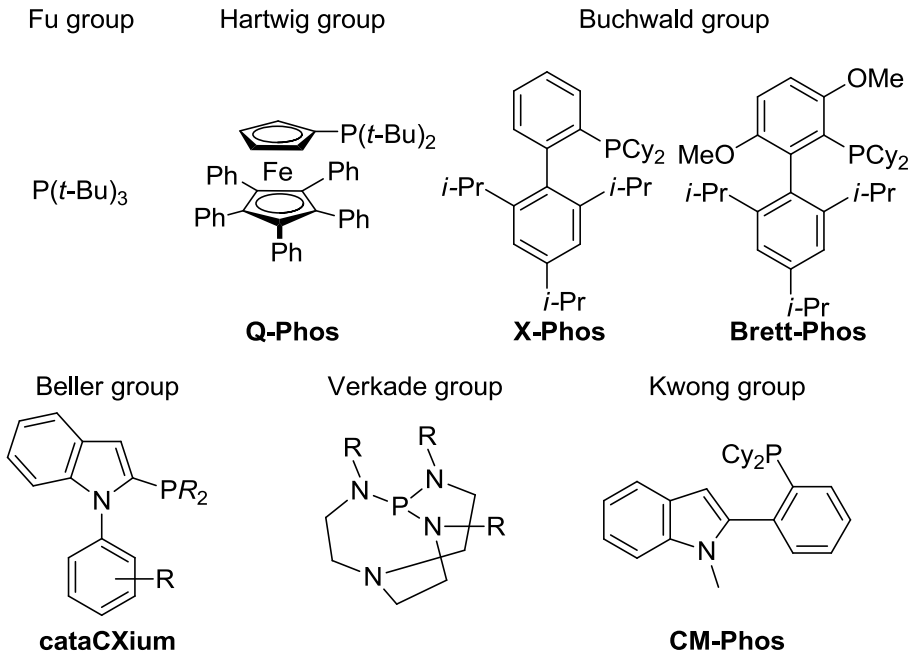
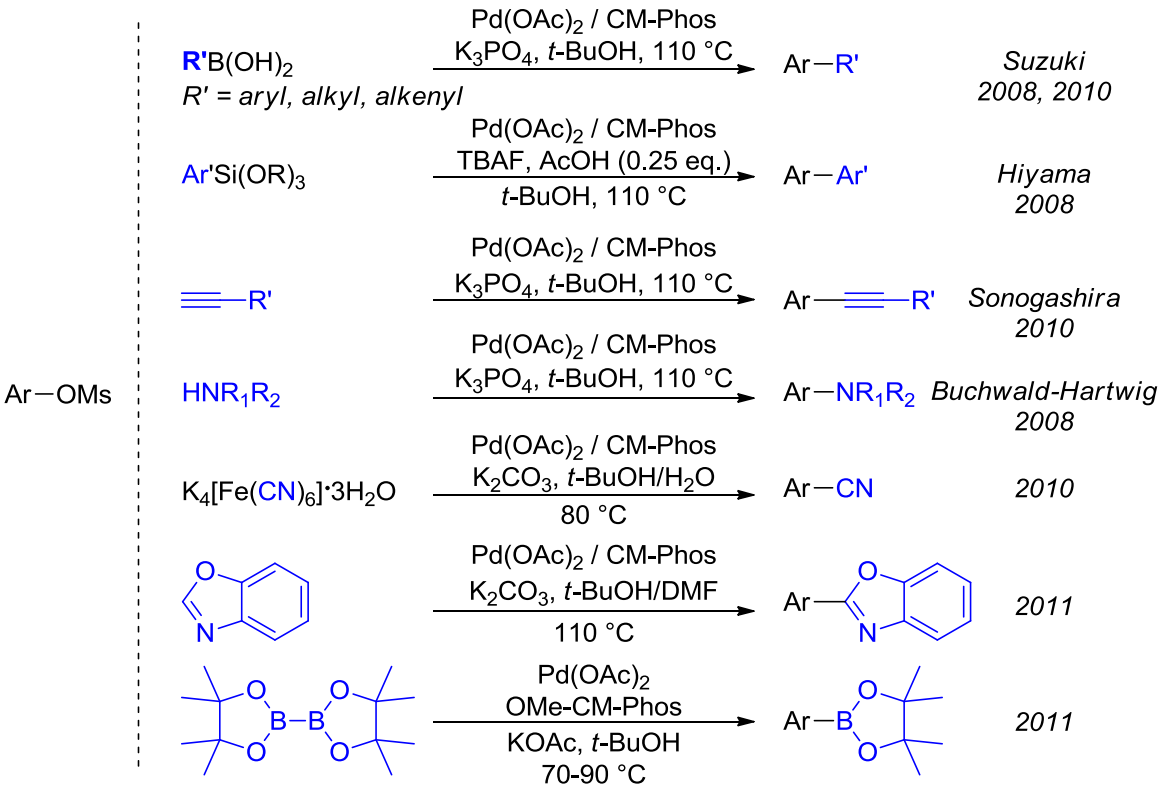


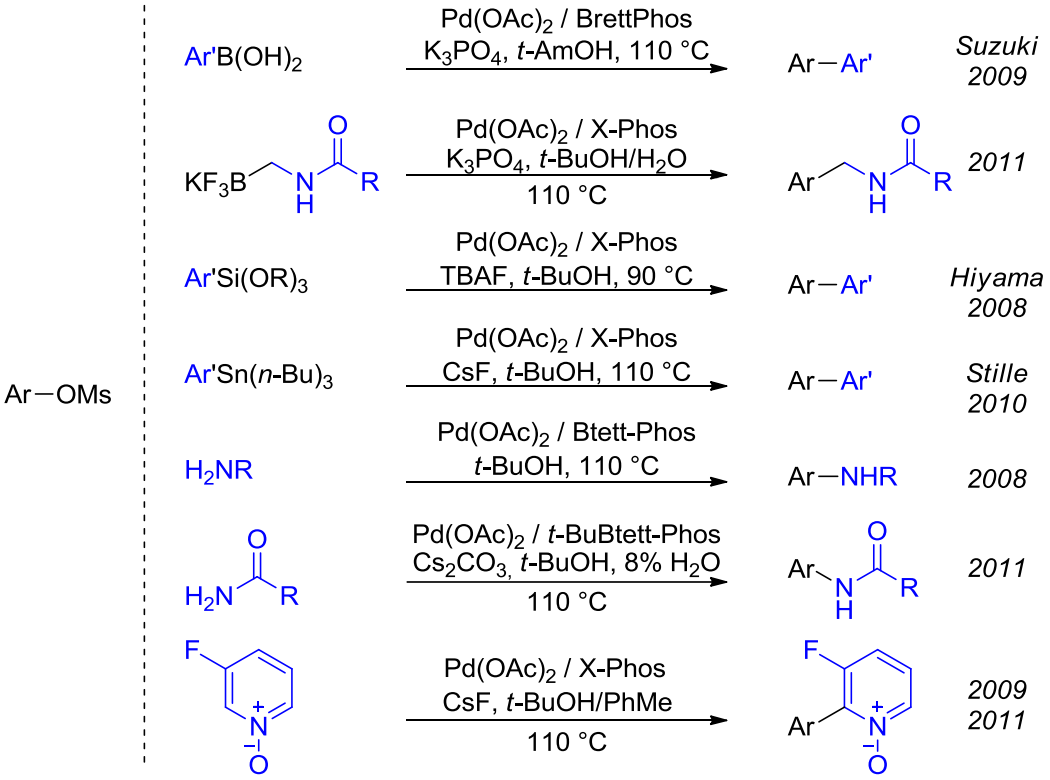
Figure 2. Recent developments on effective phosphine ligands.

In 2008, Kwong[18] reported the first general Pd-catalyzed Suzuki coupling of aryl mesylates by using an indolyl phosphine ligand CM-Phos. This catalyst system also proved amenable to other coupling reactions including Buchwald-Hartwig amination,[19] Sonogashira reaction,[20] Hiyama reaction,[21] cyanation,[22] CH arylation,[23] borylation (Scheme 6).[24]



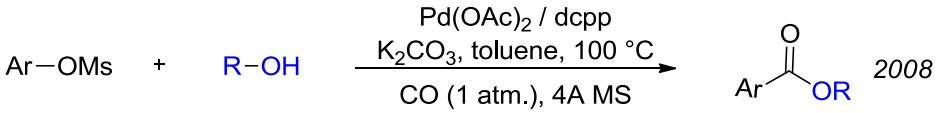
Scheme 6. CM-Phos as a versatile ligand for palladium in cross-couplings of aryl mesylates.

Palldium catalyst combined with Buchwald's ligands, namely, X-Phos and Brett-Phos (Scheme 7) also showed a high catalytic ability for the activation of aryl and alkenyl mesylates. In 2008, Wu reported the Hiyama coupling of aryl mesylates with aryl silanes, using a catalyst system consisting of $Pd(OAc)_2$ and X-Phos.[25] In 2009, Ackermann disclosed the first palladium-catalyzed direct arylation of heteroarenes using aryl sulphonates.[26] The catalyst system consisting of $Pd(OAc)_2$ and X-Phos allowed the smoothly coupling of 1,2,3-triazoles with aryl tosylates and a few eletron-deficient aryl mesylates. Replacing the heteroarenes with pyridine *N*-oxides, a range of aryl mesylates could be coupled giving the corresponding biaryls in moderate to good yields.[27] The combination of $Pd(OAc)_2$ and X-Phos also proved to be an efficient catalyst system for the Stille reaction of aryl mesylates.[28] In 2009, Buchwald disclosed that BrettPhos was also an excellent phosphine ligand for activating aryl mesylates in Suzuki-Miyaura coupling reactions.[29] Recently, Molander reported the first Pd-catalyzed C(sp2)–C(sp3) Suzuki-coupling of aryl- and heteroaryl mesylates using X-Phos.[30] In 2008, Buchwald et al. found that Brett-Phos ligand was highly effective for the palladium-catalyzed amination of aryl mesylates with primary amines.[31] Using the similar catalyst system, the first example of N-arylation of amides using aryl mesylates was also reported by Buchwald and co-workers in 2011.[32]



Scheme 7. Buchwald ligands for palladium in cross-couplings of aryl mesylates.

Whereas palladium-catalyzed carbonylation of aryl halides with carbon monoxide has been well documented, the first example of alkoxycarbonylation of aryl mesylates was developed by the research group of Buchwald recently using a catalyst system of $Pd(OAc)_2$ and a chelating ligand 1,3-bis(dicyclohexylphosphanyl)propane (dcpp) (Scheme 8).[33]



Scheme 8. Pd-catalyzed alkoxycarbonylation of aryl mesylates.

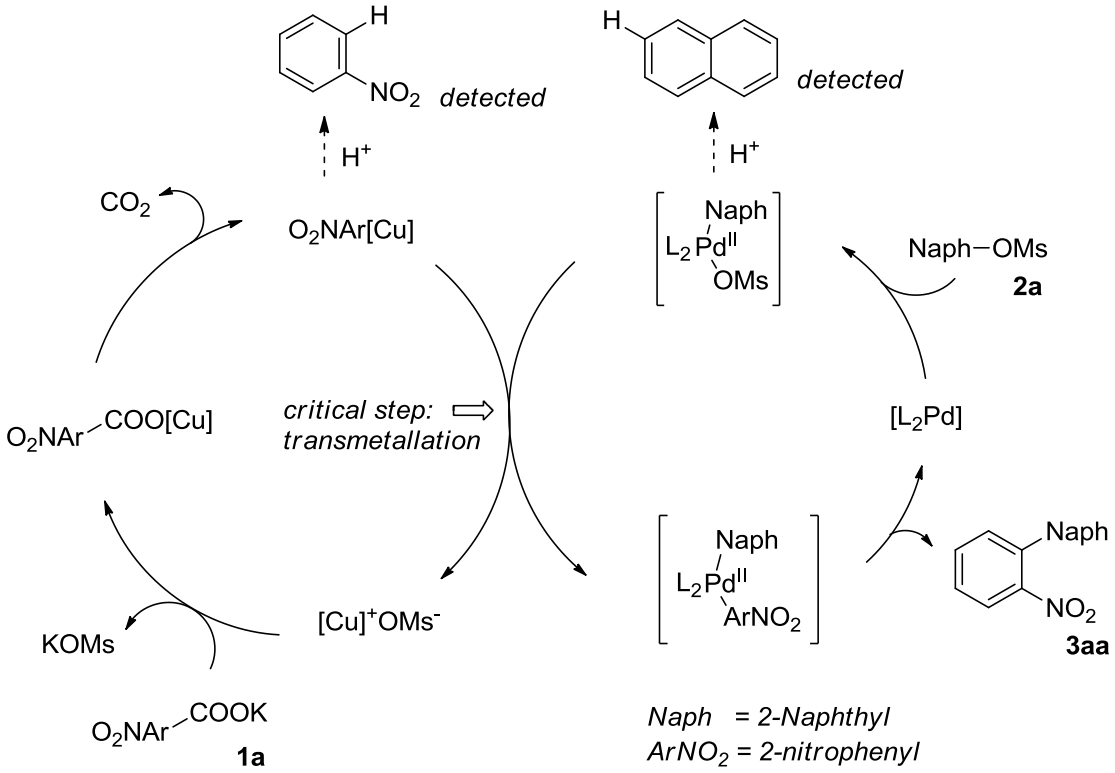
5.1.2 Mechanistic considerations of decarboxylative coupling of mesylates

In decarboxylative couplings, the use of mesylates is a particular challenge because transmetallations are known to proceed only from copper or silver to palladium but not to nickel, precluding the use of this catalyst metal.[6] Moreover, particularly electron-rich ligands, which might promote the oxidative addition of aryl/alkenyl mesylates onto palladium catalysts, tend to interfere with the decarboxylation catalyst.[4,5]

In search for an effective catalyst system for the desired decarboxylative arylation of mesylates, we chose the reaction of potassium *ortho*-nitrobenzoate (**1a**) with 2-naphthyl mesylate (**2a**) as a model. The desired biaryl (**3aa**) was formed only in trace amounts when

using phenanthroline/copper decarboxylation catalyst in combination with various palladium complexes, among them the state-of-the-art catalysts for other mesylate cross-couplings. Neither Kwong's CM-Phos, nor Buchwald's S-Phos or Brett-Phos systems proved to be effective (Table 1, entries 1-3).

In the coupling reaction using the CM-Phos ligand, significant amounts of protodecarboxylation products were observed, indicating that this ligand does not inhibit the decarboxylation step. As its ability to activate aryl mesylates is well-documented, we reasoned that the transmetallation from copper to palladium must be the critical step in the overall catalytic process depicted in Scheme 9.[34]



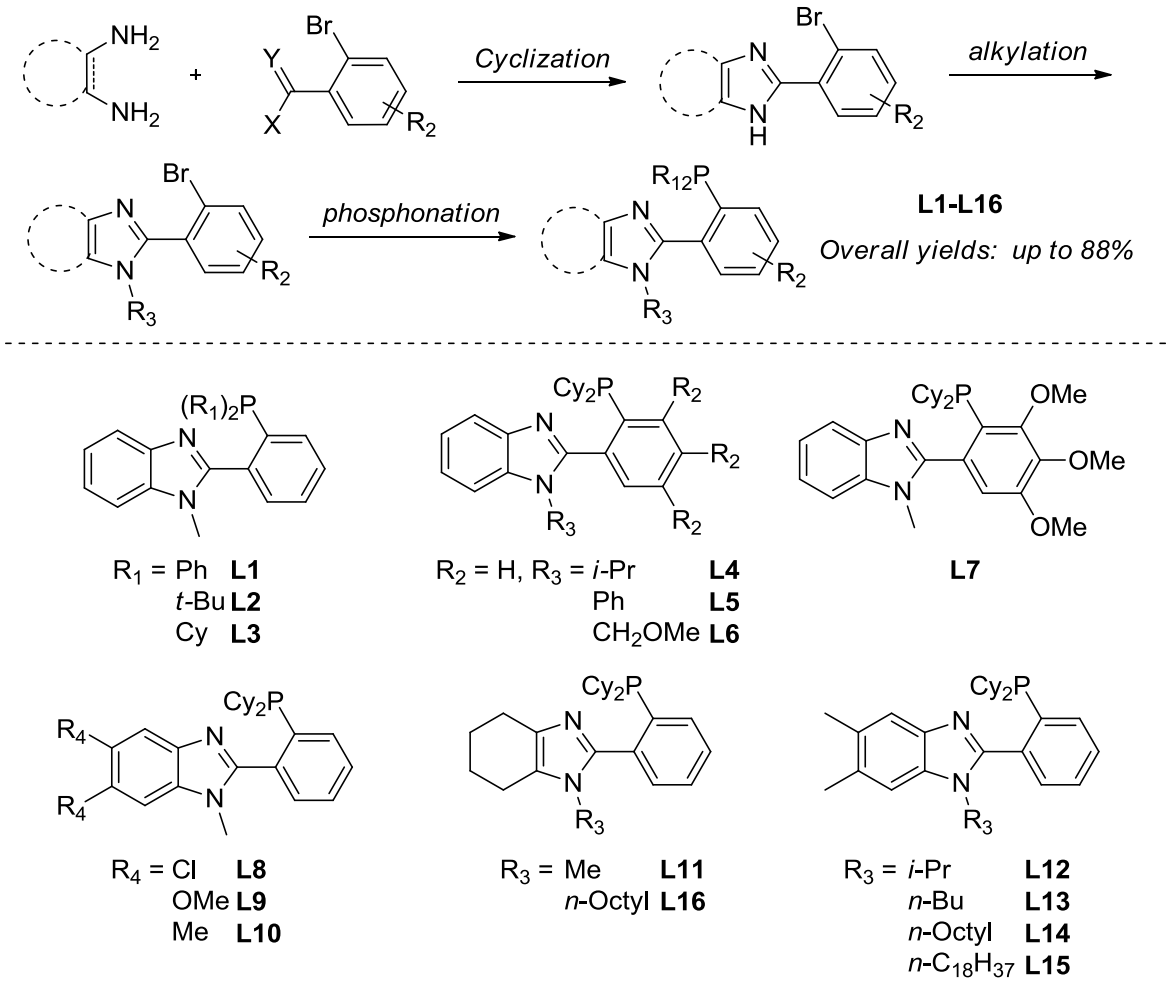
Scheme 9. Mechanism of the decarboxylative cross-coupling of aryl/alkenyl mesylates.

5.2 Results and discussion

5.2.1 Ligands designing and synthesis

In the Stille reaction, where the transmetallation step is often limiting, it has been found that the use of less strongly σ-donating tri-2-furylphosphine rather than triphenylphosphine enhances reaction rates by two orders of magnitude.[35] This ligand features a potentially coordinating heteroatom in close proximity to the phosphorus, which enhances π-back-

donation. It has also been reported that only one phosphine should be present in transmetallations to palladium.[36]



Scheme 10. Synthesis of imidazolyl phosphines.

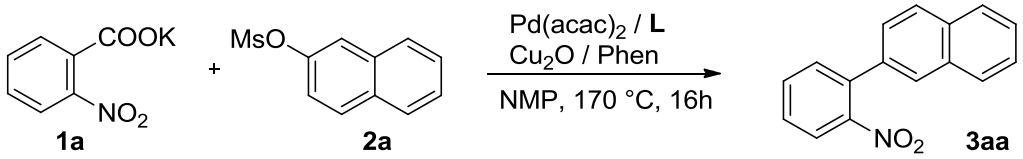
As a lead structure for ligand design, we thus chose a benzoimidazolyl skeleton rather than the indolyl system of CM-Phos. The syntheses of benzoimidazolyl phosphines were first reported by Altenbach.[37] Kwong recently used them in Suzuki couplings of aryl mesylates.[38] This ligand class should have a reduced σ-donor strength and provide an enhanced π-back-donation. Moreover, the second nitrogen atom in the imidazole moiety could also offer a weakly coordinating group that may aid an associative transmetallation step. Therefore we synthesized an array of imidazolyl phosphines via a sequence of cyclization, alkylation and phosphonation reactions (Scheme 10).

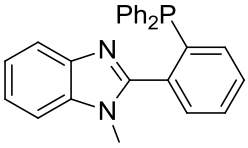
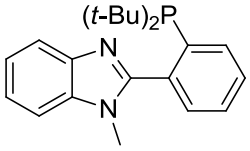
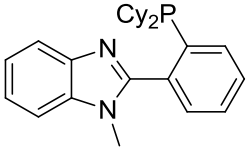
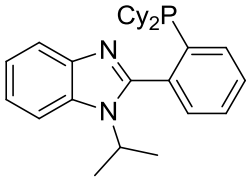
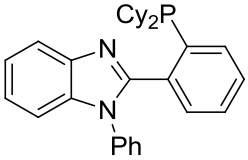
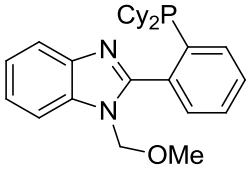
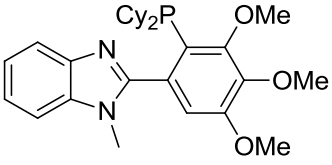
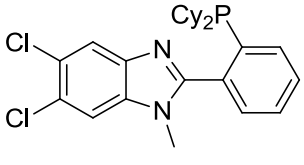
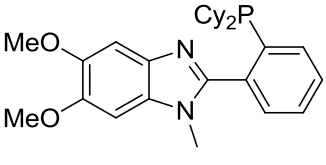
5.2.2 Development of decarboxylative cross-coupling of aryl mesylates

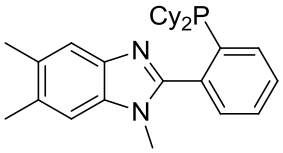
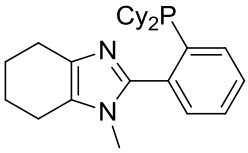
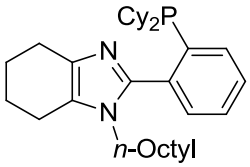
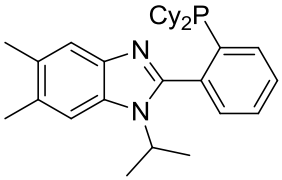
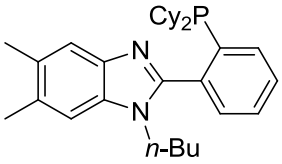
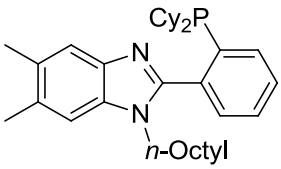
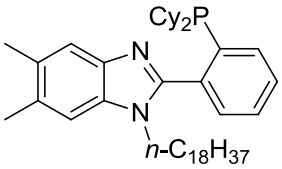
Having synthesized a series of imidazolyl phosphine ligands, we started our investigation with the evaluation of their activities in the decarboxylative cross-coupling reactions of aryl

mesylates. In the cross-coupling reaction of **1a** with **2a**, the new ligands **L1-15** directly proved to be effective (Table 1). A clear trend was visible for the influence of the phosphorus substituents (**L1-3**). Moderately bulky, electron-rich dicyclohexyl phosphine showed the highest activity (**L3**), whereas *tert*-butyl or phenyl groups were less effective. As substituent on the imidazole nitrogen (R^3), more sterically demanding groups such as phenyl (**L4**), isopropyl (**L5**) or methoxymethyl (**L6**) had a beneficial effect. When increasing the substitution on the phosphorus-bound aryl ring using alkoxy-groups in the manner of a Brett-Phos ligand (R^2=OMe, **L7**), the yields dropped. Increasing the electron density of the benzoimidazole nitrogens by methyl substituents (R^4) further improved the yields (**L10**). A tetrahydrobenzoimidazole fragment (**L8**), which would also have a high electron density on the nitrogens, was nearly as effective as **L10**. Further optimization of the *N*-substituents (R^3) on the final ligand core led to another step-up in the yields (**L13-16**), with *n*-octyl being the most effective residue.

Table 1. Study of ligand performance in the decarboxylative coupling of aryl mesylates.[a]



Ligand	Yield (%)[b]	Ligand	Yield (%)[b]
X-Phos	2	 L1	6
Brett-Phos	2		
CM-Phos	3[b]		
 L2	11	 L3	14
 L4	18	 L5	19
 L6	16	 L7	10
 L8	7	 L9	13

Ligand	Yield (%)[b]	Ligand	Yield (%)[b]
 L10	19	 L11	16
 L12	18	 L13	20
 L14	19	 L15	22
 L16	21		

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $Pd(acac)_2$ (5.0 mol%), **L** (7.5 mol%), Cu_2O (2.5 mol%), 1,10-phenanthroline (5.0 mol%), NMP (2.0 mL), 170 °C, 16 h; Yields determined by GC analysis using *n*-tetradecane as the internal standard. Cy = cyclohexyl, *i*Pr = isopropyl, *t*Bu = *tert*-butyl. [b] 50 % of protodecarboxylation product was observed.

The crystal structure of the optimal catalyst system, obtained from **L15** and $Pd(PhCN)_2Cl_2$, is shown in Figure 3.[39] The palladium center is coordinated with both amino and phosphino groups in a distorted square-planar geometry. Compared to the Pd-C_σ bond in the Pd-CM-Phos complex (1.986 Å),[19] the Pd-N bond is longer (2.0415 Å) confirming the targeted labile chelating coordination mode.

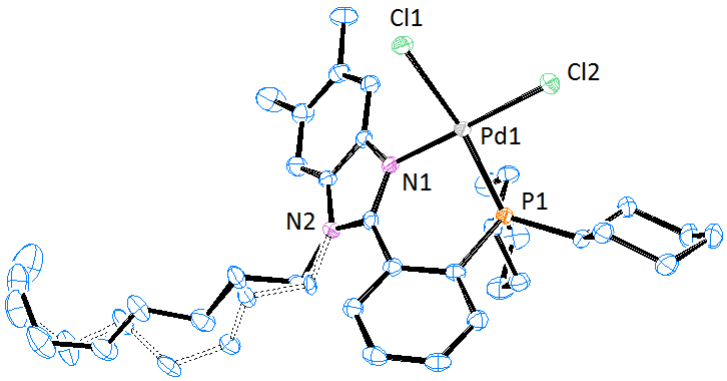
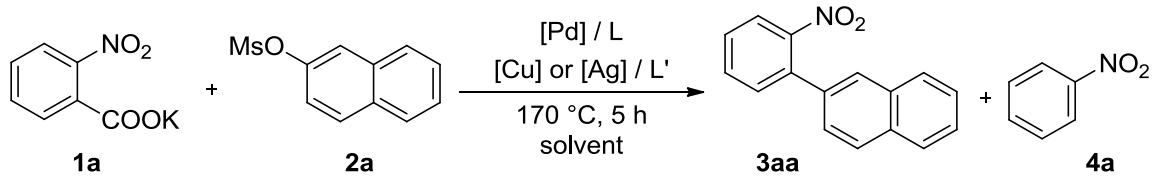


Figure 3. Crystal structure of **Pd-L15**. Hydrogen atoms haven been omitted for clarity. Selected bond distance [Å] and angles [°]: Pd(1)-N(1) 2.0415 (16), Pd(1)-P(1) 2.2393 (5), Pd(1)-Cl(1) 2.3796 (5), Pd(1)-Cl(2) 2.2897 (5), N(1)-Pd(1)-P(1) 82.97(5), Cl(2)-Pd(1)-Cl(1) 91.158(18).

The reaction conditions were systematically optimized with the goal of improving the yields by minimizing the competing protodecarboxylation and sulfonate cleavage with formation of 2-naphthol,[40] using the easy-to-handle, solid ligand **L10** (Table 2). A major step-up in yields to 68% was achieved by changing the solvent to a 1:3 mixture of NMP and mesitylene (entry 7). Changing to $Pd(dba)_2$ as the Pd-precursor, the protodecarboxylation was completely suppressed (entry 9). Further screening experiments confirmed that $Pd(dba)_2$ and Cu_2O are the most effective precatalysts (entries 8-13, 16-18). A silver catalyst is also compatible with the new catalyst system, but showed inferior catalytic activities (entries 14-15). Among the investigated nitrogen-containing ligands (entries 19-22), the best results were obtained with 3,4,7,8-tetramethyl-1,10-phenanthroline. Control experiments revealed that the decarboxylative coupling reaction requires both palladium and copper to proceed (entries 23-24). Under these optimized conditions, the use of ligand **L15**, a viscous oil, still made a positive difference. Up to 79% yield was obtained with the catalyst generated in the reaction solution (entry 25), and almost quantitative yields were obtained using the preformed complex **$PdCl_2$-L15** (entry 26). The reaction is easy to perform also in a laboratory microwave reactor (entry 27).

Having thus found an effective and easy-to-perform reaction protocol, we next investigated its scope. Various aromatic carboxylate salts were successfully coupled with 2-naphthyl mesylate using a catalyst system generated *in situ* from $Pd(dba)_2$ (5 mol%), **L15** (12 mol%), Cu_2O (2.5 mol%), 3,4,7,8-tetramethyl-1,10-phenanthroline (5 mol%) within 30 minutes at 180 °C in a laboratory microwave reactor.

Table 2. Optimization of the decarboxylative mesylate coupling.[a]



Entry	[Pd]	L	[Cu] / [Ag]	L'	solvent	Yield [%]	
						3aa	**4a**
1	$Pd(acac)_2$	L10	Cu_2O	1,10-phen	NMP	19	40
2	$Pd(acac)_2$	L10	Cu_2O	1,10-phen	DMF	9	37
3	$Pd(acac)_2$	L10	Cu_2O	1,10-phen	DMSO	0	50
4	$Pd(acac)_2$	L10	Cu_2O	1,10-phen	Diglyme	41	31
5	$Pd(acac)_2$	L10	Cu_2O	1,10-phen	Mesitylene	52	22
6	$Pd(acac)_2$	L10	Cu_2O	1,10-phen	NMP/Mes (1/1)	39	41

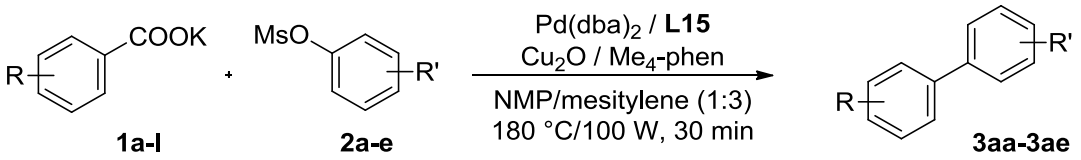
Entry	[Pd]	L	[Cu] / [Ag]	L'	solvent	Yield [%]	
						3aa	**4a**
7	$Pd(acac)_2$	L10	Cu_2O	1,10-phen	NMP/Mes (1/3)	68	25
8	$Pd(acac\text{-}F_6)_2$	L10	Cu_2O	1,10-phen	NMP/Mes (1/3)	67	22
9	$Pd(dba)_2$	L10	Cu_2O	1,10-phen	NMP/Mes (1/3)	75	0
10	$PdBr_2$	L10	Cu_2O	1,10-phen	NMP/Mes (1/3)	70	0
11	$PdCl_2$	L10	Cu_2O	1,10-phen	NMP/Mes (1/3)	73	0
12	$Pd(OAc)_2$	L10	Cu_2O	1,10-phen	NMP/Mes (1/3)	66	21
13	$Pd(PhCN)_2Cl_2$	L10	Cu_2O	1,10-phen	NMP/Mes (1/3)	70	29
14	$Pd(dba)_2$	L10	Ag_2CO_3	1,10-phen	NMP/Mes (1/3)	30	0
15	$Pd(dba)_2$	L10	Ag_2CO_3	2,6-lutidine	NMP/Mes (1/3)	20	0
16	$Pd(dba)_2$	L10	CuI[b]	1,10-phen	NMP/Mes (1/3)	75	0
17	$Pd(dba)_2$	L10	CuBr[b]	1,10-phen	NMP/Mes (1/3)	61	0
18	$Pd(dba)_2$	L10	CuCl[b]	1,10-phen	NMP/Mes (1/3)	70	0
19	$Pd(dba)_2$	L10	Cu_2O	NO_2-phen	NMP/Mes (1/3)	45	38
20	$Pd(dba)_2$	L10	Cu_2O	bathophen	NMP/Mes (1/3)	70	0
21	$Pd(dba)_2$	L10	Cu_2O	Bipy	NMP/Mes (1/3)	66	0
22	$Pd(dba)_2$	L10	Cu_2O	Me_4-phen	NMP/Mes (1/3)	77	0
23	$Pd(dba)_2$	L10	—	—	NMP/Mes (1/3)	0	0
24	—	—	Cu_2O	1,10-phen	NMP/Mes (1/3)	0	66
25	$Pd(dba)_2$	L15	Cu_2O	Me_4-phen	NMP/Mes (1/3)	79	0
26	**$PdCl_2$-L15**	—	**Cu_2O**	**Me_4-phen**	**NMP/Mes (1/3)**	**87**	**0**
27[c]	**$PdCl_2$-L15**	—	**Cu_2O**	**Me_4-phen**	**NMP/Mes (1/3)**	**90**	**0**

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), [Pd] (5.0 mol%), **L** (7.5 mol%), [Cu] or [Ag] (2.5 mol%), L' (5.0 mol %), 170 °C, 5 h; Yields determined by GC analysis using *n*-tetradecane as the internal standard. 1,10-phen = 1,10-phenanthroline; NMP = N-methyl pyrrolidine; Mes = mesitylene; Me_4-phen. = 3,4,7,8-tetramethyl-1,10-phenanthroline; NO_2-phen. = 5-nitro-1,10-phenanthroline; Bathophen = 4,6-diphenyl-1,10-phenanthroline; Bipy = 2,2´-bipyridine. [b] 5.0 mol%. [c] Microwave conditions: 180 °C / 100 W / 30 min.

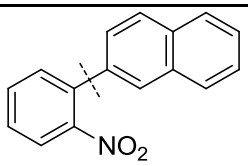
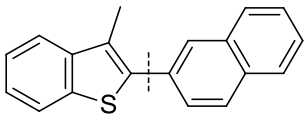
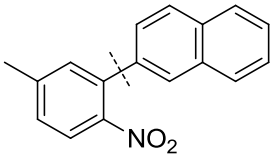
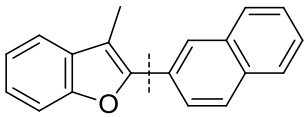
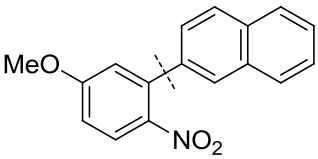
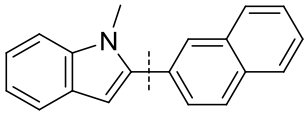
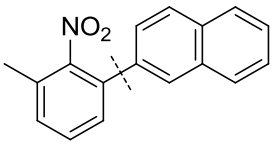
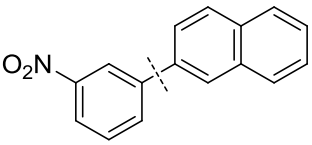
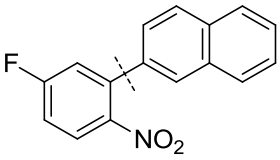
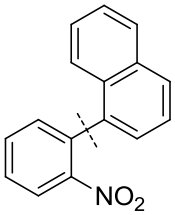
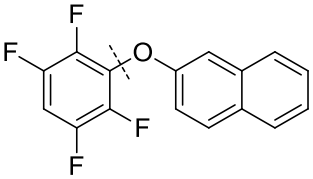
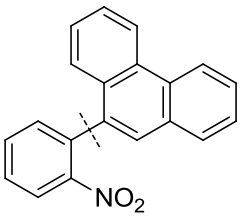
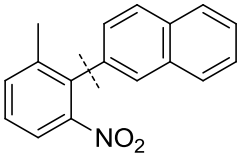
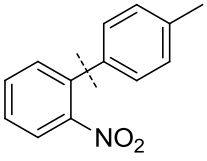
As illustrated in Table 3, various *ortho*-substituted arenecarboxylic acid salts were converted into the corresponding biaryls in high yields (**3aa**-**3ea**). Even the highly sterically demanding substrate **1g**, resulted in moderate yields. The *ortho*-methoxybezoate salt was also converted but in low yield (**3ha**). When pentafluorobenzoate salt (**1f**) was used, the desired product was obtained in only 5% yield, whereas the diaryl ether (**3fa'**) was obtained as a major product. We reasoned that this reaction probably proceeds *via* a nucleophilic substitution of the *para*-fluoride by *in situ* formed 2-naphthol,[41] followed by protodecarboxylation. Heterocyclic carboxylates were smoothly transformed into biaryls in moderate to high yields (**3ia**-**3la**).

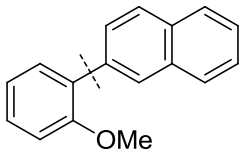
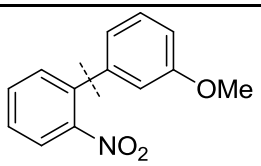
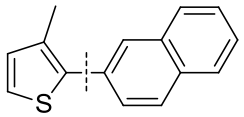
However, the *meta*-nitrobenzoate **1n** could not be converted and control experiments confirmed that the decarboxylation step was completely impeded by the phosphine ligand. Further experiments revealed that besides 2-naphthyl, other aryl mesylates could also be coupled, albeit in moderate yields (**3ab**-**3ae**).

Table 3. Decarboxylative coupling of aryl and heteroaryl carboxylates with aryl mesylates.[a]



1a-l **2a-e** **3aa-3ae**

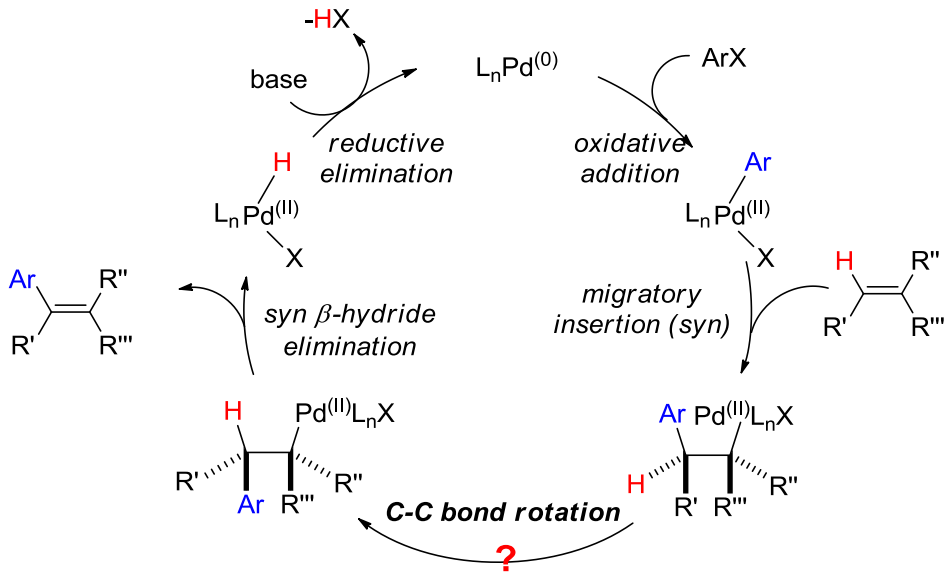
Product		Yield [%]	Product		Yield [%]
3aa		86	**3ja**		73
3ba		88	**3ka**		50
3ca		85	**3la**		62
3da		84	**3na**		0
3ea		80[b]	**3ab**		27
3fa′		43[b, c]	**3ac**		26[e,f]
3ga		50[b]	**3ad**		28[e,f]

Product		Yield [%]	Product		Yield [%]
3ha		17[d]	**3ae**		35[e,f]
3ia		45			

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), $Pd(dba)_2$ (5.0 mol%), **L15** (12.0 mol%), Cu_2O (2.5 mol%), 3,4,7,8-tetramethyl-1,10-phenanthroline (5.0 mol%), NMP (1.0 mL), mesitylene (3.0 mL), μW at 180 °C / 100 W / 30 minutes; isolated yields of two identical runs. [b] **1**/**2** ratio = 2:1. [c] 5 % of the decarboxylative product was detected by GC. [d] GC yield. [e] NMP/mesitylene = 1:5. [f] $Pd(acac)_2$ was used.

5.2.3 Development of decarboxylative cross-coupling of alkenyl mesylates

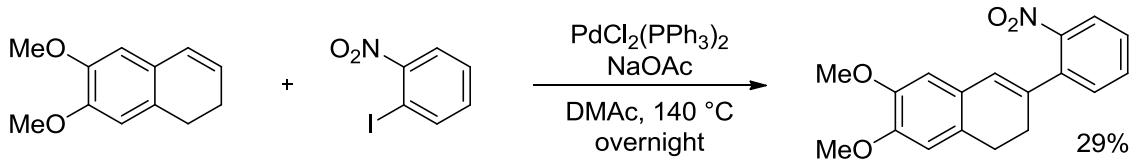
Since alkenyl mesylates are easily accessible by esterification of enolates in substantially greater structural diversity than alkenyl halides, their utilities in the cross-coupling reactions are of even higher interest than that of aryl mesylates. The corresponding aryl alkenes, especially the polysubstituted olefin products are otherwise difficult to access by Mizoroki-Heck reaction,[42] because the essential *cis*-Pd-H elimination pathway is often not feasible (Scheme 10).[43]



Scheme 10. Mechanism of the Mizoroki-Heck reaction.

This problem arises especially when the cyclic alkenes are used as the coupling partners. For instance, the coupling reaction of 1-iodo-2-nitrobenzene with 6,7-dimethoxy-1,2-

dihydronaphthalene proceed slowly even at 140 °C, resulting in 29 % of yield after 16 hours (Scheme 11).[44]

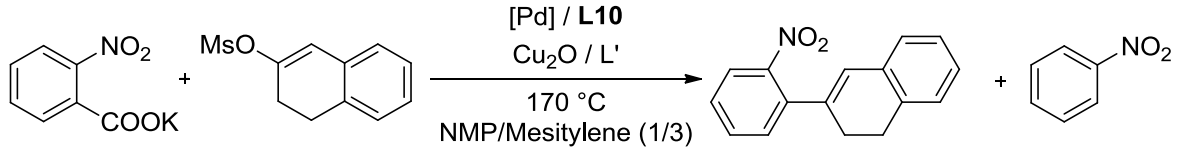


Scheme 11. Heck reaction of cyclic alkenes.

Common methods for the synthesis of polysubstituted olefins include carbonyl olefinations,[45] Suzuki reactions[46] and other coupling reactions.[47] One of the most efficient processes to access this substrate class is the Suzuki cross-coupling reaction of boron reagents with alkenyl halides or pseudohalides. However, these protocols suffer from the use of stoichiometric quantities of expensive and sensitive organometallic reagents.

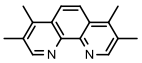
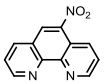
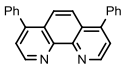
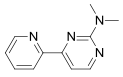
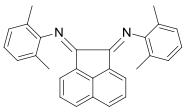
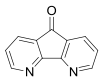
We were pleased to find that only minor adjustments were necessary to extend our new reaction concept to the alkenyl mesylates (Table 4). All the common palladium precursors showed high catalytic activities in the decarboxylative coupling reaction of aryl carboxylate **1a** with alkenyl mesylate **5a** (Table 3-13), and among them $Pd(OAc)_2$, $Pd(dba)_2$ and $[Pd(allyl)Cl]_2$ gave the best results. Further screening of the copper catalysts and the amine ligands revealed that Cu_2O combined with 2,2'-bipyridine remained as the most active decarboxylation catalyst.

Table 4. Optimization of the decarboxylative coupling reaction with alkenyl mesylate.[a]



1a **5a** **6aa** **4a**

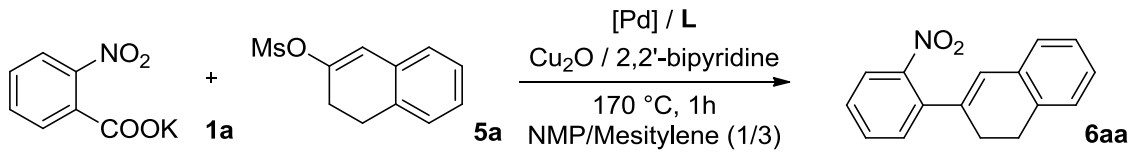
Entry	[Pd]	[Cu]	L'	Time (h)	Yield (%)	
					6aa	**4a**
1[b]	$Pd(dba)_2$	Cu_2O	1,10-phen	0.5	72	0
2	$Pd(dba)_2$	Cu_2O	1,10-phen	16	56	10
3	$Pd(dba)_2$	Cu_2O	1,10-phen	5	72	0
4	$Pd(acac)_2$	Cu_2O	1,10-phen	5	68	15
5	$Pd(acac\text{-}F_6)_2$	Cu_2O	1,10-phen	5	73	0
6	$Pd(dba)_2$	Cu_2O	1,10-phen	5	79	0
7	$PdBr_2$	Cu_2O	1,10-phen	5	64	15
8	$PdCl_2$	Cu_2O	1,10-phen	5	74	14
9	$Pd(OAc)_2$	Cu_2O	1,10-phen	5	79	0
10	$Pd(OTFA)_2$	Cu_2O	1,10-phen	5	78	0

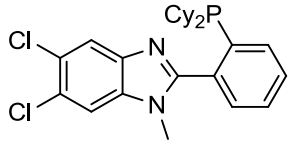
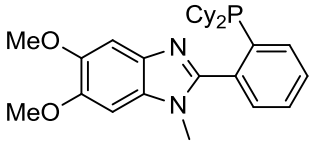
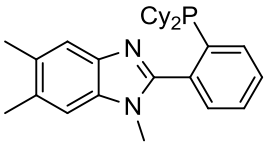
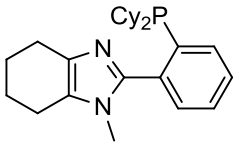
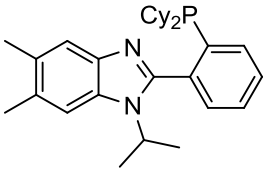
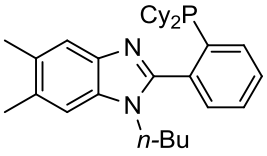
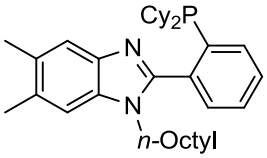
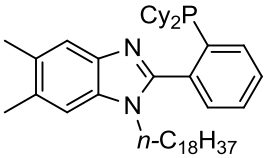
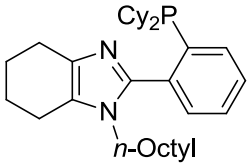
Entry	[Pd]	[Cu]	L'	Time (h)	Yield (%)	
					6aa	**4a**
11	$Pd(PhCN)_2Cl_2$	Cu_2O	1,10-phen	5	74	13
12	$Pd(COD)Cl_2$	Cu_2O	1,10-phen	5	75	14
13	$[Pd(allyl)Cl]_2$	Cu_2O	1,10-phen	5	78	0
14	$Pd(OAc)_2$	Cu_2O	1,10-phen	3	78	15
15	$Pd(OAc)_2$	Cu_2O	1,10-phen	1	80	15
16	$Pd(OAc)_2$	CuI [c]	1,10-phen	1	69	7
17	$Pd(OAc)_2$	CuBr [c]	1,10-phen	1	78	16
18	$Pd(OAc)_2$	CuCl [c]	1,10-phen	1	80	0
19	$Pd(OAc)_2$	$Cu(PPh_3)(Phen)Br$ [c]	—	1	60	19
20	$Pd(OAc)_2$	Cu_2O		1	69	23
21	$Pd(OAc)_2$	Cu_2O		1	79	15
22	$Pd(OAc)_2$	Cu_2O		1	76	19
23	**$Pd(OAc)_2$**	**Cu_2O**	**2,2'-bipyridine**	**1**	**85**	**0**
24	$Pd(OAc)_2$	Cu_2O		1	72	20
25	$Pd(OAc)_2$	Cu_2O		1	75	0
26	$Pd(OAc)_2$	Cu_2O		1	69	30
27	$Pd(OAc)_2$	Cu_2O		1	71	0

[a] Reaction conditions: **1a** (0.3 mmol), **5a** (0.45 mmol), [Pd] (5.0 mol%), **L10** (12.0 mol%), Cu_2O (2.5 mol%), L' (5 mol%), NMP (1.0 mL), mesitylene (3.0 mL), 170 °C. Yields determined by GC analysis using *n*-tetradecane as the internal standard. [b] Microwave conditions: 180 °C / 100 W / 30 min. [c] 5.0 mol%.

Other active imidazolyl phosphine ligands were also tested in this reaction, and **L8** with electron-withdrawing chloro-substituents on the benzoimidazolyl backbone was most effective as ligand for the palladium (Table 5). With the catalyst system generated *in situ* from $Pd(OAc)_2$/**L8** and Cu_2O/2,2-bipyridine, a broad array of arenecarboxylate salts were coupled with various alkenyl mesylates in high yields within only 1h (Table 6). Among the products are several that would be hard to access otherwise, for example tetrasubstituted olefins or vinyl arenes.

Table 5. Screening with ligands under optimal conditions.[a]



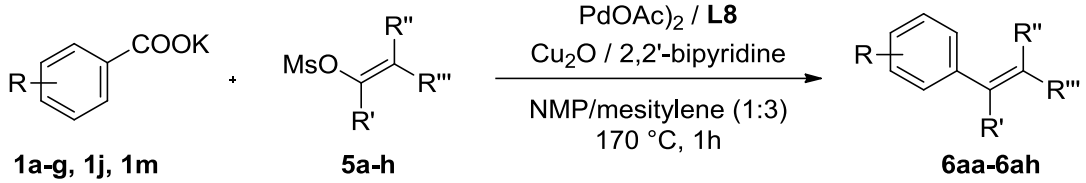
Ligand	Yield (%)	Ligand	Yield (%)
 L8	**90**	 L9	80
 L10	85	 L11	68
 L12	87	 L13	81
 L14	73	 L15	75
 L16	72		

[a] Reaction conditions: **1a** (0.3 mmol), **5a** (0.45 mmol), $Pd(OAc)_2$ (5.0 mol%), **L** (12.0 mol%), Cu_2O (2.5 mol%), 2, 2'-bypyridine (5 mol%), NMP (1.0 mL), mesitylene (3.0 mL), 170 °C, 1h. Yields determined by GC analysis using *n*-tetradecane as the internal standard.

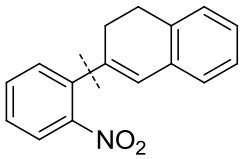
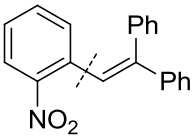
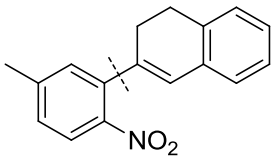
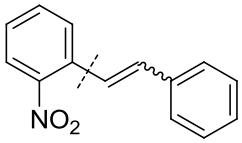
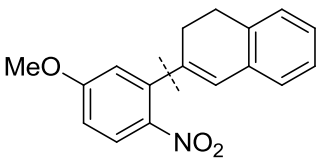
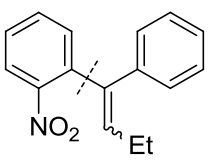
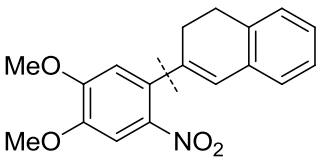
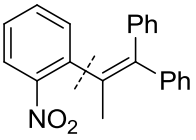
The scope of the decarboxylative coupling of alkenyl mesylates was shown in Table 6. An array of different aryl as well as heterocyclic carboxylates was successfully converted under the optimized conditions (**6aa**-**6ja**). Sterically demanding carboxylates (**1f**-**g**, **1j**) were also transferred into the corresponding products in low to moderate yields (**6fa**-**6ga**, **6ja**). The pentafluorobenzoate salt was smoothly coupled without any observation of the corresponding ether formation (**6fa**). The reaction is also broadly applicable with regard to the alkenyl mesylates. The most simple vinyl mesylate (**5g**) was also transferred into *ortho*-nitrostyrene in 54% yield (**6ag**). This might provide another economical and practical way to access such

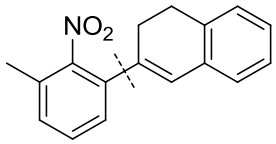
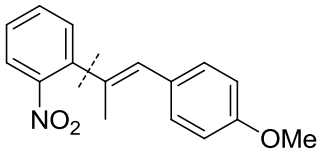
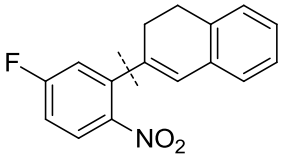
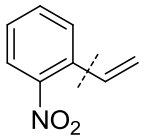
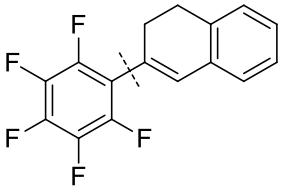
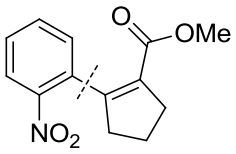
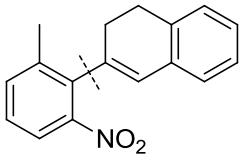
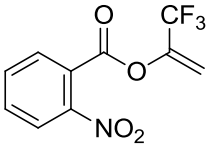
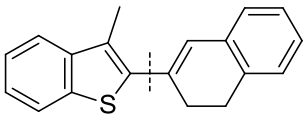
strong electron deficient styrenes. The main procedures for the synthesis of *ortho*-nitrostyrene include Suzuki or Stille coupling of special vinyl reagents, [48] Heck coupling, [49] semihyrogenation of alkynes,[50] and Wittig reaction.[51] These methods suffered from either low turnover frequencies or expensive and toxic reagents. Less sterically hindered vinyl mesylates such as **5b** and **5c** showed high activity towards the decarboxylative coupling (**6ab** and **6ac**), whereas the ratio of *E*- and *Z*-isomers of the stilbene was slightly increased after the reaction (**6ac**). However, when the relatively electron-deficient vinyl mesylate bearing trifluoromethyl substituent (**5i**) was employed in the optimal conditions, only the corresponding ester product was obtained in low yield (**6ai′**). Internal alkenyl mesylates regardless of the aryl-(**5d**) or alkyl-substituted olefins (**5e-f**) were smoothly converted in moderate to good yields (**6ad**-**6af**). Even conjugated alkenyl mesylates were converted in moderate yields (**6ah**). No experiments have yet been performed with stereo-isomerically pure alkenyl mesylates, but when starting from *E*/*Z* mixtures, it appears as if the ratio between *E* and *Z* configurated products increases slightly in the course of the reaction.

Table 6. Decarboxylative coupling of aryl and heteroaryl carboxylates with alkenyl mesylates.[a]



1a-g, 1j, 1m **5a-h** **6aa-6ah**

Product		Yield [%]	Product		Yield [%]
6aa		86	**6ab**		83
6ba		82	**6ac**		86[b]
6ca		84	**6ad**		40[c,d]
6ma		83	**6ae**		63

Product		Yield [%]	Product		Yield [%]
6da		85	**6af**		73
6ea		80	**6ag**		54[e]
6fa		22	**6ah**		21[f]
6ga		42	**6ai′**		21[e]
6ja		54			

[a] Reaction conditions: **1** (0.5 mmol), **5** (0.75 mmol), $Pd(OAc)_2$ (5.0 mol%), **L8** (12.0 mol%), Cu_2O (2.5 mol%), 2,2'-bypyridine (5.0 mol%), NMP (1.0 mL), mesitylene (3.0 mL), 170 °C, 1h; isolated yields of two identical runs. [b] *E*/*Z*-isomers = 2.8:1 (*E*/*Z*-isomers of starting material = 2.3:1) [c] **1**/**5** ratio = 2:1. [d] *E*/*Z*-isomers = 1:2 (*E*/*Z*-isomers of starting material = 1:3.2). [e] **1**/**5** ratio = 1:3. [f] **1**/**5** ratio = 1.5:1.

5.3 Conclusions

In summary, the use of customized imidazolyl phosphines for the first time allows the use of aryl and alkenyl mesylates in decarboxylative cross-coupling reactions. This is a decisive step in leading this relatively young reaction concept to synthetic maturity. The variation of the ligands allowed us to identify two complementary protocols for the coupling of aryl and alkenyl mesylates respectively. Both methods show high efficiencies and functional group tolerance. This important discovery will open up new opportunities for a rapid development in this field, although the first protocol is restricted to activated aryl mesylates. The coupling of multi-substituted alkenyl mesylates is of particular interest, as it provides a convenient access to polysubstituted olefins that are otherwise hard to synthesize. Further optimization of the catalyst system with the goal of increasing the substrate scope, lowering the reaction temperatures and performing fully stereo-retentive cross-couplings of isomerically pure alkenyl mesylates are still desirable.

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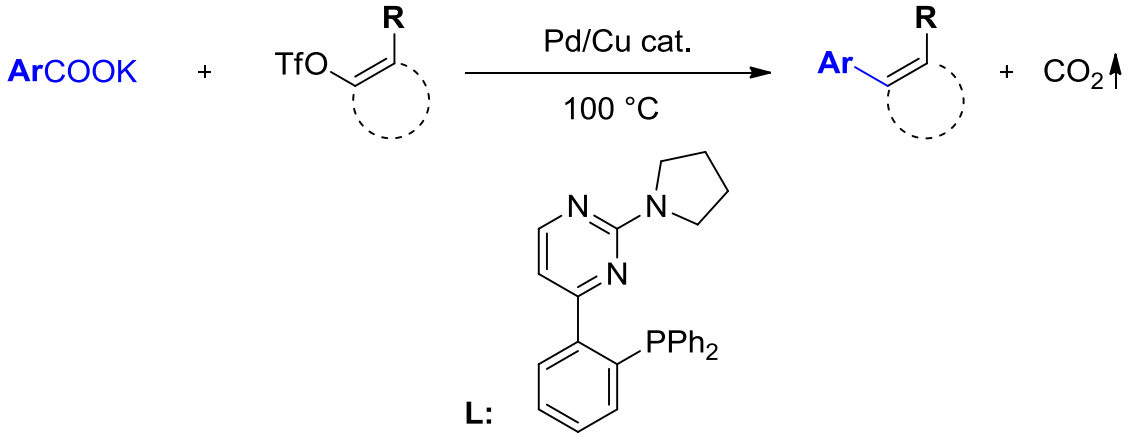
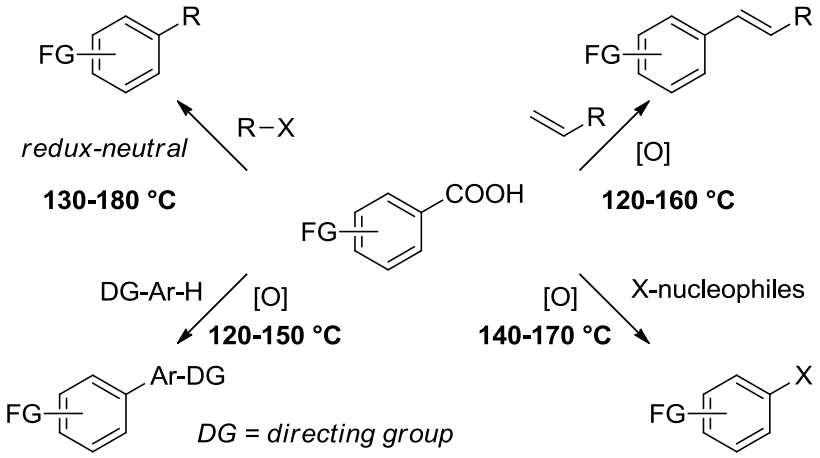
Chapter 6

Low-Temperature Decarboxylative Cross-Coupling Reactions Promoted by Customized Pyrimidinyl Phosphine Ligands



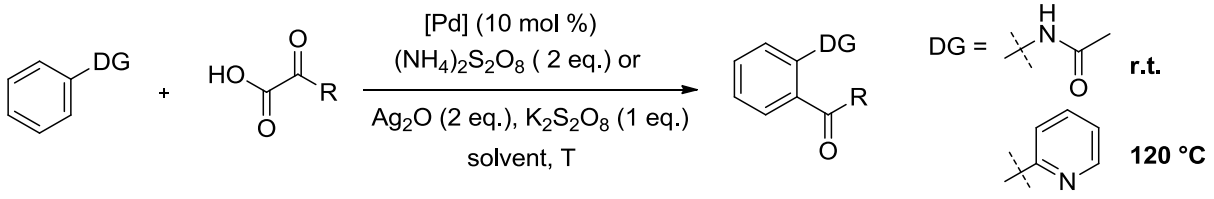
6.1 Introduction

Within the last decades, significant developments have advanced the decarboxylative cross-coupling reactions towards being powerful alternatives for regiospecific C-C and C-heteroatom bond formations.[1] Although substantial efforts made in the past several years strongly broaden the applications of decarboxylative cross-coupling reactions in a wide spectrum of coupling reactions, their practical applicability is still limited by relatively high reaction temperatures, especially in the case of redox-neutral process, which represents one of the most efficient and versatile methods for the C-C bond formations (Scheme 1).



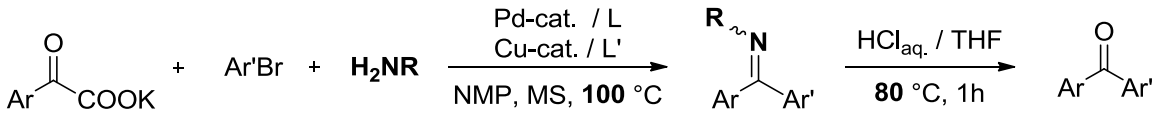
Scheme 1. Decarboxylative coupling reactions.

In oxidative decarboxylative cross-coupling reactions, due to the use of excessive oxidants, often Ag_2CO_3, which can also serve as a decarboxylation catalyst, the reaction temperatures could be somewhat reduced to around 120 °C. The only one exception involves the oxidative decarboxylative cross-coupling of *N*-phenylacetamides with oxocarboxylic acids (Scheme 2).[2] In the presence of stoichiometric amounts of a strong oxidant, $(NH_4)_2S_2O_8$, oxocarboxylic acids readily undergo decarboxylation at room temperature, generating acylating reagents for the *in situ* formed amide-direct palladacycle. However, when changing the directing group to pyridine, the similar decarboxylative dehydrogenative cross-couplings occurred at 120 °C.[3]



Scheme 2. Pd-catalyzed oxidative decarboxylative coupling of oxocarboxylic acids with arenes bearing directing groups.

In chapter 4, we have described a breakthrough to lower the reaction temperature by introducing a primary amine into the reaction mixture, in which case the activation barrier of decarboxylation step would be reduced by the *in situ* formed α-iminocarboxylates (Scheme 3).[4] This new strategy employed allows us to conduct the decarboxylative cross-coupling of oxocarboxylic acids with aryl halides at 100 °C, that is 70 °C lower than the formerly reported protocol, whereas it is only applicable to α-oxocarboxylic acids.[5]

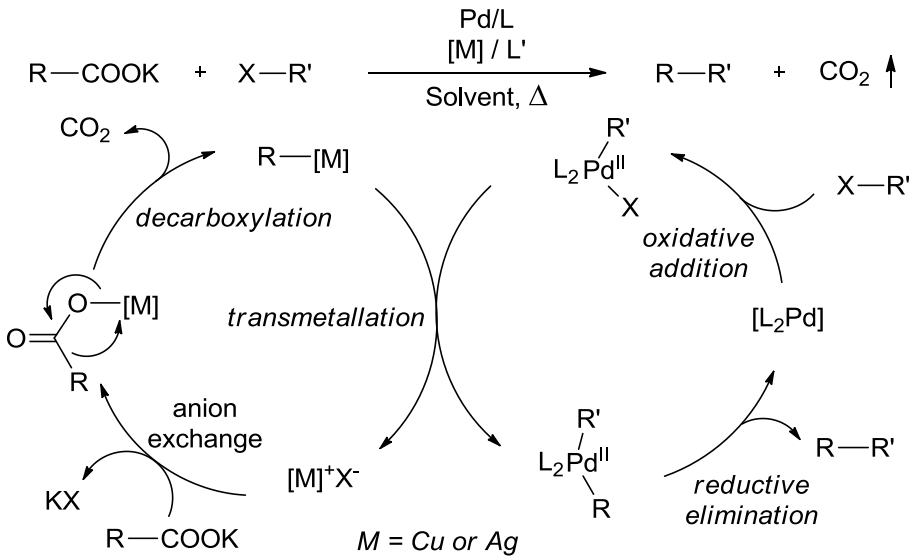


Scheme 3. Access to ketones and imines by Pd/Cu-catalyzed decarboxylative cross-couplings.

Although a few examples involving the low-temperature oxidative decarboxylative coupling reactions have been developed, they are only applicable to specific substrates, in which certain directing groups need to be pre-embeded. Moreover, all these methods suffer from using expensive oxidants in excessive quantities, resulting in low functional-group tolerance. By contrast, the redox-neutral decarboxylative processes normally require bimetallic catalysts in both catalytic quantities. In the above chapters, we have shown that redox-neutral decarboxylative cross-coupling reactions mediated by Pd/Cu[6] and Pd/Ag[7] bimetallic catalyst systems have a particularly broad substrate scope and high functional-group tolerance in both coupling partners. In this context, the key challenge currently facing us is to establish a new catalyst system that allows the redox-neutral decarboxylative cross-coupling reactions to proceed efficiently at much lower temperatures.

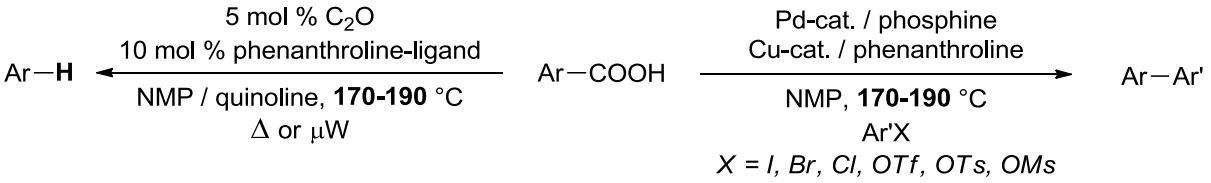
6.2 Mechanistic considerations

In redox-neutral decarboxylative coupling reactions, a copper or silver catalyst is required to release carbon nucleophiles by the extrusion of CO_2. These organometallic fragments are transmetallated to the palladium catalyst, where their couplings with aryl electrophiles take place (Scheme 4). The difficulties in the decarboxylation and transmetallation steps strongly influence the rate of the whole coupling process.



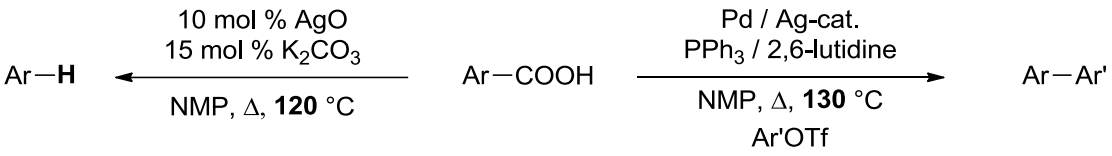
Scheme 4. Mechanism of the neutral-redox decarboxylative cross-coupling reactions.

During the mechanistic studies carried out in our group, we have demonstrated that the decarboxylation constitutes the rate determining step in most cases.[8] In the presence of a coper-phenanthroline complex, the decarboxylation of most of the aromatic carboxylic acids occurs efficiently at temperatues above 170 °C (Scheme 5), [9] and as a result the decarboxylative coupling process takes place normally at temperatures within a range of 170-190 °C.[10] The development of an effective decarboxylation catalyst appeared to be an obvious task with the goal of achieving low-temperature redox-neutral decarboxylative coupling reactions.



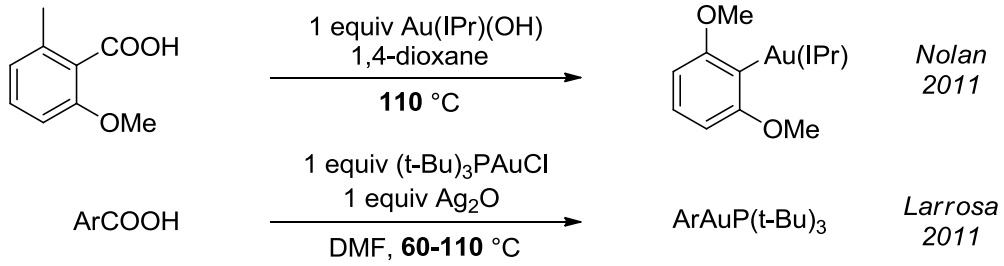
Scheme 5. Redox-neutral decarboxylative reactions using copper as decarboxylation co-catalysts.

DFT calculations led us to find a silver-based catalyst with improved protodecarboxylation activity at temperatures as low as 80 °C (Scheme 6).[11] A new catalyst system consisting of a silver co-catalyst with a palladium salt was thus developed, that allows the decarboxylative cross-coupling of aryl carboxylic acids with aryl triflates to occur readily at 130 °C, which is 50 °C higher than the protodecarboxylation in the case of the coupling reactions starting from 2-nitrobenzoic acid, indiating that the transmetallation step is crucial to the whole catalytic transformation.[12]



Scheme 6. Redox-neutral decarboxylative reactions using silver as decarboxylation co-catalysts.

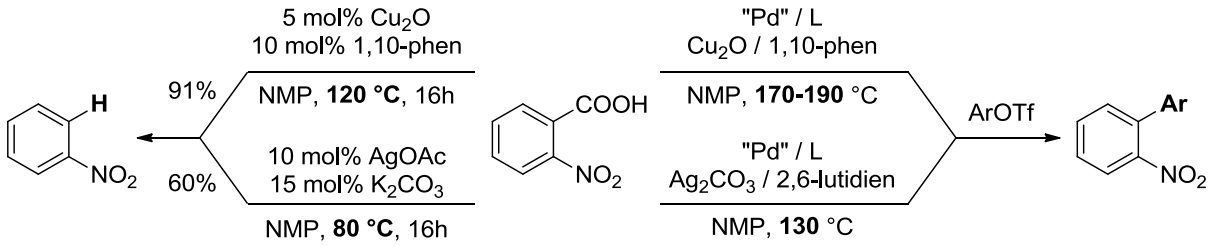
Our DFT calculations [13] also show that gold catalyst is even more effective for the protodecarboxylation compared to silver. Recently, this hypothesis was verified by the research groups of Nolan[14] and Larrosa (Scheme 7),[15] however, the resulting C–Au bond in the aryl gold intermediates is extremely strong to the extent that the transfer of these aryl gold species to other metal catalysts is greatly hampered. Palladium[16] and rhodium[17] could also facilitate the protodecarboxylation, albeit restricted to specific substrates such as polyfluoro- and dimethoxy-aryl carboxylic acids.



Scheme 7. Gold-catalyzed protodecarboxylation of aromatic carboxylic acids.

Although the Pd/Ag-catalyzed redox-neutral decarboxylative cross-coupling reactions could proceed at only 130 °C, all the attempts towards a further decline of reaction temperatures based on the improvement of decarboxylation catalyst have all failed so far. Our aim in this project is to develop a new catalyst system that allows efficient cross-couplings of (hetero)aryl carboxylic acids with aryl halides or pseudohalides at an unprecedentedly low reaction temperature.

In the presence of silver and coper catalysts, decarboxylation of 2-nitrobenzoic acid occurs readily at temperatues as low as 80 °C and 120 °C (Scheme 8), repectively. However, their efficient cross-coupling reactions with aryl halides or pseudohalides take place only when the reaction temperature reaches 130 °C for silver, and 170 °C for copper. These big differences again imply that the transmetallation step might be the actual rate determing step in the decarboxylative coupling reactions that start from 2-nitrobenzoic acid.[18] It is noteworthy that the difficulty of this step will, even be incressed at low reaction temperatures.[19]



Scheme 8. Protodecarboxylation and decarboxylative coupling of 2-nitrobenzoic acid.

Therefore, the solution to achieve low-temperature decarboxylative cross-couplings will not only lie in the development of more efficient decarboxylation catalysts, but also depends on the improvement of the coupling catalysts. A balance between the decarboxylation and transmetallation has to be established in such a way that both of these two steps would be facilitated at a low temperature.

Our investigation on the ligand effects in the transmetallction step in chapeter 5 indicates that the transmetallation step can be accelerated by employing a specific phosphine ligand that features a potentially coordinating heteroatom in close proximity to the phosphorus, which enchances π-back-donation. We envisage that a modification of such phosphine ligand by introducting a multi-nitrogen-donor moiety that could also offer a potentially coordinationg site to a copper catalyst would probably bring the two metal catalysts sufficiently close to each other, resulting in a positive impact on both decarboxylation and transmetallation processes (Figure 1).

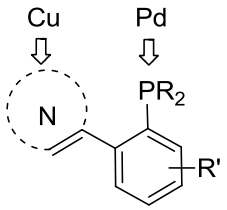


Figure 1. A potential ligand model for both decarboxylation and coupling catalysts.

In search of a potential candidate which would facilitate both decarboxylation and transmetallation, the pyrimidinyl phosphine ligands developed by the group of W. R. Thiel fullfill these criteria (Figure 2). These heterocyclic phosphines feature a pyrimidinyl moiety, containing multiple nitrogen donor atoms, along with a 2-heteroarylphenyl phospino group, which could coordinate to the copper and palladium atoms respectively. These new ligands have achieved highly catalytic activites for the Pd-catalyzed Suzuki-Miyaura cross-coupling of aryl boronic acids with aryl halides (Scheme 9).[20]

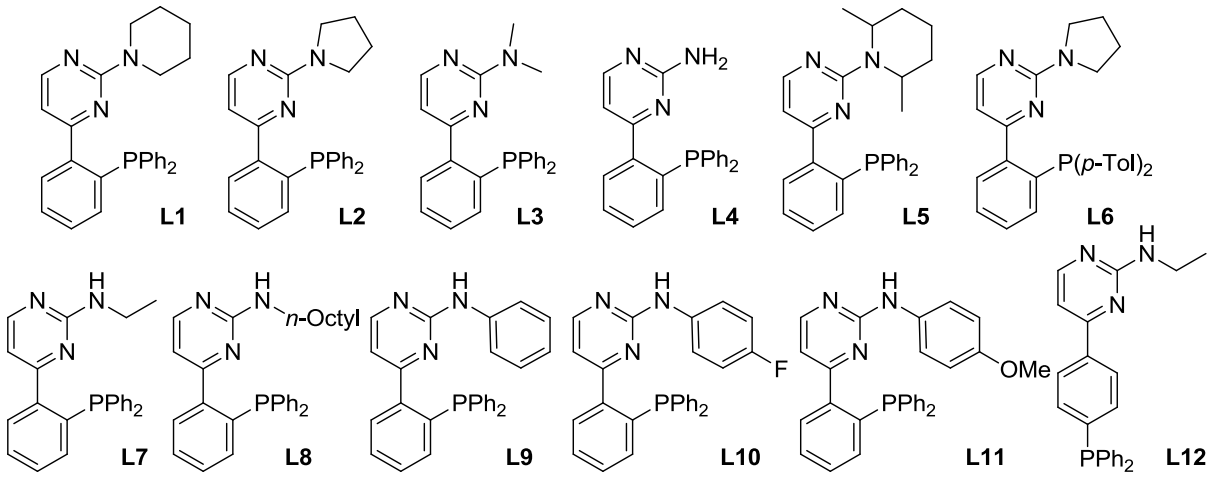
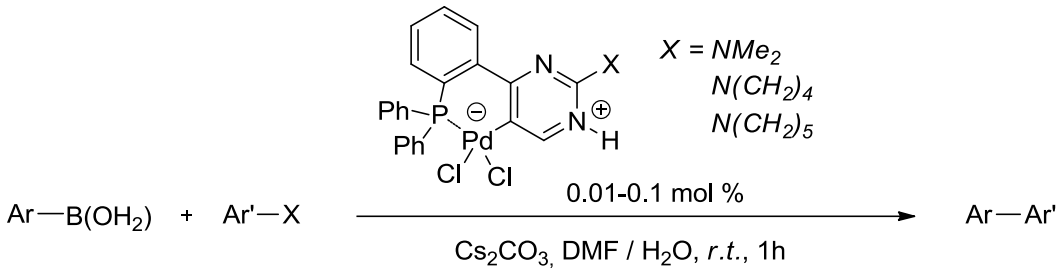


Figure 2. Pyrimidinyl phosphine ligands developed by Thiel.

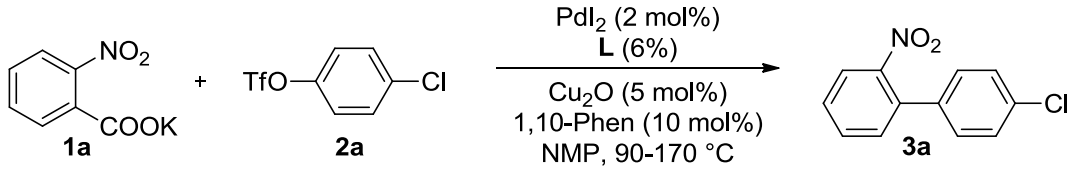


Scheme 9. Application of Thiel ligands in Suzuki-Miyaura reactions.

6.3 Results and discussion

We started our investigation by employing four typical Thiel phosphine ligands in the decarboxylative cross-coupling of 2-nitrobenzoate (**1a**) with 4-chlorophenyl triflate (**2a**) at different temperatures (Table 1). These pyrimidinyl phosphines showed highly catalytic activities comparable to the standard ligand P(*p*-Tol)$_3$ at elevated temperatures such as 150 °C and 170 °C. However, the differences become obvious when the reactions were conducted at 110 °C. Using the Thiel ligands, especially L2 and L3, we still observed quantative yields of the desired products, while only small quantities were detected when using P(*p*-Tol)$_3$. Below 90 °C, P(*p*-Tol)$_3$ was completely inactive, whereas L1-L3 could still give satisfactory results.

Table 1. Preliminary study on the decarboxylative coupling by using Thiel ligands.[a]



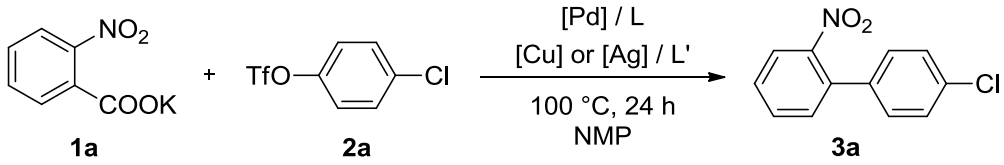
Entry	L	Yield (%)			
		90 °C (24h)	110 °C (24h)	150 °C (2h)	170 °C (2h)
1	P(*p*-Tol)$_3$	0	25	92	91
2	**L1**	27	69	90	88
3	**L2**	21	97	85	85
4	**L3**	18	92	95	95
5	**L4**	0	37	46	57

[a] Reaction conditions: 0.5 mmol of potassium carboxylate, 1 mmol of triflate, 5 mol% Cu_2O, 10 mol% 1,10-phenanthroline, 2 mol% PdI_2, 6 mol% L, 2.0 mL of NMP, 150 °C, 2 h; 170 °C, 1 h, GC yield without calibration.

The fact that the decarboxylative cross-coupling of 2-nitrobenzoate with 4-chlorophenyl triflate readily occurs at temperatures as low as 90 °C encouraged us to further optimize the reaction conditions at 100 °C (Table 2). This transformation could still undergo slowly when the 1,10-phenanthroline was excluded (entries 5-7), while the reaction was completely inhibited when the preformed copper complex [CuPhenPPh$_3$Br] was used instead of Cu_2O (entries 8-10). These results indicate that there is no fast ligand exchange within the reaction mixture. The real decarboxylation catalyst involves a copper complex which probably contains both 1,10-phenanthroline and the pyrimidinyl phosphine ligands.

The ratio of the two substrates is crucial for the reaction, and the yield was increased by using an excessive amount of benzoate **1a** (Table 2, entries 12-13). Other pyrimidinyl phosphines were also investigated for the catalytic reaction (entries 14-20). Yields were much lower when using the sterically congested ligand L5 (entry 14). All ligands containing an NH group turned out to be less effective than the ones bearing tertiary amino nitrogen atom (entries 15-19). However, among these secondary amino substituted phosphines, the electron-rich ones (entries 15-16, 19) showed higher catalytic activities compared to those ligands containing electron-withdrawing groups (entries 17-18). Silver co-catalysts for the decarboxylation were also compatible with these new ligands, but are less effective (entries 21-22). Changing PdI_2 to Pd(acac)$_2$ led to further improved results (entries 23-24), while replacing the phenyl substituent in the phosphino moiety by a *p*-tolyl group did not significantly affect the observed yield (entry 24).

Table 2. Optimization of the low-temperature decarboxylative cross-couplings.[a]



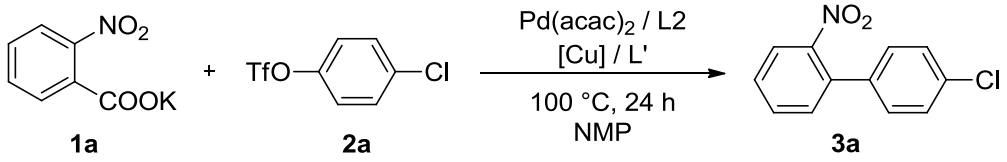
Entry	[Pd]	L	[Cu] / [Ag]	L'	Yield [%]
1	PdI_2	P(*p*-Tol)$_3$	Cu_2O	1,10-phen	16
2	PdI_2	L1	Cu_2O	1,10-phen	37
3	PdI_2	L2	Cu_2O	1,10-phen	40
4	PdI_2	L3	Cu_2O	1,10-phen	30
5	PdI_2	L1[b]	Cu_2O	—	20
6	PdI_2	L2[b]	Cu_2O	—	20
7	PdI_2	L3[b]	Cu_2O	—	11
8	PdI_2	L1[b]	[$CuPhenPPh_3Br$][c]	—	0
9	PdI_2	L2[b]	[$CuPhenPPh_3Br$][c]	—	0
10	PdI_2	L3[b]	[$CuPhenPPh_3Br$][c]	—	0
11	PdI_2	P(*p*-Tol)$_3$	Cu_2O	1,10-phen	23
12	PdI_2	L1	Cu_2O	1,10-phen	60
13	PdI_2	L2	Cu_2O	1,10-phen	65
14	PdI_2	L5	Cu_2O	1,10-phen	5
15	PdI_2	L7	Cu_2O	1,10-phen	37
16	PdI_2	L8	Cu_2O	1,10-phen	48
17	PdI_2	L9	Cu_2O	1,10-phen	29
18	PdI_2	L10	Cu_2O	1,10-phen	26
19	PdI_2	L11	Cu_2O	1,10-phen	45
20	PdI_2	L12	Cu_2O	1,10-phen	21
21	$PdCl_2$[d]	L1[e]	Ag_2CO_3	2,6-lutidine[f]	41
22	$PdCl_2$[d]	L2[e]	Ag_2CO_3	2,6-lutidine[f]	18
23	$Pd(acac)_2$	L2	Cu_2O	1,10-phen	82
24	$Pd(acac)_2$	L6	Cu_2O	1,10-phen	77

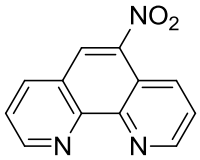
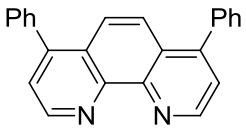
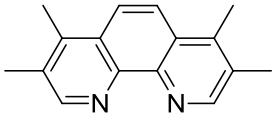
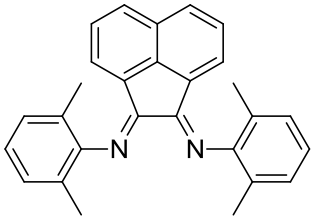
[a] Reaction conditions: **1a** / **2a** = 1:1.5 (entries 1-10), **1a** / **2a** = 1:1.5 (entries 11-23), [Pd] (2.0 mol%), L (6.0 mol%), [Cu] or [Ag] (5.0 mol%), L' (10.0 mol%), NMP (2.0 mL), 100 °C, 24 h; Yields determined by GC analysis using *n*-tetradecane as the internal standard. 1,10-phen = 1,10-phenanthroline; NMP = N-methyl pyrrolidine. [b] 15.0 mol%. [c] 10.0 mol%. [d] 3.0 mol%. [e] 9.0 mol%. [f] 20.0 mol%.

We next investigated the influence of the decarboxylation co-catalysts on the low-temperature decarboxylative cross-coupling process (Table 3). Different copper catalyst precursors, along

with the common chelating nitrogen ligands were screened under the preliminarily optimized conditions. CuBr showed a catalytic activity similar to Cu_2O (entry 3), while CuCl was less effective (entry 2). All the preformed copper complexes gave rather low yields, presumably due to the lack of the coordination sites for the pyrimidinyl phosphine ligands (entries 4-6). As for the tested chelating nitrogen ligands, the phenanthroline type showed higher activities (entries 7-10). However, ligands containing strong electron withdrawing groups such as NO_2 led to extremely poor yield (entry 7).

Table 3. Screening of copper sources and their supporting ligands.[a]

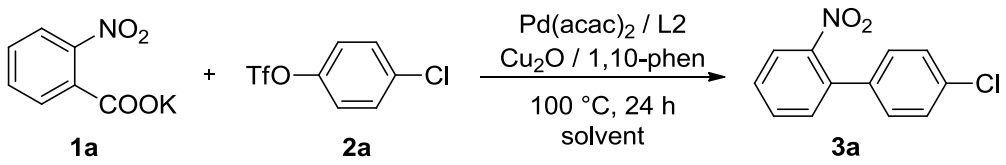


Entry	[Cu]]	L’	Yield [%]
1	Cu_2O	1,10-phen	82
2	CuCl	1,10-phen	60
3	CuBr	1,10-phen	80
4	$[CuPhenPPh_3Cl]$[b]	—	29
5	$[CuPhenPPh_3Br]$[b]	—	20
6	$[CuPhen(PPh_3)_2NO_2]$[b]	—	15
7	Cu_2O		9
8	Cu_2O		72
9	Cu_2O		66
10	Cu_2O		17

[a] Reaction conditions: **1a** / **2a** = 1:1.5, $Pd(acac)_2$ (2.0 mol%), L2 (6.0 mol%), [Cu] (5.0 mol%), L’ (10.0 mol%), NMP (2.0 mL), 100 °C, 24 h; Yields determined by GC analysis using *n*-tetradecane as the internal standard. [b] 10.0 mol%.

Several commonly used solvents for decarboxylative cross-couplings have also been employed in our low-temperature process (Table 4). The unpolar solvent mesitylene was not compatible with this transformation due to the poor solubility of benzoate (entry 2), whereas the introduction of NMP could dramatically improve the yields (entries 4-5). Other more polar solvents such as quinoline, DMF, DMSO and diglyme could be used for the catalytic reaction, albeit resulting in lower yields (entries 3, 6-8). The fact that the coupling reaction could even take place with moderate yields in the presence of small quantities of water indicates that the transmetallation step is greatly facilitated by the new pyrimidinyl phosphine ligands, so that the hydrolytic cleavage of the aryl copper species was suppressed (entry 9).

Table 4. Screening of solvent.[a]



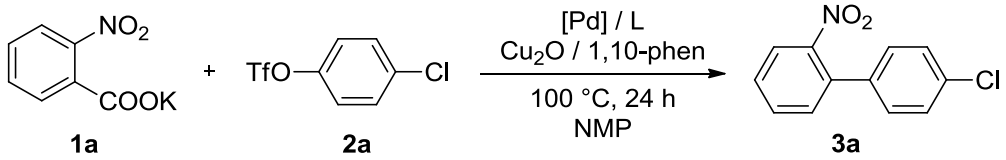
Entry	Solvent	Yield [%]
1	NMP	82
2	mesitylene	0
3	quinoline	57
4	NMP / mesitylene (1 / 2)	8
5	NMP / mesitylene (2 / 1)	68
6	NMP / DMF (3 / 1)	73
7	NMP / DMSO (3 / 1)	67
8	NMP / diglyme (3 / 1)	53
9	NMP[b]	60

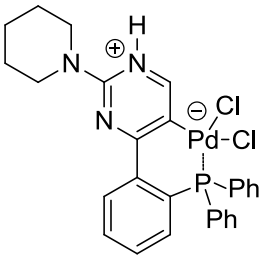
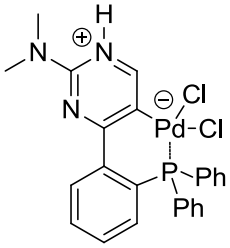
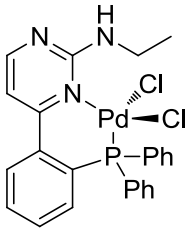
[a] Reaction conditions: **1a** / **2a** = 1:1.5, $Pd(acac)_2$ (2.0 mol%), L2 (6.0 mol%), Cu_2O (5.0 mol%), 1,10-phenantrholine (10.0 mol%), NMP (2.0 mL), 100 °C, 24 h; Yields determined by GC analysis using *n*-tetradecane as an internal standard. [b] 2 equivalents of water were added to the reaction mixture.

In order to shed more light on the mechanism of this low-temperature decarboxylative coupling reaction, we tested the reaction with preformed palladium complexes prepared by Dr. Saeid Farsadpour from the group of Prof. Thiel (Table 5). These palladium complexes have proved to be efficient for the Suzuki-Miyaura coupling of arylbronic acids with aryl halides even at room temperature. When our reactions were conducted using palladium precursors and phosphine ligands separately, a clear trend could be perceptible: L1 > L3 > L7 (entries 1-3). However, this tendency was completely lost when the preformed palladium complexes

were used under the same reaction conditions, and only traces of the desired products were detected (entries 4-6). These results further imply that the new pyrimidinyl phosphine ligands are probably part of a complicated complex which bridges palladium and copper species.

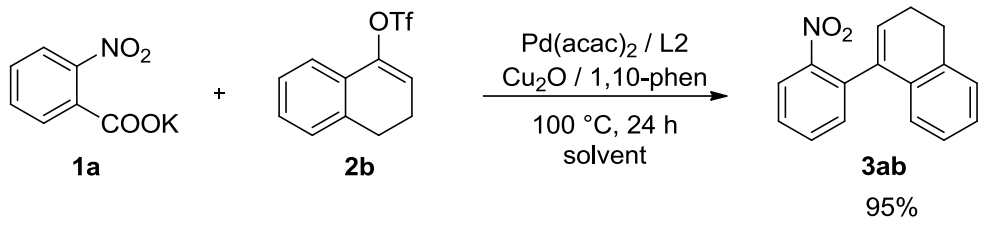
Table 5. Control experiments with different Pd complexes as catalysts.[a]



Entry	[Pd]	L	[Cu]]	L'	Yield [%]
1	$PdCl_2$	L1	Cu_2O	1,10-phen	79
2	$PdCl_2$	L3	Cu_2O	1,10-phen	40
3	PdI_2	L7	Cu_2O	1,10-phen	37
4	 **$PdCl_2$-L1**	—	Cu_2O	1,10-phen	10
5	 **$PdCl_2$-L3**	—	Cu_2O	1,10-phen	9
6	 **$PdCl_2$-L7**	—	Cu_2O	1,10-phen	9

[a] Reaction conditions: **1a** / **2a** = 1:1.5, [Pd] (2.0 mol%), L (6.0 mol%), [Cu] (5.0 mol%), L' (10.0 mol%), NMP (2.0 mL), 100 °C, 24 h; Yields determined by GC analysis using *n*-tetradecane as the internal standard.

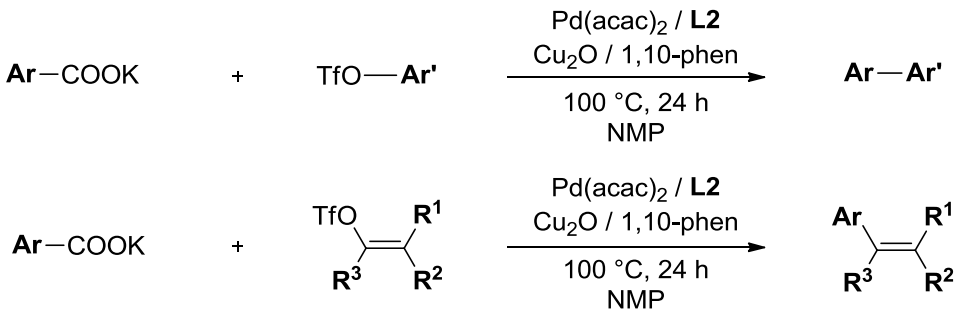
The new catalyst system is not restricted to aryl triflates. The internal vinyl triflate 2b was also smoothly converted into the corresponding product in quantative yield (Scheme 10).



Scheme 10. Decarboxylative cross-coupling of benzoate with vinyl triflate.

6.4 Conclusions and outlook

In summary, we have developed a new catalyst system that for the first time allows the decarboxylative coupling at only 100 °C, which is 70 °C lower than the standard process. A new class of pyrimidinyl phosphine ligands developed by the group of Thiel plays a prominent role in the low-temperature process, in which a complicated Pd/Cu bimetallic complex bridged by the ligand might be formed. Several preformed palladium complexes containing the new ligands were employed in the coupling reactions, albeit resulting in extremely low yields. These control experiments further imply that a complicated Pd-Cu complex bridiging by the pyrimidinyl phosphines is probably formed in the reaction. After systematic optimization of the reaction conditions, the decarboxylative cross-coupling of 2-nitrobenzoate with 4-chlorophenyl triflate could readily occur at 100 °C, forming the corresponding biaryl in almost quantative yield. Moreover, the optimal conditions are also applicable to vinyl triflates. This is of great interest, since the alkenyl triflates are accessible in broader diversity than the corresponding halides. The full investigation of a wide range of (hetero)aryl carboxylic acids along with aryl and alkenyl triflates is subject to research in our group (Scheme 10).



Scheme 10. Decarboxylative coupling of (hetero)aryl carboxylates with aryl / alkenyl triflates.

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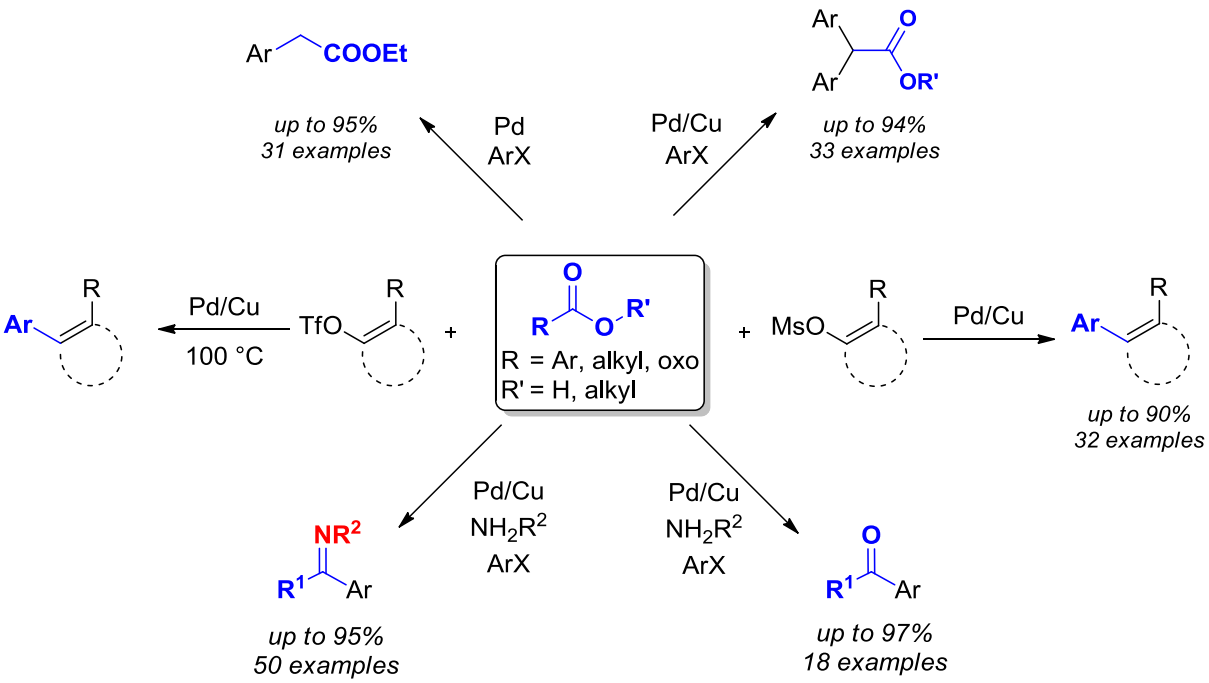
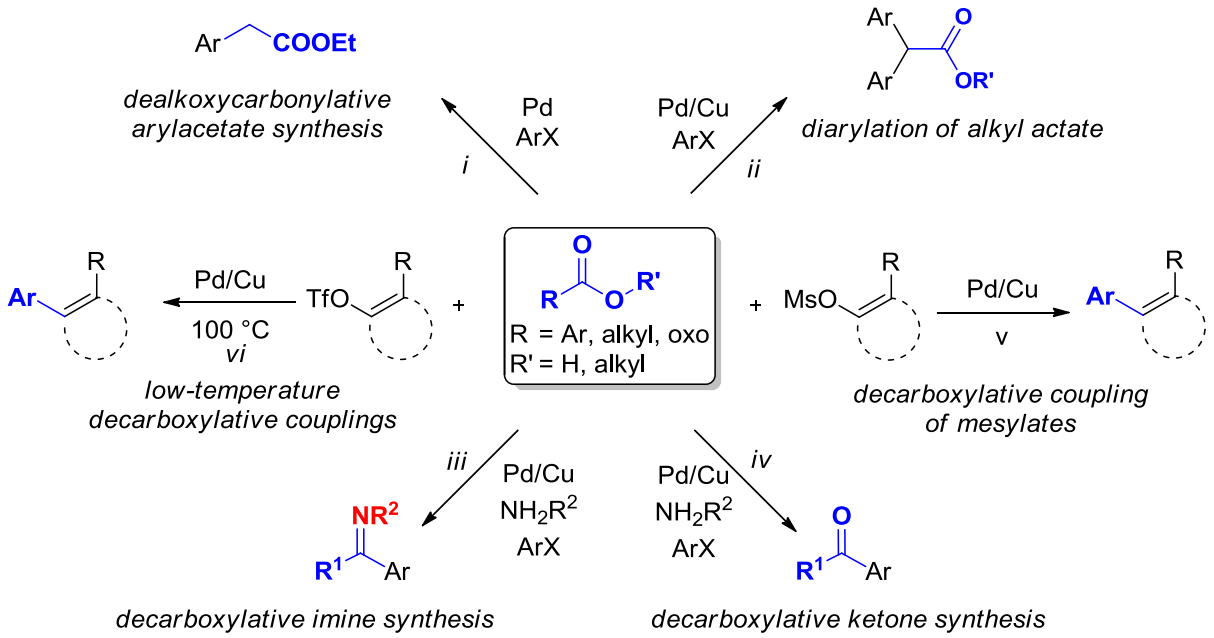
Chapter 7

Summary and Outlook



In this thesis, applications of carboxylic acids and their derivatives in transition metal-catalyzed cross-coupling reactions were explored. In five related projects, several synthetically useful methods for the sustainable synthesis of important organic building blocks such as aryl acetates, diaryl acetates, imines, ketones, biaryls, styrenes and poly-substituted alkenes through the activation of carboxylic acids and their derivatives were successfully established (Scheme 1).



Scheme 1. Carboxylic acids and their derivatives in cross-coupling reactions.

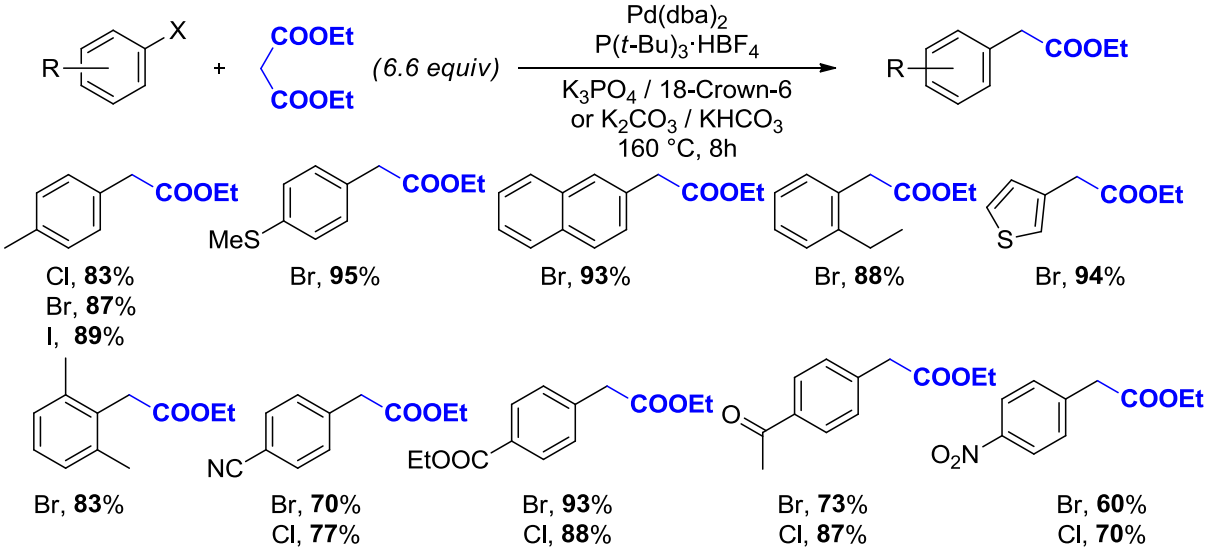
In the fist project, an efficient and practical protocol for the synthesis of arylacetate esters through the dealkoxycarbonlative cross-coupling reaction between aryl halides and malonates was developed (Scheme 1, i). In addition to arylacetates, a straightforward approach to the α-diarylacetates from acetic acid esters was then developed in the second project (ii). Activation of the α-proton of esters by a copper catalyst allowed the deprotonation of esters even in the presence of mild bases. In the rest part of this thesis, several important achievements in decarboxylative cross-coupling reactions were demonstrated (iii-vi). The addition of a primary amine into the coupling reaction of α-oxocarboxylic acids and aryl halides led to an unprecedented low-temperature redox-neutral decarboxylative coupling process, providing a green and efficient method for the preparation of azomethines (iii). A minor modification of this protocol allowed us to easily access the corresponding ketones (iv). The decarboxylative coupling of robust aryl mesylates as well as polysubstituted alkenyl mesylates using our customized imidazolyl phosphine ligands was also realized, further expanding the scope of carbon electrophiles in decarboxylative coupling reactions (v). Variation of the ligands led to

two complementary protocols, providing the corresponding biaryls and polysubstituted olefins in high yields. In the end, an important breakthrough in redox-neutral decarboxylative coupling reactions was achieved (vi). The use of a new class of pyrimidinyl phosphine ligands developed by the group of W. R. Thiel dramatically reduced the reaction temperatures of decarboxylative couplings between aromatic carboxylic acids and aryl or alkenyl triflates. The new catalyst system for the first time allowed the efficient decarboxylative biaryls synthesis at only 100 °C.

Dealkoxycarbonylative coross coupling of malonates (i)

In the first project, a new and convenient entry to pharmaceutically and biologically important arylacetates was developed. In this protocol, aryl malonates serve as both solvent and starting materials. Our strategy involves the cross-coupling of malonates between aryl halides, followed by the alkoxydecarbonylation of the arylated malonate intermediates. A new catalyst system that not only allows the efficient coupling reaction, but also facilitates the subsequent decarboxylation step is thus required.

The dealkoxycarbonylation step proceeds rapidly for electron-deficient and sterically demanding derivatives, but is much slower for electron-rich 2-arylmalonates. Two complementary reaction protocols were necessary to provide a general synthetic entry to alkyl 2-arylacetates. The optimal conditions for the coupling of electron-rich aryl halides involve $Pd(dba)_2$ (0.5 mol%) / $P(t\text{-}Bu)_3{\bullet}HBF_4$ (1.1 mol%) as the catalyst and 18-crown-6 (0.5 equiv.) / potassium phosphate (2.8 equiv.) as the base. This base / crown ether combination is crucial for a quantitative dealkoxycarbonylation (Scheme 2).



Scheme 2. Dealkoxycarbonylative coupling of malonates with electron-rich aryl halides.

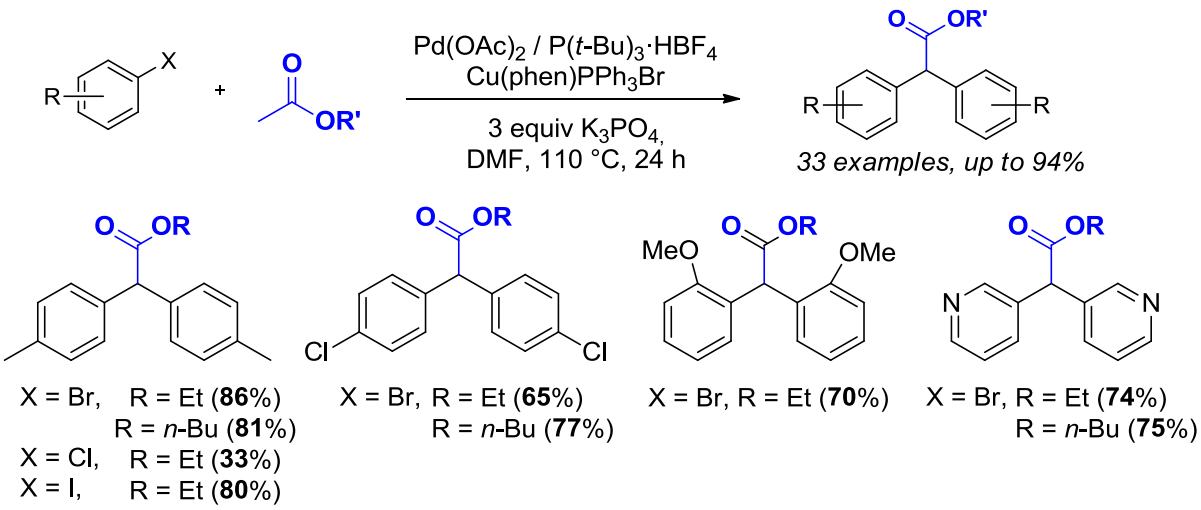
In contrast, electron-deficient and sterically demanding aryl halides were efficiently coupled in the absence of crown ether, using a 1:1 potassium carbonate / bicarbonate mixture as the base (Scheme 2). This way, the competing protodehalogenation of the aryl halides, otherwise a major side reaction, was effectively suppressed.

Diarylation of alkyl acetates (ii)

In a related project, a straightforward approach to diarylacetates through the Pd/Cu-catalyzed di-α-arylation of simple acetic acid esters was then developed. The precedent synthetic methods mainly focused on the arylation of 2-arylacetic acids and their derivatives. The diarylation of acetic acid esters with aryl halides appeared to be an attractive approach, since these substrates are available in great structural variety at low cost. However, in contrast to 2-arylacetates (ethyl 2-phenylacetate: $pK_{a(DMSO)}$ = 22.7), simple acetic acid esters are much harder to deprotonate (ethyl acetate: $pK_{a(DMSO)}$ = 29.5), so that the use of expensive and hard-to-handle bases such as MHMDS (M = K or Na), LDA, or alkali metal alkoxides seems to be unavoidable in arylation processes of these compounds.

A new catalyst system consisting of a palladium catalyst and a copper complex enabling the the use of mild base for the deprotonation of non-activated esters was therefore developed. The addition of catalytic quantities of a phenanthroline copper phosphine complex stabilized the enolate intermediate to the extent that even mild bases were sufficient to promote the conversion of these esters into copper enolates. These intermediates could then be coupled with aryl halides at a palladium catalyst under regeneration of the copper co-catalyst.

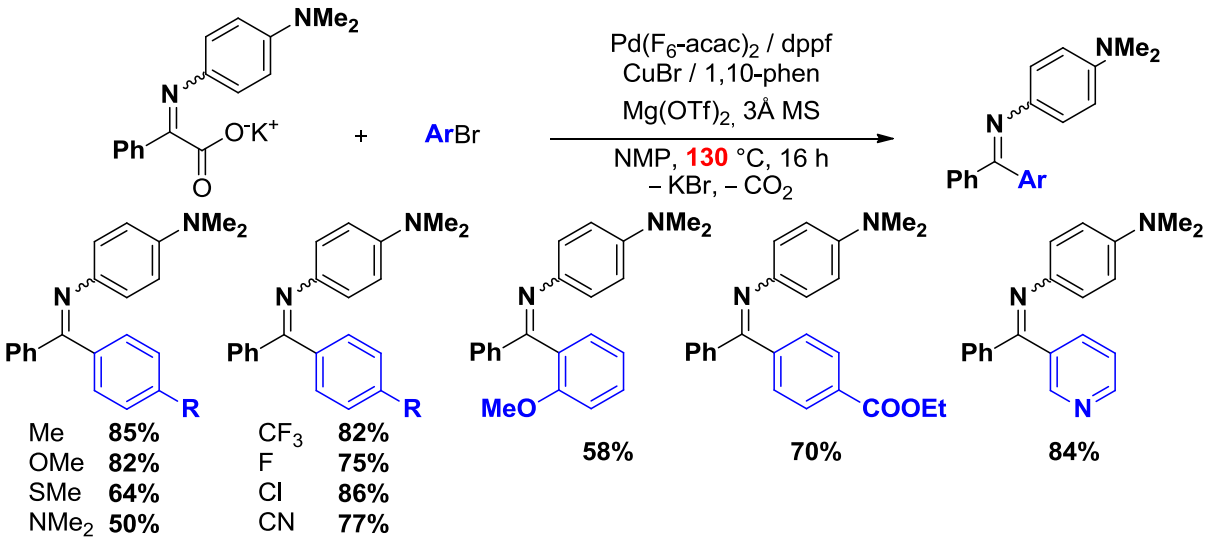
After intricate catalyst development, a catalyst system consisting of the phenanthroline copper phosphine catalyst Cu(phen)PPh_3Br (2.4 mol%), and a palladium co-catalyst ($Pd(OAc)_2$ (2.2 mol%) / P(*t*-Bu)$_3$•HBF_4 (4.4 mol%) was found to be most effective (Scheme 3). It allowed the coupling of alkyl acetates with various aryl halides in the presence of potassium phosphate. These are unprecedentedly mild conditions for the arylation of simple esters. Control experiments confirm that the copper and palladium catalysts are both required for the first arylation step, whereas the second arylation proceeds much faster and does not require the copper co-catalyst. The discovery that the α-C–H bond of simple esters could be activated by catalytic amounts of copper species in the presence of mild base is likely to open up new opportunities for the design of related coupling reactions with C-H functionalization.



Scheme 3. Di-α-arylation of simple alkyl acetic acid esters.

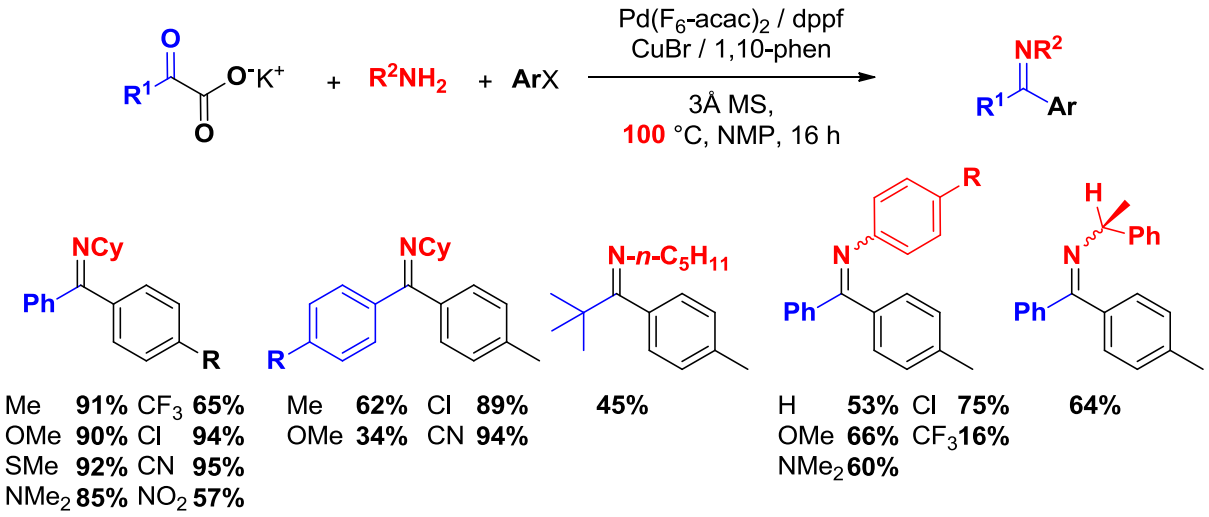
Decarboxylative imine and ketone synthesis (iii)

In the third project, a one-pot low-temperature decarboxylative process for the convenient preparation of azomethines and ketones from oxocarboxylic acids was developed. Via condensation with primary amines, α-oxocarboxylates (which decarboxylate only at 170 °C) were converted into the corresponding α-iminocarboxylates, which lost CO_2 at much lower temperatures (80-100 °C). The coupling of the intermediately formed imidoyl anion equivalents led to the formation of azomethines. To validate this hypothesis, a stable preformed α-iminocarboxylate was thus prepared and used directly for the decarboxylative coupling reactions. Various aryl halides were successfully converted into the corresponding imines in good yields at only 130 °C, which is already 40 °C lower than the previous protocol (Scheme 4).



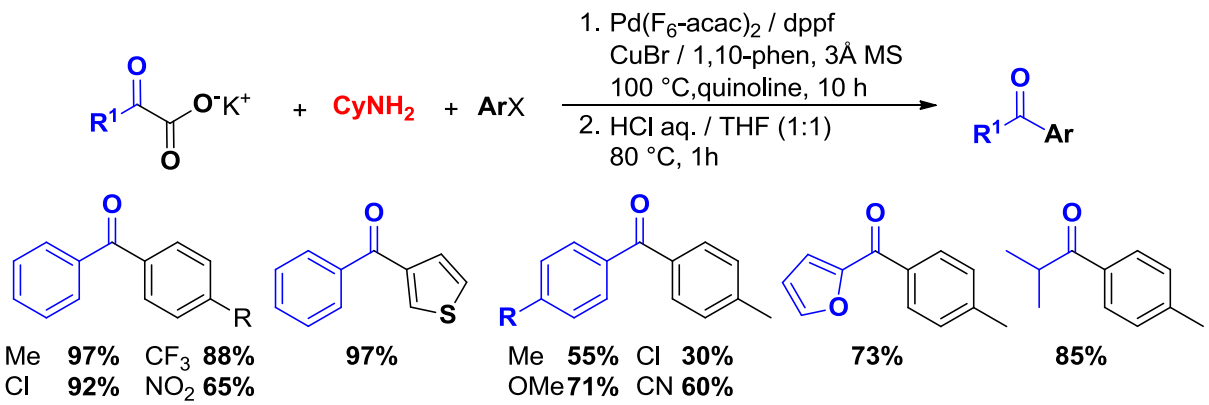
Scheme 4. Synthesis of azomethines from preformed α-iminocarboxylate.

The further optimization of the reaction conditions led to an efficient one-pot protocol that allowed the convenient assembly of three easily available building blocks into synthetically valuable azomethines (Scheme 5). In contrast to most other synthetic approaches to this substance class, all three substituents could thus independently be varied. The decarboxylative redox-neutral cross-coupling reactions for the first time occurred at 100 °C. This unprecedented tandem imine condensation / decarboxylative coupling reaction of α-oxocarboxylates opens up new opportunities for the design of various other decarboxylative transformations, including arylations with C-H activation, 1,2- and 1,4-additions, and allylation reactions.



Scheme 5. Decarboxylative one-pot imine synthesis.

In addition to the imine synthesis, a variety of ketones was readily accessed via a minor adjustment of the previous protocol (Scheme 6). Moreover, when the imine was treated with a 3:1 mixture of sodium borohydride and aluminium chloride, the corresponding amine could be easily obtained.

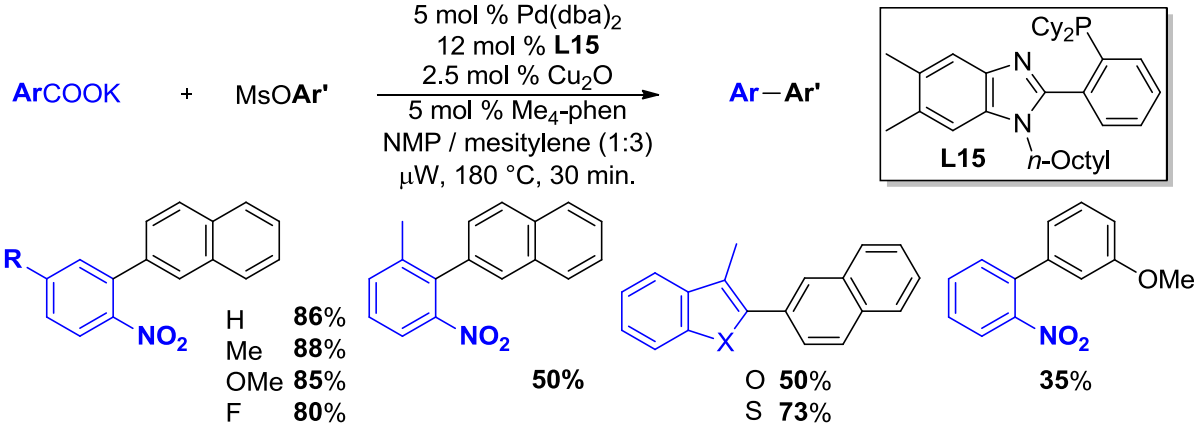


Scheme 6. Low-temperature decarboxylative one-pot ketone synthesis.

Decarboxylative coupling of aryl and alkenyl mesylates (iv)

With the help of a new class of imidazolyl phosphine ligands, a breakthrough in neutral-redox decarboxylative cross-coupling reactions was achieved, for the first time utilized extremely unreactive aryl methanesulfonates (mesylates) as carbon electrophiles. Aryl and alkenyl mesylates are particularly attractive carbon electrophiles for applications in both laboratory synthesis and large-scale manufacturing processes, since they are easily accessible at low cost by esterification of the corresponding phenols and carbonyl enolates with inexpensive methanesulfonyl chlorides or anhydrides. These small, stable, inexpensive but rather unreactive sulfonates are economically and ecologically advantageous in comparison to the large *p*-toluenesulfonates or the expensive trifluormethanesulfonates. However, there are only a few ligand systems which permit the use of these compounds in transition metal catalysis. Prior to our experiments with 2-benzimidazolyl-aryl phosphines, all the attempts to achieve a decarboxylative coupling of aryl mesylates turned out to be in vain. Our ligands, together with Pd originating from $Pd(dba)_2$, are capable of activating aryl mesylates and, at the same time permit a transmetallation from copper to palladium.

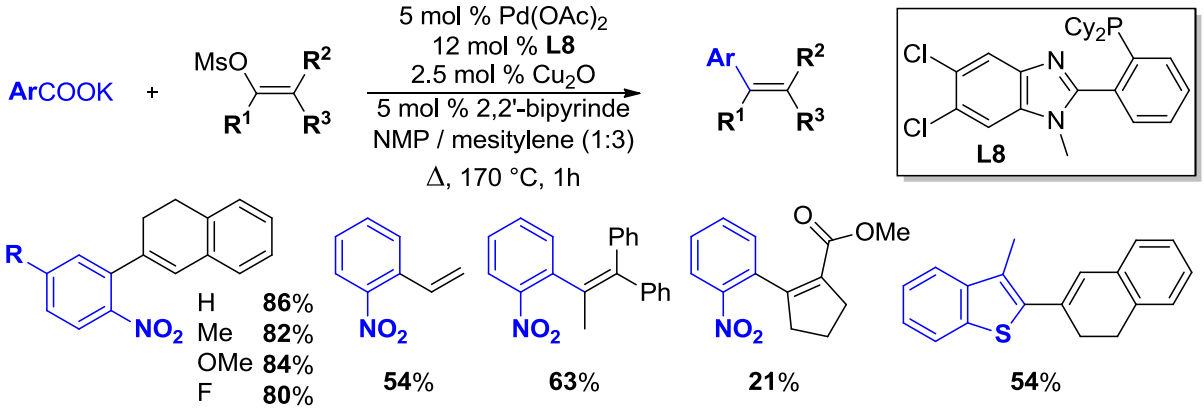
A series of benzoimidazolyl phosphines was thus synthesized and applied in the decarboxylative coupling of aromatic carboxylic acids with aryl mesylates. After intricate optimizations of the reaction parameters, a bimettalic Pd/Cu catalyst system containing a customized benzoimidazolyl phosphine for the palladium precursor and a bidentate nitrogen-chelating ligand for copper salt was thus developed (Scheme 7).



Scheme 7. Decarboxylative cross-coupling of aromatic carboxylic acids with aryl mesylates.

By employing the dichloro-substituted benzoimidazolyl phosphine ligand, our new reaction concept was successfully extended to the alkenyl mesylates (Scheme 8). The decarboxylative cross-coupling of mesylates described herein provides a convenient access to a broad array of

products, including tetrasubstituted alkenes and vinyl arenes, which are hard to access by other means.

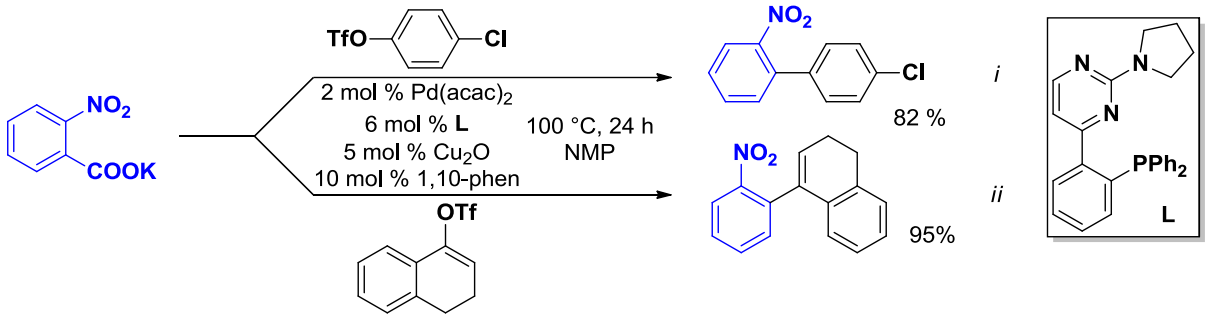


Scheme 8. Decarboxylative cross-coupling of aromatic carboxylic acids with alkenyl mesylates.

Low-temperature decarboxylative couplings (v)

In the last project, the temperature bottleneck of redox-neutral decarboxylative cross-coupling reactions was finally overcome. Unlike the low-temperature one-pot decarboxylative process using an additional amine as the additive described in chapter 4, the strategy used herein was to lower the energy barrier of both decarboxylation and transmetallation steps by rational ligand design and intricate reaction development. An ideal ligand class that features a combination of the chelating nitrogen moiety and the phosphino group, which is capable of complexing with both copper and palladium catalysts, would thus fit these criteria. In close collaboration with Prof. Thiel, a new catalyst system that for the first time allowed the decarboxylative coupling to occur at only 100 °C (70 °C lower than the standard process) was developed. The pyrimidinyl phosphine ligands developed by the group of Thiel played a prominent role on the low-temperature process, in which a complicated Pd/Cu bimetallic complex bridged by the ligand might be formed. The mechanistic details are still unkown at this stage.

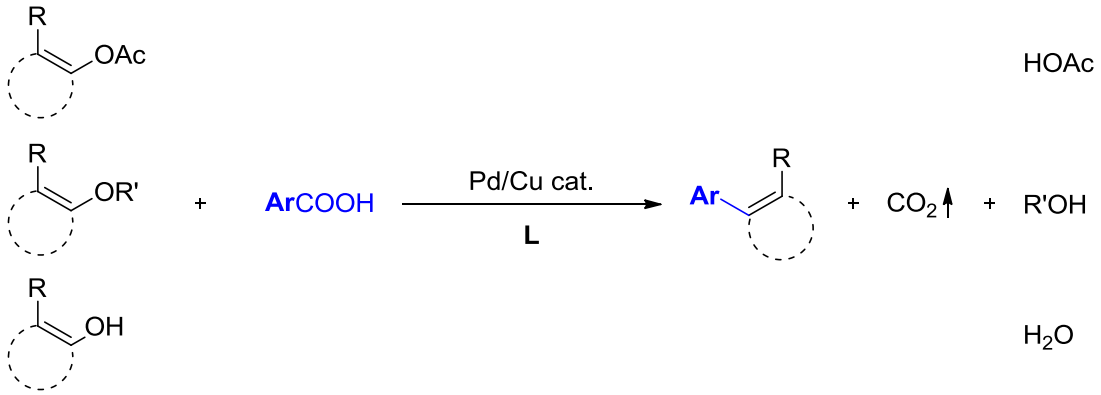
After systematic optimization of the reaction conditions, the decarboxylative cross-coupling of 2-nitrobenzoate with 4-chlorophenyl triflate could readily occur at 100 °C, forming the corresponding biaryl in almost quantative yield (Scheme 9, i). Moreover, the optimal conditions were also applicable to vinyl triflates (ii). This is of great interest, since the alkenyl triflates are accessible in broader diversity than the corresponding halides. The full investigation on a wide range of (hetero)aryl carboxylic acids along with aryl and alkenyl triflates is ongoing work in our group.



Scheme 9. Low-temperature decarboxylative cross-coupling of aromatic carboxylic acids with aryl and alkenyl triflates.

Outlook

Five related projects that make use of carboxylic acids and their dervativies as starting materials described in this thesis constitute several important discoveries in decarboxylative cross-coupling reactions. At this stage, we have successfully extended the carbon electrophiles unsed in decarboxylative cross-coupling reactions to simple, but unreactive mesylates by employing imidazolyl phosphine ligands, which greatly facilitate the transmetallation step. The next obvious challenge in the filed will be to further expand the scope of carbon eletrophiles to more robust carbon electrophiles such as aryl acetates, ethers, and even phenols (Scheme 10).



Scheme 10. The use of various caron eletrophiles in decarboxylative couplings.

However, the reactivity of aryl acetates and methoxylated aromatic compounds are exetremely lower compared to aryl mesylates, due to the dramatic increase in the basicity (Figure 1).[1] With the help of transition metals including Ni,[2] Pd,[3] Ru,[4] Rh,[5] and Fe[6], several research groups have successfully realized the activation of C–O bonds in aryl ethers and carboxylates, followed by a subsequent coupling process, providing new methodologies for C–C and C–heteroatom bond formations.[7] The key solution to achieve decarboxylative couplings of aryl acetates, ethers and even phenols will probably depend on the development

of novel and efficient ligands that permit the transmetallation from copper or sivler to one of those aforementioned metals.

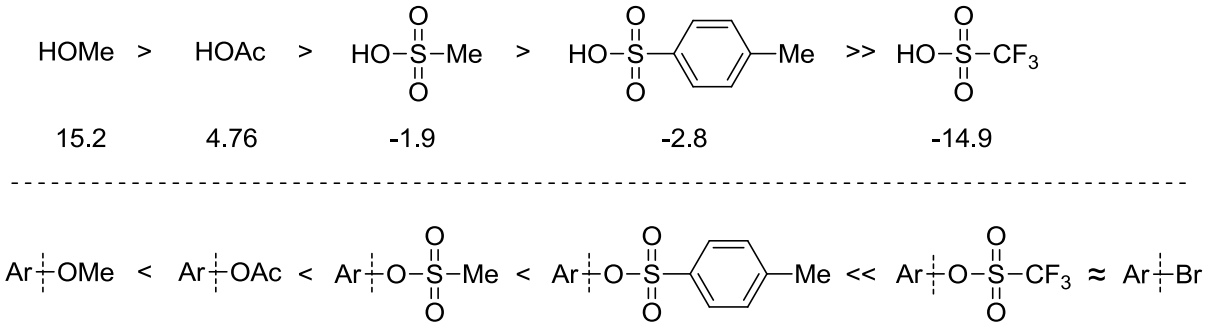


Figure 1. Various caron eletrophiles.

Very recently, Cahiez *et al.*[8] disclosed a low-temperature decarboxylative cross-coupling process (130 °C) by using aliphatic amines such as tetramethylethylenediamine (TMEDA) or hexamethylenetetra-amine (HMTA) as ligands instead of the aromatic heterocyclic amines (quinoline, phenanthroline) for the copper co-catalyst. This new finding represents another important route to low-temperature decarboxylative couplings by accelerating the rate of the decarboxylation step. We are optimistic that the border of the reaction temperature of decarboxylative coupling reactions will be further overcome by the combination of these aliphatic amines with our customized pyrimidyl phosphine ligands.

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Chapter 8

Experimental Section

8.1 General Techniques

8.1.1 Chemicals and Solvents

All commercially available chemicals were used without any further purification. Air and moisture sensitive chemicals were stored under nitrogen or argon. Reaction vessels were usually charged with solid starting materials and reagents, evacuated (oil pump ≤ 10-3 mbar) to remove oxygen and moisture, then backfilled with nitrogen. Solvents and liquid reagents were added under an atmosphere of nitrogen. Solvents were purified following standard literature techniques and stored over 3Å molecular sieves. Inorganic salts such as KF, K_2CO_3, or K_3PO_4 were dried under vacuum at 120 °C for 3 hours and stored under nitrogen. Copper salts were dried under vacuum at 60 °C for 1 hour.

8.2 Analytical Methods

8.2.1 Thin Layer Chromatography

TLC was performed using analytical silica gel plates 60 F254 and analytical neutral alumina plates by Polygram Alox N/UV_{254} by Merk and Macherey-Nagel. The silica gel (230-400 mesh, 60 Å) used for column chromatography was purchased from Aldrich.

8.2.2 Gas Chromatography

For GC-analysis a Hewlett Packard 6980 chromatograph was used. The carrier gas was nitrogen with a flow rate of 149 mL/min (0.5 bar pressure). The temperature of the injector was 220 °C. The split-ratio was 1:100. For separation, an Agilent HP-5-column with 5 % phenyl-methyl-siloxane (30 x 320 μm x 1.0 μm, 100/ 2.3-30-300/ 3) was used. The following temperature program was implemented: starting temperature 60 °C (2 min), linear temperature increase (30 °C min^{-1}) to 300 °C, end temperature 300 °C (13 min).

8.2.3 Mass Spectroscopy

Mass spectrometry was performed using a Varian Saturn 2100 T GC-MS. The ionization was done by EI AGC. The intensities of the signals are relative to the highest peak. For fragments with isotopes, only the most intensive peak of the isotope is given. High resolution mass spectra were acquired on a GC-MS-TOF spectrometer using EI-ionization (Waters).

Electrospray ionization mass spectrometry (ESI-MS) was performed with a Bruker Esquire 3000plus ion trap instrument. The ion source was used in positive electrospray ionization mode. Scan speed was 13000 m/z / s in normal resolution scan mode (0.3 FWHM / m/z), scan

range was at least 50 to 1500 m/z. All spectra were accumulated for at least one minute. Sample solutions in toluene at concentrations of 0.007 M were continuously infused into the ESI chamber at a flow rate of 4 µL/min using a syringe pump. Nitrogen was used as drying gas with a flow rate of 3.0 L/min at 300 °C. The solutions were sprayed at a nebulizer pressure of 4 psi (275.8 mbar) and the electrospray needle was typically held at 4.5 kV. The instrument was controlled by the Bruker Esquire Control 5.3 software, and data analysis was performed using Bruker Data Analysis 3.4 software.

8.2.4 High-Performance Liquid Chromatography

HPLC analysis was carried out using a Shimadzu HPLC equipped with a Merck KGaA reversed phase column LiChroCart©PAH C 18, with a particle diameter of 5 µm. The instrument was operated at a constant temperature of 60 °C and a pressure of 200 bar. Acetonitrile and water were used as eluents with a flow rate of 2 mL/min. Gradient: 15 % acetonitrile for 3 min linear increase to 85 % within 7 min, hold for 1 min, decrease to 15 % within 1 min. and hold for 50 seconds. 5 µL of sample were injected as standard amount into the Rheodyne. This amount can be varied manually through the Shimadzu sequence program Class-VP.

8.2.5 Infrared Spectroscopy

Infrared spectra were recorded with a Perkin-Elmer Fourier Transform Infrared Spectrometer FT/IR. Solids were thoroughly ground, and mixed with potassium bromide and pressed into a pellet. Liquids were measured as a thin film between sodium chloride plates. Absorbance bands are shown in wave numbers (cm^{-1}). Intensities are abbreviated: vs (very strong), s (strong), m (medium), w (weak) and b (broad).

8.2.6 Nuclear Magnetic Resonance Spectroscopy

Proton-, fluorine-, phosphorus-, boron- and decoupled carbon-NMR spectra were recorded with a Bruker FT-NMR DPX 200, a DPX 400 and a Bruker Avance 600 spectrometer. The frequency and solvent used are described separately for each substance. Chemical shifts are given in units of the δ-scale in ppm. Shifts for ^{1}H-spectra are calibrated to the proton signal of the solvent used (chloroform: 7.25 ppm, dimethyl sulfoxide: 2.50 ppm, methanol: 3.35 ppm, water: 4.75 ppm), for ^{13}C-spectra respectively to the deuterated solvent (chloroform: 77.0 ppm, dimethyl sulfoxide: 37.7 ppm, methanol: 49.3 ppm). The atom numbering within products is not according to the IUPAC rules. The multiplicity of the signals is abbreviated by the following letters: Coupling constants are given in Hertz (Hz). Processing and interpretation

was performed with ACD/Labs 7.0 and ACD/Labs 12.0 software (Advanced Chemistry Development Inc.)

Signals are abbreviated as s (singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), td (triplet of doublet), q (quartet), quin (quintet), sext (sextet), hept (heptet), m (multiplet), br (broad).

8.2.7 Elemental Analysis

CHNS-elemental analysis was performed with a Perkin-Elmer Elemental Analyzer EA 2400 CHNS.

8.2.8 Melting Point

Melting points were measured in a glass capillary tube with a Mettler FP61 automatic measuring apparatus.

8.3 High-throughput Experiments

In order to perform a large number of experiments, a specially manufactured setup was used. All reactions were carried out in 20 mL headspace vials that were closed and clamped shut with aluminum caps fitted with a Teflon-coated butyl rubber septum (both commercially available at Macherey & Nagel).

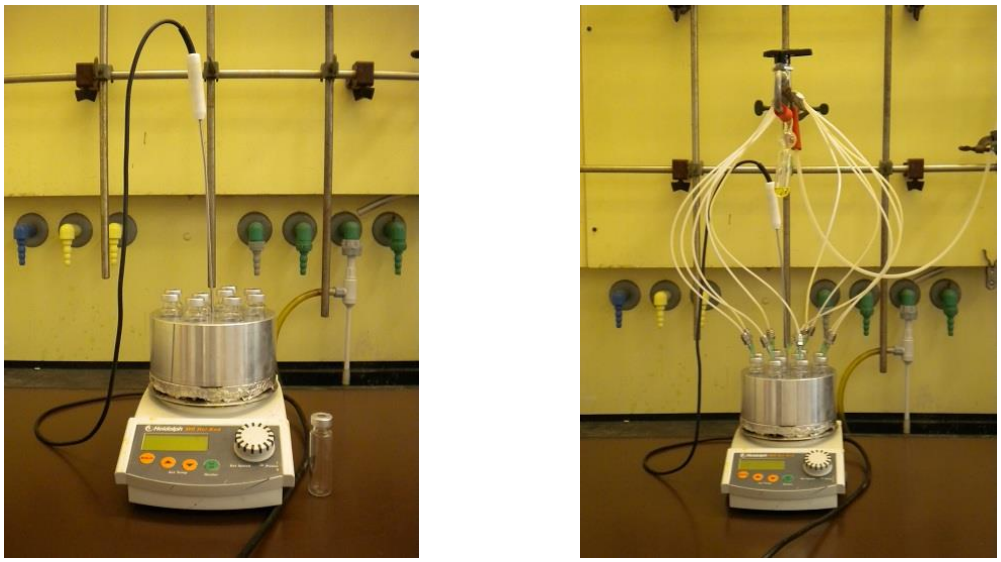


Figure 1. *Aluminum block, magnetic stirrer and vacuum distributer*

In an 8 cm high round aluminum block, which fits on the hot plate of a regular laboratory heater in diameter, 10 of these 20 mL headspace vials can be tempered between 25°C and 180 °C. An 11th smaller hole drilled in the middle of the block creates room to hold the thermometer of the heater. A similar setup was used for reactions in autoclaves, except that a

4 cm aluminum block containing 8 holes for 10 mL head space vials and a small hole for the thermometer. This aluminum block is designed to fit inside the autoclave. Figure 1 shows a magnetic stirrer, aluminum block and vacuum distributer (spider) (Fiture 1).

To correctly evacuate and refill 10 reaction vessels with inert gas at the same time, special vacuum distributors were manufactured to be connected to the Schlenk-line.

A steel tubing is linked to ten 3 mm Teflon tubes, which are equipped on the opposite end with adaptors for Luer-Lock syringe needles. The steel tubing can be connected to the Schlenk-line just like any other laboratory equipment by a steel olive and vacuum tubing. To perform 10 or more reactions in parallel, the following protocol was used. All solid substances were weighed in the reaction vessels, an oven-dried, hot 20 mm stir bar added and each vessel closed with a separate cap using flanging pliars. All 10 vessels were transferred to one of the aforementioned aluminum cases and evacuated using syringe needles connected to the vacuum steel tubing.

The reaction vessels were evacuated and refilled with nitrogen. Using standard sterile and Hamilton syringes all liquid reagents, stock solutions of reagents and solvents were added and the vessels were evacuated and refilled with nitrogen 3 times. After removal of the needles, the aluminum case was tempered to the desired temperature. Every temperature description is the case temperature, which only differs by maximum 2 °C from the actual reaction media temperature.

After the reaction time and subsequent cooling to room temperature, any over pressure was released with a needle and *n*-tetradecane was added as internal strandard with a Hamilton syringe. The reaction vials were opened carefully. 2 mL of ethyl acetate were added to dilute the reaction mixture, then mixed thoroughly with a disposable pipette to ensure a homogenous mixture. A 0.25 mL sample was collected and extracted with 2.5 mL of ethyl acetate and 2 mL of aqueous 1M HCl solution (acidic work up) or saturated potassium bicarbonate solution (basic work up). The organic layer was filtered through a pipette filled with a cotton plug and $NaHCO_3$ / magnesium sulfate (in case of acidic work up) or only $MgSO_4$, directly into a GC-vial. After analyzing sample the GC and, if necessary GC-MS, the contents of all work-up and analysis vials were recombined and the product isolated using standard procedures, deposed on silica-gel and purified by flash chromatography using a Combi Flash Companion-Chromatography apparatus from Isco-Systems.

The developed experimental setups and an electronic laboratory journal allowed a substantial amount of reactions to be performed during the course of this PhD. Approximately 4300 reactions would have consumed a much longer time when using standard laboratory

techniques. Preparative reactions were performed mostly in standard laboratory oven-dried glass ware. The following experimental section describes all reaction procedures and observations mentioned in chapters 2-6. Yields are isolated yields unless explicitly mentioned. All compounds were analyzed by melting point (for solids), ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR (for fluorinated compounds), ^{31}P-NMR (for phosphorous-containing compounds), GC-MS or ESI-MS, IR spectroscopy, and elemental analysis or HR-MS.

8.4 Reactions under Microwave-Irradiation

All microwave radiation experiments were carried out in a CEM-Discover® LabMate mono-mode microwave apparatus equipped with an IntelliVent™ pressure control system and a vertically-focused IR temperature sensor. The reaction was monitored with CEM's ChemDriver software. After the irradiation period, the reaction vessel was cooled rapidly (60-120 sec) to ambient temperature by air jet cooling.

8.5 Practical Synthesis of 2-Arylacetic Acid Esters via Palladium-Catalyzed Dealkoxycarbonylative Coupling of Malonates with Aryl Halides

8.5.1 General Methods for the Synthesis of Ethyl 2-Arylacetates

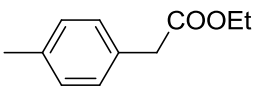
Method A:

A 20 mL Schlenk tube equipped with a rubber cap and a stirrer bar was charged with aryl halides (1.00 mmol), bis(dibenzylideneacetone)palladium(0) (0.005 mmol), tri-*tert*-butyl-phosphonium tetrafluoroborate (0.011 mmol), potassium phosphate (2.8 mmol), 18-crown-6 (0.5 mmol) and diethyl malonate (6.6 mmol). The reaction vessel was evacuated and filled with nitrogen three times. The reaction mixture was stirred at 160 °C for 8-12 hours. After the reaction was complete, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting solution was washed successively with water (20 mL), saturated sodium bicarbonate solution (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification of the residue by column chromatography (SiO_2, hexane/ethyl acetate gradient) gave the corresponding products.

Method B:

A 20 mL Schlenk tube equipped with a rubber cap and a stirrer bar was charged with aryl halides (1.00 mmol), bis(dibenzylideneacetone)palladium (0) (0.005 mmol), tri-*tert*-butyl-phosphonium tetrafluoroborate (0.011 mmol), potassium carbonate (1.5 mmol), potassium bicarbonate (1.5 mmol) and diethyl malonate (6.6 mmol). The reaction vessel was evacuated and refilled with nitrogen three times. The reaction mixture was stirred at 160 °C for 8 hours. Upon completion, the reaction mixture was cooled and diluted with ethyl acetate. The solution was washed successively with water (20 mL), saturated sodium bicarbonate solution (20 mL) and then with brine (20 mL), dried over $MgSO_4$, filtered, and the solvents removed *in vacuo*. Purification of the residue by column chromatography (SiO_2, hexane/ethyl acetate gradient) gave the corresponding products.

8.5.2 Synthesis of Aryl acetates

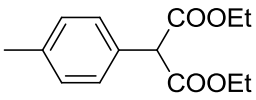


Ethyl 2-(*p*-tolyl)acetate (**2.2-3a**) [CAS No. 14062-19-2]

Compound **2.2-3a** was synthesized according to general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 4-bromotoluene (171 mg, 123 μL, 1.00 mmol) or 4-chlorotoluene (128 mg, 120 μL, 1.00 mmol) or 4-iodotoluene (218 mg, 1.00 mmol). After purification by

flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3a** (155 mg, 87 %; 148 mg, 83 %; 159mg, 89 %) was obtained as a colorless oil.

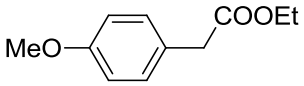
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.16 (q, *J* = 8.0 Hz, 2H), 3.58 (s, 2H), 2.34 (s, 3H), 1.26 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.8, 136.6, 131.1, 129.2, 129.1, 60.8, 41.0, 21.0, 14.2 ppm. EI-MS (70 eV), *m/z* (%): 178 (34) [M^+], 106 (10), 105 (100). IR (NaCl): $\tilde{\nu}$ = 2980 (vs), 2927 (m), 1735 (vs), 1515 (m), 1446 (m), 1367 (m), 1301 (m), 1253 (m), 1152 (m), 1032 (m), 809 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{11}H_{14}O_2$: 178.0094, *m/z* found: 178.1000.



Diethyl 2-(*p*-tolyl)malonate (**2.2-5a**) [CAS No. 29148-27-4]

Compound **2.2-5a** was obtained as a byproduct in the synthesis of **2.2-3a**.

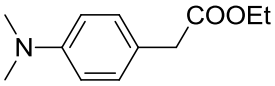
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 4.59 (s, 1H), 4.26-4.16 (m, 4H), 2.36 (s, 3H), 1.27 (t, *J* = 8.0 Hz, 6H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 168.3, 137.9, 129.8, 129.3, 129.1, 61.7, 57.6, 21.1, 14.0 ppm. EI-MS (70 eV), *m/z* (%): 250 (19) [M^+], 178 (73), 177 (80), 150 (34), 149 (89), 132 (54), 105 (100) 77 (48). IR (NaCl): $\tilde{\nu}$ = cm^{-1}. Anal. Calcd. for $C_{14}H_{18}O_4$: C 80.56, H 7.51; found: C 80.77, H 7.20.



Ethyl 2-(4-methoxyphenyl)acetate (**2.2-3b**) [CAS No. 14062-18-1]

Compound **2.2-3b** was synthesized according to general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 4-bromoanisole (187 mg, 128 µL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 10:90), **2.2-3b** (183 mg, 94 %) was obtained as a light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 4.16 (q, *J* = 8.0 Hz, 2H), 3.80 (s, 3H), 3.56 (s, 2H), 1.26 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.8, 158.6, 130.1, 126.1, 113.9, 60.7, 55.1, 40.4, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 194 (35) [M^+], 121 (100), 91 (11), 78 (13), 77 (17). IR (NaCl): $\tilde{\nu}$ = 2980 (vs), 2935 (m), 1734 (vs), 1612 (m), 1513 (s), 1465 (m), 1301 (m), 1247 (m), 1176 (m), 1154 (m), 1032 (m), 820 (m) cm^{-1}. Anal. Calcd. for $C_{11}H_{14}O_3$: C 68.02, H 7.27; found: C 67.35, H 7.32.

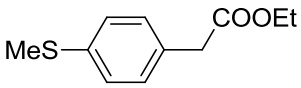


Ethyl 2-(4-(dimethylamino)phenyl)acetate (**2.2-3c**) [CAS-No. 17078-29-4]

Compound **2.2-3c** was synthesized according to general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 4-bromo-N,N-dimethylaniline (200 mg, 1.00 mmol). After

purification by flash column chromatography (SiO_2, ethyl acetate - hexane 10:90), **2.2-3c** (199 mg, 96 %) was obtained as a light green oil.

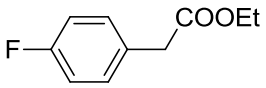
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 4.14 (q, *J* = 8.0 Hz, 2H), 3.52 (s, 2H), 2.93 (s, 6H), 1.26 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.2, 149.6, 129.7, 121.9, 112.7, 60.5, 40.6, 40.4, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 208 (14), 207 (67) [M^+], 134 (100), 118 (12). IR (NaCl): $\tilde{\nu}$ = 2980 (vs), 2935 (m), 1732 (vs), 1615 (s), 1523 (vs), 1344 (m), 1255 (m), 1149 (m), 1032 (m), 947 (m), 809 (m) cm^{-1}. Anal. Calcd. for $C_{12}H_{17}NO_2$: C 69.54, H 8.27, N 6.76; found: C 68.52, H 8.02, N 6.65.



Ethyl 2-(4-(methylthio)phenyl)acetate (**2.2-3d**) [CAS-No. 14062-27-2]

Compound **2.2-3d** was synthesized according to general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 4-bromothioanisole (203 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3d** (199 mg, 95 %) was obtained as a white solid, M.p. 57-58 °C.

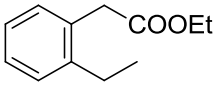
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25-7.18 (m, 4H), 4.14 (q, *J* = 8.0 Hz, 2H), 3.56 (s, 2H), 2.46 (s, 3H), 1.24 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.5, 137.1, 131.0, 129.7, 126.9, 60.7, 40.8, 16.0, 14.2 ppm. EI-MS (70 eV), *m/z* (%): 211 (16), 210 (100) [M^+], 137 (88), 121 (9). IR (KBr): $\tilde{\nu}$ = 1730 (vs), 1495 (m), 1469 (m), 1366 (m), 1225 (m), 1031 (m), 802 (s) cm^{-1}. Anal. Calcd. for $C_{11}H_{14}O_2S$: C 62.83, H 6.71, S 15.25; found: C 62.90, H 6.74, S 15.35.



Ethyl 2-(4-fluorophenyl)acetate (**2.2-3e**) [CAS-No. 587-88-2]

Compound **2.2-3e** was synthesized according to general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 1-bromo-4-fluorobenzene (175 mg, 110 µL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3e** (157 mg, 86 %) was obtained as a colorless oil.

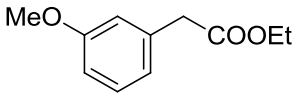
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (dd, *J* = 8.0 Hz, *J* = 4.0 Hz, 2H), 7.01 (t, *J* = 8.0 Hz, 2H), 4.16 (q, *J* = 8.0 Hz, 2H), 3.59 (s, 2H), 1.26 (t, *J* = 8.0 Hz, 3H) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -115.9 (m, Ar-F) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.3, 161.9 (d, $^1J_{C\text{-}F}$ = 245.4 Hz), 130.7 (d, $^3J_{C\text{-}F}$ = 7.1 Hz), 129.8 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 115.3 (d, $^2J_{C\text{-}F}$ = 22.2 Hz), 60.8, 40.4, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 182 (21) [M^+], 109 (100). IR (NaCl): $\tilde{\nu}$ = 2982 (vs), 2937 (m), 1735 (vs), 1604 (m), 1510 (s), 1368 (m), 1224 (m), 1155 (m), 1031 (m), 826 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{10}H_{11}FO_2$: 182.0743, *m/z* found: 182.0732.



Ethyl 2-(2-ethylphenyl)acetate (**2.2-3f**) [CAS-No. 105337-78-8]

Compound **2.2-3f** was synthesized according to general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 1-bromo-2-ethylbenzene (185 mg, 139 µL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3f** (170 mg, 88 %) was obtained as a light yellow oil.

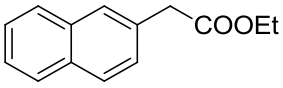
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.27-7.16 (m, 4H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 4.17 (q, *J* = 8.0 Hz, 2H), 3.68 (s, 2H), 2.70 (q, *J* = 8.0 Hz, 2H), 1.29-1.23 (m, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.6, 142.5, 132.0, 130.3, 128.4, 127.4, 125.9, 60.7, 38.5, 25.7, 14.8, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 193 (4), 192 (24) [M^+], 146 (29), 119 (100), 91 (54), 77 (21). IR (NaCl): $\tilde{\nu}$ = 2980 (vs), 2935 (m), 1734 (vs), 1615 (m), 1583 (w), 1513 (s), 1246 (s), 1032 (m), 821 (m) cm^{-1}. Anal. Calcd. for $C_{12}H_{16}O_2$: C 74.97, H 8.39; found: C 74.63, H 8.39.



Ethyl 2-(3-methoxyphenyl)acetate (ASC-3g) [CAS-No. 35553-92-5]

Compound **2.2-3g** was synthesized according to general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 3-bromoanisole (187 mg, 128 µL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 10:90), **2.2-3g** (180 mg, 93 %) was obtained as a light yellow oil.

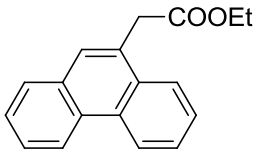
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25 (t, *J* = 8.0 Hz, 1H), 6.91-6.81 (m, 3H), 4.17 (q, *J* = 8.0 Hz, 2H), 3,81 (s, 3H), 3.60 (s, 2H), 1.27 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.4, 159.6, 135.5, 129.4, 121.5, 114.8, 112.5, 60.8, 55.1, 41.4, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 195 (7), 194 (50) [M^+], 121 (100), 91 (37), 78 (17), 77 (26). IR (NaCl): $\tilde{\nu}$ = 2979 (vs), 1731 (vs), 1601 (s), 1586 (m), 1492 (m), 1368 (m), 1262 (m), 1031 (m), 870 (m), 773 (m) cm^{-1}. Anal. Calcd. for $C_{11}H_{14}O_3$: C 68.02, H 7.27; found: C 68.05, H 7.42.



Ethyl 2-(naphthalene-2-yl)acetate (**2.2-3h**) [CAS-No. 2122-70-5]

Compound **2.2-3h** was synthesized according to general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 2-bromonaphthaline (207 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 10:90), **2.2-3h** (200 mg, 93 %) was obtained as a light yellow oil.

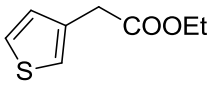
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.87-7.79 (m, 3H), 7.75 (s, 1H), 7.51-7.42 (m, 3H), 4.18 (q, *J* = 8.0 Hz, 2H), 3.79 (s, 2H), 1.27 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.5, 133.4, 132.4, 131.6, 128.1, 127.9, 127.61, 127.58, 127.3, 126.0, 125.7, 60.9, 41.6, 14.2 ppm. EI-MS (70 eV), *m/z* (%): 215 (10), 214 (57) [M^+], 141 (100), 115 (31). IR (NaCl): $\tilde{\nu}$ = 2980 (vs), 2936 (m), 1734 (vs), 1601 (m), 1508 (m), 1368 (m), 1258 (m), 1159 (m), 1031 (s), 859 (m), 818 (m), 802 (m). 759 (m), 742 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{14}H_{14}O_2$: 214.0994; found: 214.0994



Ethyl 2-(phenanthren-9-yl)acetate (**2.2-3i**) [CAS-No. 101723-22-2]

Compound **2.2-3i** was synthesized according to general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 9-bromophennathrene (257 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3i** (240 mg, 91 %) was obtained as a white solid. M.p. 83-84 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.77-8.70 (m, 1H), 8.67 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.70-7.59 (m, 5H), 4.19 (q, *J* = 8.0 Hz, 2H), 4.11 (s, 2H), 1.24 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.5, 131.5, 131.1, 130.7, 130.2, 129.1, 128.8, 128.3, 126.8, 126.7, 126.6, 126.4, 124.4, 123.1, 122.4, 61.0, 39.8, 14.1 ppm. EI-MS (70 eV), m/z (%): 265 (19), 264 (100) [M^+], 192 (19), 191 (34), 190 (27), 165 (14). IR (KBr): $\tilde{\nu}$ = 2982 (w), 1731 (vs), 1602 (m), 1495 (m), 1415 (m), 1365 (m), 1328 (m), 1182 (s), 1151 (m), 1025 (m), 895 (m), 793 (m), 771 (m), 753 (m), 728 (m), 715 (m) cm^{-1}. Anal. Calcd. for $C_{18}H_{16}O_2$: C 81.79, H 6.10; found: C 81.76, H 6.12.

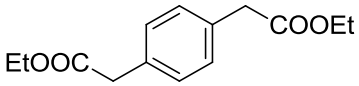


Ethyl 2-(thiophen-3-yl)acetate (**2.2-3j**) [CAS-No. 2122-70-5]

Compound **2.2-3j** was synthesized according to general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 3-bromothiophene (163 mg, 94 µL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3j** (160 mg, 94 %) was obtained as a light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29-7.26 (m, 1H), 7.14 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 4.16 (q, *J* = 8.0 Hz, 2H), 3.64 (s, 2H), 1.26 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.1, 133.7, 128.5, 125.6, 122.7, 60.9, 35.9, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 171 (10), 170 (58) [M^+], 98 (22), 97 (100). R (NaCl): $\tilde{\nu}$ = 2979 (s), 2937 (m), 1733 (vs), 1464

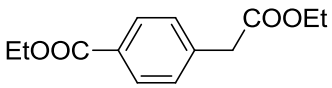
(m), 1369 (m), 1259 (m), 1206 (m), 1155 (m), 1028 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_8H_{10}O_2S$: 170.0402, *m/z* found: 170.0403.



Diethyl 2,2′-(1,4-phenylene)diacetate (**2.2-3k**) [CAS-No. 36076-26-3]

Compound **2.2-3k** was synthesized according to general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 1-bromo-4-chlorobenzene (191 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3k** (171 mg, 68 %) was obtained as a light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23 (s, 4H), 4.13 (q, *J* = 8.0 Hz, 2H), 3.28 (s, 2H), 1.24 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.5, 132.9, 129.4, 60.8, 41.0, 14.1 ppm. EI- MS (70 eV), *m/z* (%): 250 (21) [M^+], 178 (20), 177 (100), 105 (32), 104 (40), 91 (29), 78 (15), 77 (12). IR (NaCl): $\tilde{\nu}$ = 2983 (vs), 2938 (s), 1735 (vs), 1612 (m), 1368 (m), 1277 (s), 1032 (s), 854 (m) cm^{-1}. Anal. Calcd. for $C_{14}H_{18}O_4$: C 67.18, H 7.25; found: C 66.93, H 7.12.



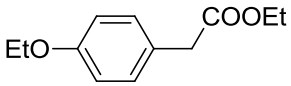
Ethyl 2-(4-(ethoxycarbonyl)phenyl)acetate (**2.2-3l**) [CAS-No. 3516-89-0]

Compound **2.2-3l** was synthesized through an *in situ* esterification of the dealkoxycarbonylative cross-coupling product according to the general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 4-bromobenzoic acid (201 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3l** (208 mg, 88 %) was obtained as a light yellow oil.

Compound **2.2-3l** was also synthesized according to the general procedure B from diethyl malonate (1.0 ml, 6.6 mmol) and ethyl 4-bromobenzoate (229 mg, 160 µL, 1.00 mmol) or ethyl 4-chlorobenzoate (185 mg, 156 µL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3l** (219 mg, 93 %; 208 mg, 88 %) was obtained as a light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.37 (q, *J* = 8.0 Hz, 2H), 4.16 (q, *J* = 8.0 Hz, 2H), 3.67 (s, 2H), 1.39 (t, *J* = 8.0 Hz, 3H), 1.25 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.8, 166.3, 139.1, 129.7, 129.2, 61.0, 60.9, 41.3, 14.3, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 237 (15), 236 (5) [M^+], 208 (11), 191 (39), 180 (13), 163 (100), 149 (18), 136 (25), 135 (47), 119 (13), 118 (18), 107 (40), 91 (24), 90 (28), 89 (35), 77 (13). IR (NaCl): $\tilde{\nu}$ = 2983 (vs), 2938 (m), 1735 (vs), 1718 (vs), 1612 (m),

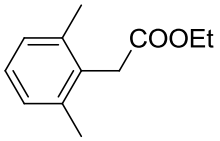
1368 (m), 1277 (s), 1106 (m), 1032 (s) cm^{-1}. Anal. Calcd. for $C_{13}H_{16}O_4$: C 66.09, H 6.83; found: C 66.07, H 6.96.



Ethyl 2-(4-ethoxyphenyl)acetate (**2.2-3m**) [CAS-No. 40784-88-1]

Compound **2.2-3m** was synthesized through an *in situ* etherification of the dealkoxycarbonylative cross-coupling product according to the general procedure A from diethyl malonate (1.0 ml, 6.6 mmol) and 4-bromophenol (173 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3m** (186 mg, 89 %) was obtained as a light yellow oil.

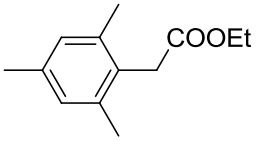
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 4.13 (q, *J* = 8.0 Hz, 2H), 4.00 (q, *J* = 8.0 Hz, 2H), 3.53 (s, 2H), 1.39 (t, *J* = 8.0 Hz, 3H). 1.24 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.9, 158.0, 130.2, 126.0, 114.5, 63.4, 60.7, 40.5, 14.8, 14.1 ppm. MS (70 eV), m/z (%): 210 (29), 209 (20) [M^+], 137 (100), 136 (72), 107 (99), 106 (41), 91 (21), 89 (94), 78 (90). IR (NaCl): $\tilde{\nu}$ = 2979 (vs), 2935 (s), 1735 (vs), 1613 (m), 1583 (m), 1513 (vs), 1246 (m), 1156 (m), 1032 (m), 922 (w), 822 (w) cm^{-1}. Anal. Calcd. for $C_{12}H_{16}O_3$: C 69.21, H 7.74; found: C 68.68, H 7.69.



Ethyl 2-(2,6-dimethylphenyl)acetate (**2.2-3n**) [CAS-No. 105337-15-3]

Compound **2.2-3n** was synthesized according to general procedure B from diethyl malonate (1.0 ml, 6.6 mmol) and 2-bromo-*m*-xylene (185 mg, 134 µL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3n** (156 mg, 81 %) was obtained as a light yellow oil.

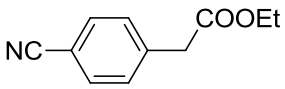
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.11-7.03 (m, 3H), 4.16 (q, *J* = 8.0 Hz, 2H), 3.70 (s, 2H), 2.35 (s, 6H), 1.26 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.2, 137.1, 131.7, 128.0, 126.9, 60.6, 35.4, 20.2, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 193 (9), 192 (37) [M^+], 119 (100), 118 (51), 91 (27). IR (NaCl): $\tilde{\nu}$ = 2979 (vs), 1734 (vs), 1589 (m), 1472 (m), 1445 (m), 1327 (m), 1246 (m), 1152 (s), 1031 (s), 769 (m) cm^{-1}. Anal. Calcd. for $C_{12}H_{16}O_2$: C 74. 97, H 8.39; found: C 74.65, H 8.31.



Ethyl 2-mesitylacetate (2.2-3o) [CAS-No. 5460-08-2]

Compound **2.2-3o** was synthesized according to the general procedure B from diethyl malonate (1.0 ml, 6.6 mmol) and 2-bromomesitylene (199 mg, 153 µL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3o** (172 mg, 83 %) was obtained as a light yellow oil.

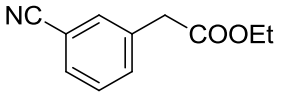
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.89 (s, 2H), 4.17 (q, *J* = 8.0 Hz, 2H), 3.7 (s, 2H), 2.33 (s, 6H), 2.29 (s, 3H), 1.27 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.4, 136.9, 136.3, 128.8, 128.7, 60.6, 35.0, 20.8, 20.1, 14.1 ppm. EI-MS (70 eV), m/z (%): 207 (7), 206 (42) [M^+], 133 (100), 132 (39), 117 (12), 105 (15), 91 (14). IR (NaCl): $\tilde{\nu}$ = 2977 (vs), 2919 (vs), 1734 (vs), 1613 (s), 1580 (m), 1485 (m), 1445 (m), 1157 (m), 1030 (s), 850 (s), 783 (m) cm^{-1}. Anal. Calcd. for $C_{13}H_{18}O_2$: C 75.69, H 8.80; found: C 75.67, H 8.79.



Ethyl 2-(4-cyanophenyl)acetate (2.2-3p) [CAS-No. 1528-41-2]

Compound **2.2-3p** was synthesized according to the general procedure B from diethyl malonate (1.0 ml, 6.6 mmol) and 4-bromobenzonitrile (182 mg, 1.00 mmol) or 4-chlorobenzonitrile (139 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 10:90), **2.2-3p** (132 mg, 70 %; 145 mg, 77 %) was obtained as a white solid. M.p. 93 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 4.15 (q, *J* = 8.0 Hz, 2H), 3.66 (s, 2H), 1.24 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.2, 139.4, 132.2, 130.1, 118.6, 111.1, 61.2, 41.3, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 190 (2), 189 (2) [M^+], 161 (11), 145 (7), 117 (77), 116 (100), 90 (14), 89 (32). IR (NaCl): $\tilde{\nu}$ = 2230 (s), 1735 (vs), 1609 (m), 1510 (m), 1471 (m), 1366 (m), 1343 (m), 1220 (s), 1172 (s), 1112 (m), 1031 (s), 827 (s), 757 (s) cm^{-1}. Anal. Calcd. for $C_{11}H_{11}NO_2$: C 69.83, H 5.86, N 7.40; found: C 69.83 , H 6.00, N 7.25.

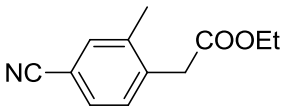


Ethyl 2-(3-cyanophenyl)acetate (2.2-3q): [CAS-No. 210113-91-0]

Compound **2.2-3q** was synthesized according to general procedure B from diethyl malonate (1.0 ml, 6.6 mmol) and 3-bromobenzonitrile (182 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 10:90), **2.2-3q** (145 mg, 77%) was obtained as a white solid. M.p. 50 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.56 (s, 1H), 7.52 (dd, *J* = 12.0 Hz, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 8.0 Hz, 1H), 4.14 (q, *J* = 8.0 Hz, 2H), 3.62 (s, 2H), 1.24 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-

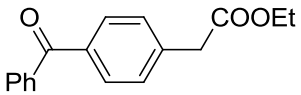
NMR (101 MHz, $CDCl_3$): δ = 170.3, 135.5, 133.8, 132.8, 130.7, 129.2, 118.5, 112.5, 61.2, 40.6, 14.0 ppm. EI-MS (70 eV), *m/z* (%): 190 (2), 189 (4) [M^+], 161 (17), 145 (5), 117 (83), 116 (100), 90 (13), 89 (33). IR (KBr): $\tilde{\nu}$ = 2981 (w), 2229 (s), 1733 (vs), 1414 (m), 1369 (m), 1340 (m), 1245 (s), 1168 (vs), 1028 (s), 865 (m), 817 (s), 746 (s), 686 (s) cm^{-1}. Anal. Calcd. for $C_{11}H_{11}NO_2$: C 69.83, H 5.86, N 7.40; found: C 69.60, H 5.83, N 7.33.



Ethyl 2-(4-cyano-2-methylphenyl)acetate (2.2-3r)

Compound **2.2-3r** was synthesized according to general procedure B from diethyl malonate (1.0 ml, 6.6 mmol) and 4-bromo-3-methylbenzonitrile (200 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 10:90), **2.2-3r** (190 mg, 93 %) was obtained as a light yellow oil.

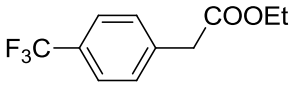
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.49-7.41 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 4.14 (q, *J* = 8.0 Hz, 2H), 3.65 (s, 2H), 2.33 (s, 3H), 1.23 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.1, 138.3, 133.6, 130.9, 129.8, 118.8, 111.1, 61.2, 39.2, 19.4, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 204 (9), 203 (29) [M^+], 157 (19), 131 (40), 130 (100), 129 (20), 104 (16), 103 (37), 102 (12), 77 (23). IR (NaCl): $\tilde{\nu}$ = 2981 (vs), 2935 (s), 2229 (vs), 1731 (vs), 1607 (m), 1569 (w), 1499 (m), 1367 (s), 1334 (s), 1256 (s), 1234 (s), 1216 (s), 1174 (s), 1162 (s), 1030 (s), 886 (w), 838 (w), 808 (w), 788 (w) cm^{-1}. Anal. Calcd. for $C_{12}H_{13}NO_2$: H 6.45, C 70.92, N 6.89; found: H 6.61, C 70.63, N 6.56.



Ethyl 2-(4-benzoylphenyl)acetate (2.2-3t) [CAS-No. 24021-67-8]

Compound **2.2-3t** was synthesized according to general procedure B from diethyl malonate (1.0 ml, 6.6 mmol) and 4-bromobenzophenone (261 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 5:95), **2.2-3t** (255 mg, 95 %) was obtained as a white solid. M.p. 61 °C.

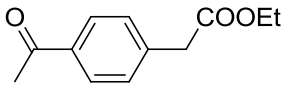
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.77 (t, *J* = 8.0 Hz, 4H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 4.16 (q, *J* = 8.0 Hz, 2H), 3.68 (s, 2H), 1.25 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 196.2, 170.8, 138.8, 137.5, 136.3, 132.3, 130.3, 129.9, 129.2, 128.2, 61.1, 41.3, 14.1 ppm. EI-MS (70 eV), m/z (%): 269 (25), 268 (99) [M^+], 196 (44), 195 (70), 192 (94), 168 (100), 105 (69), 89 (51), 77 (51). IR (KBr): $\tilde{\nu}$ = 2981 (vs), 2935 (m), 1734 (vs), 1654 (vs), 1607 (s), 1578 (m), 1446 (m), 1277 (m), 1150 (m), 1029 (m), 701 (s) cm^{-1}. Anal. Calcd. for $C_{17}H_{16}O_3$: C 76.10, H 6.01; found: C 75.99, H 6.07.



Ethyl 2-(4-(trifluoromethyl)phenyl)acetate (2.2-3u) [CAS-No. 721-63-1]

Compound **2.2-3u** was synthesized according to general procedure B from diethyl malonate (1.0 ml, 6.6 mmol) and 4-bromobenzotrifluoride (227 mg, 142 µL, 1.00 mmol) or 4-chlorobenzotrifluoride (184 mg, 136 µL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 10:90), **2.2-3u** (190 mg, 82 %; 170 mg, 73 %) was obtained as a white solid. M.p. 37 °C.

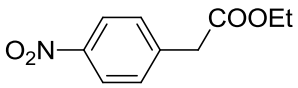
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 4.17 (q, *J* = 8.0 Hz, 2H), 3.68 (s, 2H), 1.27 (t, *J* = 8.0 Hz, 3H) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = 62.6 (s, Ar-F) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.7, 138.1, 129.6, 129.4 (q, $^2J_{C\text{-}F}$ = 32.3 Hz), 125.4 (q, $^3J_{C\text{-}F}$ = 4.0 Hz), 124.1 (q, $^1J_{C\text{-}F}$ = 272.7 Hz), 61.1, 41.0, 14.0 ppm. EI-MS (70 eV), *m/z* (%): 233 (7), 232 (5) [M^+], 213 (14), 204 (18), 160 (23), 159 (100). IR (KBr): $\tilde{\nu}$ = 2983 (vs), 2938 (s), 1735 (vs), 1619 (m), 1586 (w), 1420 (m), 1326 (vs), 1164 (s), 1124 (s), 1067 (s), 1020 (m), 823 (w) cm^{-1}. Anal. Calcd. for $C_{11}H_{11}F_3O_3$: C 56.90, H 4.77; found: C 56.50, H 4.98.



Ethyl 2-(4-acetylphenyl)acetate (2.2-3v) [CAS-No. 1528-42-3]

Compound **2.2-3v** was synthesized according to general procedure B from diethyl malonate (1.0 ml, 6.6 mmol) and 4-bromoacetophenone (199 mg, 1.00 mmol) or 4-chloroacetophenone (155 mg, 130 µL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 15:85), **2.2-3v** (150 mg, 73 %; 180 mg, 87 %) was obtained as a white solid. M.p. 61 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.14 (q, *J* = 8.0 Hz, 2H), 3.65 (s, 2H), 2.57 (s, 3H), 1.23 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 197.6, 170.7, 139.4, 135.9, 129.7, 128.5, 61.1, 41.3, 26.6, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 207 (10) [M^+], 191 (100), 163 (21), 133 (20), 118 (10), 105 (35), 89 (21). IR (KBr): $\tilde{\nu}$ = 1735 (vs), 1683 (s), 1607 (m), 1472 (m), 1368 (m), 1269 (m), 1110 (m), 1031 (m), 957 (w) cm^{-1}. Anal. Calcd. for $C_{12}H_{14}O_3$: C 69.88, H 6.84; found: C 69.80, H 6.90.



Ethyl 2-(4-nitrophenyl)acetate (2.2-3w) [CAS-No. 2122-70-5]

Compound **2.2-3w** was synthesized according to general procedure B from diethyl malonate (1.0 ml, 6.6 mmol) and 1-bromo-4-nitrobenzene (202 mg, 1.00 mmol) or 1-chloro-4-

nitrobenzene (158 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate - hexane 15:85), **2.2-3w** (125 mg, 60 %; 147 mg, 70 %) was obtained as a yellow solid. M.p. 61 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 4.16 (q, *J* = 8.0 Hz, 2H), 3.17 (s, 2H), 1.25 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.1, 147.1, 141.4, 130.2, 123.7, 61.4, 41.0, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 210 (29), 209 (20) [M^+], 137 (100), 136 (72), 107 (99), 106 (41), 91 (21), 89 (94), 78 (90). IR (KBr): $\tilde{\nu}$ = 2984 (m), 1734 (vs), 1604 (m), 1521 (s), 1348 (m), 1223 (m), 1174 (m), 1030 (m), 859 (m), 807 (m), 718 (m) cm^{-1}. Anal. Calcd. for $C_{10}H_{11}NO_4$: C 57.41, H 5.30, N 6.70; found: C 57.61, H 5.50, N 6.30.

8.6 Palladium/Copper-Catalyzed Di-α-arylation of Acetic Acid Esters

8.6.1 Preparation of Copper Complexes (3.2-8b-i)

The copper complex precursors $Cu(PPh_3)_3X$ were prepared according to literature precedures.[1]

Synthesis of $Cu(PPh_3)_3I$ [CAS-No. 15709-82-7]

CuI (952 mg, 5 mmol) and triphenylphosphine (3.94 g, 15 mmol) was refluxed for 3h in chloroform (20 mL) and the hot, clear solution was filtered. On slow cooling and evaporation of the solvent, the products seperated as colourless crystals (4.6 g, 94%). M.p. 152-153 °C. IR (KBr): $\tilde{\nu}$ = 3052 (w), 1480 (s), 1434 (s), 1087 (s), 741 (s), 733 (s), 689 (vs) cm^{-1}. Anal. Calcd. for $C_{54}H_{45}CuIP_3$: H 4.64, C 66.36; found: H 4.72, C 66.14.

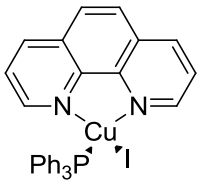
Synthesis of $Cu(PPh_3)_3Br$ [CAS-No. 15709-74-7]

CuBr (2.87 g, 20 mmol) and triphenylphosphine (15.74 g, 60 mmol) was refluxed for 3h in chloroform (70 mL) and the hot, clear solution was filtered. On slow cooling and evaporation of the solvent, the products seperated as colourless crystals (16 g, 86%). M.p. 171-172°C. IR (KBr): $\tilde{\nu}$ = 3047 (w), 1480 (s), 1435 (s), 1090 (s), 741 (s), 734 (s), 692 (vs) cm^{-1}. Anal. Calcd. for $C_{54}H_{45}CuBrP_3$: H 4.88, C 69.72; found: H 4.51, C 68.98.

Synthesis of $Cu(PPh_3)_3Cl$ [CAS-No. 15709-76-9]

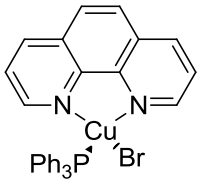
CuCl (495 mg, 5 mmol) and triphenylphosphine (3.94 g, 15 mmol) was refluxed for 3h in chloroform (20 mL) and the hot, clear solution was filtered. On slow cooling and evaporation of the solvent, the products seperated as colourless crystals (3.8 g, 86%). M.p. 169-170 °C. IR (KBr): $\tilde{\nu}$ = 3047 (w), 1480 (s), 1435 (s), 1092 (s), 744 (s), 734 (s), 692 (vs) cm^{-1}. Anal. Calcd. for $C_{54}H_{45}CuClP_3$: C 73.22; H 5.12, found: C 72.41, H 5.10.

The copper complexes $[Cu(Phen)(PPh_3)X]$ were prepared according to literature procedures.[2]



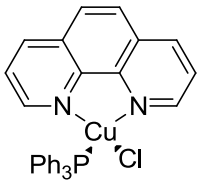
[Cu(Phen)(PPh$_3$)I] (**3.2-8b)** [CAS-No. 25753-85-9]

In an Erlenmeyer flask equipped with a Teflon-coated magnetic stirrer, tris(triphenylphosphine)copper(I) iodide (977 mg, 1 mmol) was added to chloroform (50 mL). After complete dissolution, 1,10-phenanthroline (180 mg, 1 mmol) was then added. The colorless solution immediately changed to orange. The contents of the flask were stirred for 25 minutes at room temperature. Afterwards the solvent was removed under reduced pressure to afford an orange-yellow solid. Recrystallization was achieved by layering diethyl ether (40 mL) onto a solution of the solid in dichloromethane (20 mL), giving a bright yellow solid (530 mg, 84 %). M.p. 223-224 °C (decomposed). IR (KBr): $\tilde{\nu}$ = 3034 (w), 1478 (m), 1434 (s), 1092 (s), 858 (s), 847 (s), 739 (m), 729 (m), 691 (vs) cm^{-1}. Anal. Calcd. for $C_{30}H_{23}CuIN_2P$: C 56.93, H 3.66, N 4.43; found: C 56.53, H 3.78, N 4.43.



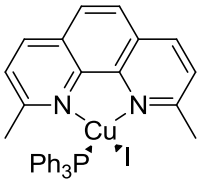
[Cu(Phen)(PPh$_3$)Br] (**3.2-8c)** [CAS-No. 25753-84-8]

In an Erlenmeyer flask equipped with a Teflon-coated magnetic stirrer, tris(triphenylphosphine)copper(I) bromide (3.7 g, 4 mmol) was added to chloroform (100 mL). After complete dissolution, 1,10-phenanthroline (721 mg, 4 mmol) was then added. The colorless solution immediately changed to orange. The contents of the flask were allowed to stir for 25 minutes at room temperature. Afterwards the solvent was removed under reduced pressure to afford an orangeyellow solid. Recrystallization was achieved by layering diethyl ether (40 mL) onto a solution of the solid in dichloromethane (20 mL) giving a bright yellow solid (2.1 g, 90 %). M.p. 256-257 °C (decomposed). IR (KBr): $\tilde{\nu}$ = 3015 (w), 1509 (m), 1480 (m), 1435 (m), 1425 (m), 1365 (m), 1217 (m), 1095 (m), 846 (s), 745 (s), 727 (s), 696 (vs) cm^{-1}. Anal. Calcd. for $C_{30}H_{23}CuBrN_2P$: C 61.50, H 3.96, N 4.78; found: C 61.44, H 4.05, N 4.74.



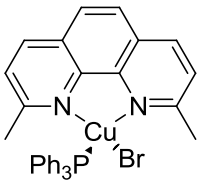
[Cu(Phen)(PPh$_3$)Cl] (**3.2-8d)** [CAS-No. 14751-81-6]

In an Erlenmeyer flask equipped with a Teflon-coated magnetic stirrer, tris(triphenylphosphine)copper(I) chloride (3.7 g, 4 mmol) was added to chloroform (100 mL). After complete dissolution, 1,10-phenanthroline (721 mg, 4 mmol) was then added. The colorless solution immediately changed to orange. The contents of the flask were stirred for 25 minutes at room temperature. Afterwards the solvent was removed under reduced pressure to afford an orangeyellow solid. Recrystallization was achieved by layering diethyl ether (40 mL) onto a solution of the solid in dichloromethane (20 mL), giving a bright yellow solid (2.1 g, 90 %). M.p. 248-249 °C (decomposed). IR (KBr): $\tilde{\nu}$ = 3014 (w), 1509 (w), 1480 (w), 1434 (m), 1426 (m), 1365 (m), 1217 (m), 1096 (m), 845 (s), 745 (s), 727 (s), 696 (vs) cm^{-1}. Anal. Calcd. for $C_{30}H_{23}CuClN_2P$: C 61.50, H 3.96, N 4.78; found: C 61.44, H 4.05, N 4.74.



[Cu(neocup)(PPh$_3$)I] (**3.2-8e)** [CAS-No. 828935-28-0]

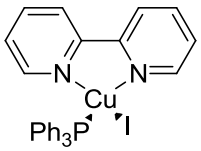
In an Erlenmeyer flask equipped with a Teflon-coated magnetic stirrer, tris(triphenylphosphine)copper(I) iodide (977 mg, 1 mmol) was added to chloroform (50 mL). After complete dissolution, neocuproine (208 mg, 1 mmol) was then added. The colorless solution immediately changed to orange. The contents of the flask were allowed to stir for 25 minutes at room temperature. Afterwards the solvent was removed under reduced pressure to afford an orangeyellow solid. Recrystallization was achieved by layering diethyl ether (40 mL) onto a solution of the solid in dichloromethane (20 mL) giving a yellow solid (560 mg, 85 %). M.p. > 300 °C (decomposed). IR (KBr): $\tilde{\nu}$ = 3053 (w), 1588 (m), 1500 (m), 1480 (m), 1434 (s), 1373 (m), 1361 (m), 1090 (m), 870 (s), 753 (s), 740 (s), 692 (vs) cm^{-1}. Anal. Calcd. for $C_{32}H_{27}CuIN_2P \cdot ½\ CH_2Cl_2$: C 55.49, H 4.01, N 3.98; found: C 55.61, H 4.12, N 4.06.



[Cu(neocup)(PPh$_3$)Br] (**3.2-8f**) [CAS-No. 391684-10-9]

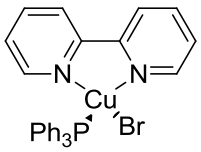
In an Erlenmeyer flask equipped with a Teflon-coated magnetic stirrer, tris(triphenylphosphine)copper(I) bromide (1.4 g, 1.5 mmol) was added to chloroform (50 mL). After complete dissolution, neocuproine (312 mg, 1.5 mmol) was then added. The colorless solution immediately changed to orange. The contents of the flask were stirred for 25 minutes at room temperature. Afterwards the solvent was removed under reduced pressure to afford an orange-yellow solid. Recrystallization was achieved by layering diethyl ether (40 mL) onto a solution of the solid in dichloromethane (20 mL), giving a bright yellow solid (850 mg, 92 %). M.p. 276-277 °C. IR (KBr): $\tilde{\nu}$ = 3050 (w), 1587 (m), 1498 (m), 1480 (m), 1434 (s), 1090 (m), 869 (s), 753 (s), 740 (s), 691 (vs) cm^{-1}. Anal. Calcd. for $C_{32}H_{27}CuBrN_2P$: C 62.60, H 4.43, N 4.56; found: C 62.50, H 4.61, N 4.63.

The copper complexes [Cu(bpy)(PPh$_3$)X] were prepared according to literature procedures.[3]



[Cu(bpy)(PPh$_3$)I] (**3.2-8g**) [CAS-No. 25753-82-6]

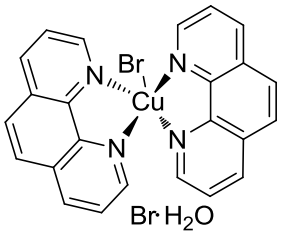
A mixture of CuI (400 mg, 2.1 mmol), 2,2'-bipyridine (328 mg, 2.1 mmol), and PPh$_3$ (551 mg, 2.1 mmol) was stirred for 30 min in CH_3CN. The starting materials dissolved to give an orange solution from which fine orange crystals of the compound precipitated (940 mg, 74 %). M.p. 215-216 °C (Lit.[3] 234-248 °C). IR (KBr): $\tilde{\nu}$ = 3053 (w), 3011 (w), 1592 (m), 1478 (m), 1465 (m), 1434 (s), 1307 (m), 1093 (s), 757 (vs), 744 (vs), 693 (vs) cm^{-1}. Anal. Calcd. for $C_{28}H_{23}CuIN_2P$: C 55.23, H 3.81, N 4.60; found: C 51.27, H 3.66, N 4.56.



[Cu(bpy)(PPh$_3$)I] 3.2-8h [CAS-No. 25753-81-5]

A mixture of CuI (400 mg, 2.1 mmol), 2,2'-bipyridine (301 mg, 2.1 mmol), and PPh$_3$ (551 mg, 2.1 mmol) was stirred for 30 min in CH_3CN. The starting materials dissolved to give an orange solution from which fine orange crystals of the compound precipitated (830 mg, 74 %). M.p 217-218 °C (Lit.[3] 234-248 °C). IR (KBr): $\tilde{\nu}$ = 3053 (w), 3009 (w), 1591 (m), 1478 (m),

1465 (m), 1435 (s), 1307 (m), 1094 (s), 745 (vs), 694 (vs) cm^{-1}. Anal. Calcd. for $C_{28}H_{23}BrCuN_2P$: C 59.85, H 4.13, N 4.99; found: C 59.21, H 4.21, N 4.97.



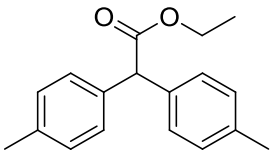
[Cu(bpy)(PPh$_3$)I] (**3.2-8i**) [CAS-No. 199582-45-1]

This compound was prepared according to literature methods.[4] Copper(II) bromide (1.11 g, 5 mmol) and 1,10-phenanthroline monohydrate (1.98 g, 10 mmol) were dissovled in 20 mL of MeOH/H_2O (1:1, 20 mL) and the solution was refluxed for 2 h under stirring. Dark green crystallline precipitate was separated from the warm solution, washed with MeOH/H_2O (1:1), chloroform, and diethyl ether. Recrystallization from MeOH/H_2O (1:1) gave a green solid (2.64 g, 88 %). M.p. > 300 °C. IR (KBr): $\tilde{\nu}$ = 3490 (m), 3298 (w), 3231 (w), 1582 (w), 1515 (m), 1426 (s), 1226 (m), 851 (vs), 721 (vs) cm^{-1}. Anal. Calcd. for $C_{24}H_{18}Br_2CuN_4O$: C 47.90, H 3.01, N 9.31; found: C 47.98, H 3.17, N 9.35.

8.6.2 General Procedure for the Pd/Cu-Catalyzed Diarylation

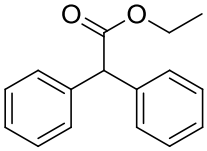
An oven-dried 20 mL vessel equipped with a septum cap and a stirrer bar, was charged with potassium phosphate (636.8 mg, 3.0 mmol). The reaction vessel was evacuated and flushed with nitrogen three times. Subsequently, a solution of the corresponding aryl halide (1.0 mmol), alkyl acetate (5.0 mmol), palladium acetate (4.5 mg, 0.02 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (13.0 mg, 0.044 mmol), [Cu(Phen)(PPh$_3$)Br] (14.0 mg, 0.024 mmol) and the internal standard *n*-tetradecane (50 µL) in DMF (3 mL) was added via syringe. The resulting mixture was stirred at 110 °C for 24 h, and the crude reaction mixture was cooled, diluted with ethyl acetate. The solution was washed successively with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate gradient) or Kugelrohr distillation *in vacuo* (180-250 °C, 3.0×10^{-2} mBar), yielding the corresponding products **3.2-6**.

8.6.3 Sythesis of Diaryl Acetates



Ethyl 2,2-di(*p*-tolyl)acetate (**3.2-6aa**) [CAS-No. 23597-04-8]

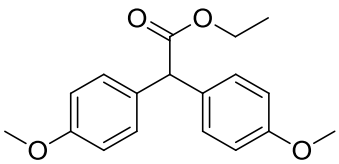
Compound **3.2-6aa** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 4-bromotoluene (171 mg, 126 µL, 1.0 mmol). After distillation, **3.2-6aa** (115 mg, 86 %) was obtained as a white solid, m.p. 65 °C.^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.0 Hz, 4H), 7.13 (d, *J* = 8.0 Hz, 4H), 4.95 (s, 1H), 4.21 (q, *J* = 8.0 Hz, 2H), 2.33 (s, 6H), 1.26 (t, *J* = 8.0 Hz, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.7, 136.7, 136.0, 129.2, 128.4, 61.0, 56.3, 21.0, 14.1 ppm; EI-MS (70 eV), *m/z* (%): 296 (4) [M^+], 195 (100), 180 (27), 165 (25); IR (KBr): $\tilde{\nu}$ = 2977 (m), 1732 (vs), 1508 (s), 1477 (m), 1368 (m), 1277 (m), 1149 (s), 1020 (m), 806 (m), 777 (m), 755 (s) cm^{-1}; Anal. Calcd. for $C_{18}H_{20}O_2$: C 80.56, H 7.51; found: C 80.77, H 7.20.



Ethyl 2,2-diphenylacetate (**3.2-6ab**) [CAS-No. 3468-99-3]

Compound **3.2-6ab** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.66 mL, 5.0 mmol) and bromobenzene (157 mg, 105 µL, 1.0 mmol). After distillation, **3.2-6ab** (108 mg, 90 %) was obtained as a white solid, m.p. 59 °C.

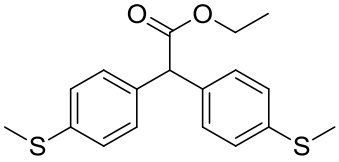
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.30-7.20 (m, 10H), 4.98 (s, 1H), 4.17 (q, *J* = 8.0 Hz, 2H), 1.22 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.5, 138.7, 128.6, 128.5, 127.2, 61.2, 57.1, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 240 (11) [M^+], 167 (100), 165 (40). IR (KBr): $\tilde{\nu}$ = 1728 (vs), 1597 (m), 1582 (m), 1511 (vs), 1490 (m), 1454 (s), 1369 (m), 1345 (m), 1309 (m), 1277 (m), 1187 (m), 1021 (m), 744 (m), 707 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{16}H_{16}O_2$: 240.1150, *m/z* found: 240.1155.



Ethyl 2,2-bis(4-methoxyphenyl)acetate (**3.2-6ac**) [CAS-No. 121090-64-0]

Compound **3.2-6ac** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 4-bromoanisole (187 mg, 126 µL, 1.0 mmol). After distillation, **3.2-6ac** (140 mg, 93 %) was obtained as colorless oil.

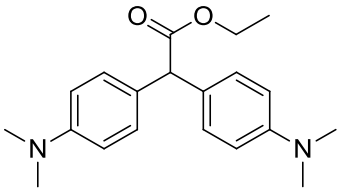
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.0 Hz, 4H), 6.85 (d, *J* = 8.0 Hz, 4H), 4.91 (s, 1H), 4.19 (q, *J* = 8.0 Hz, 2H), 3.78 (s, 6H), 1.25 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.0, 158.6, 131.3, 129.5, 113.9, 61.0, 55.4, 55.2, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 300 (7) [M^+], 227 (100), 196 (5), 169 (11). IR (NaCl): $\tilde{\nu}$ = 2956 (m), 2835 (s), 1733 (vs), 1610 (vs), 1583 (m), 1511 (vs), 1463 (m), 1303 (m), 1250 (m), 1178 (m), 1152 (m), 1033 (m), 833 (m), 812 (m) cm^{-1}. Anal. Calcd. for $C_{18}H_{20}O_4$: C 71.98, H 6.71; found: C 71.94, H 6.61.



Ethyl 2,2-bis(4-(methylthio)phenyl)acetate (3.2-6ad)

Compound **3.2-6ad** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 4-bromothioanisole (203 mg, 1.0 mmol). After distillation, **3.2-6ad** (140 mg, 84 %) was obtained as colorless oil.

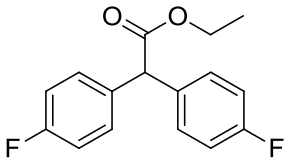
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25-7.18 (m, 8H), 4.92 (s, 1H), 4.20 (q, *J* = 8.0 Hz, 2H), 2.45 (s, 6H), 1.25 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.2, 137.4, 135.4, 128.9, 126.7, 61.2, 55.9, 15.7, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 333 (7), 332 (33) [M^+], 259 (100), 165 (26). IR (NaCl): $\tilde{\nu}$ = 2979 (s), 2918 (s), 1732 (vs), 1596 (s), 1493 (s), 1437 (s), 1152 (m), 1093 (m), 1028 (m), 1016 (m), 798 (s) cm^{-1}. Anal. Calcd. for $C_{18}H_{20}O_2S_2$: C 65.02, H 6.06, S 19.29; found: C 64.83, H 5.66, S 18.97.



Ethyl 2,2-bis(4-(dimethylamino)phenyl)acetate (3.2-6ae) [CAS-No. 74283-75-3]

Compound **6ae** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 4-bromo-*N*,*N*-dimethylaniline (200 mg, 1.0 mmol). After distillation, **6ae** (120 mg, 74 %) was obtained as a blue solid, m.p. 72 C.

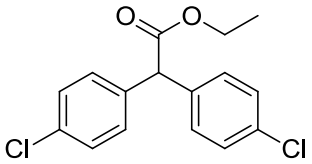
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 12.0 Hz, 4H), 6.70 (d, *J* = 12.0 Hz, 4H), 4.85 (s, 1H), 4.20 (q, *J* = 8.0 Hz, 2H), 2.92 (s, 12H), 1.26 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.5, 149.5, 129.1, 127.4, 112.6, 60.7, 55.3, 40.8, 14.2 ppm. EI-MS (70 eV), *m/z* (%): 327 (7), 326 (30) [M^+], 253 (100), 237 (16), 165 (6). IR (KBr): $\tilde{\nu}$ = 2957 (m), 1725 (vs), 1611 (vs), 1520 (vs), 1350 (s), 1154 (s), 1061 (s), 948 (s), 802 (s), 747 (m) cm^{-1}. Anal. Calcd. for $C_{20}H_{26}N_2O_2$: C 73.59, H 8.03, N 8.58; found: C 73.60, H 8.02, N 8.18.



Ethyl 2,2-bis(4-fluorophenyl)acetate (3.2-6af) [CAS-No. 386-99-2]

Compound **3.2-6af** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 4-fluorotoluene (175 mg, 110 µL, 1.0 mmol). After distillation, **3.2-6af** (130 mg, 94 %) was obtained as colorless oil.

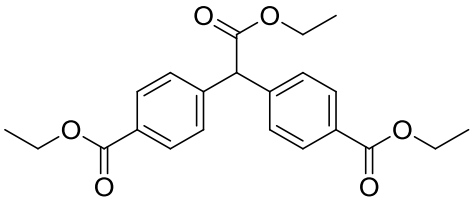
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -115.2 (m, Ar-F) ppm. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.19 (t, *J* = 8.0 Hz, 4H), 6.93 (t, *J* = 8.0 Hz, 4H), 4.89 (s, 1H), 4.13 (q, *J* = 8.0 Hz, 2H), 1.17 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.2, 162.0 (d, $^{1}J_{C\text{-}F}$ = 246.4 Hz), 134.4 (d, $^{4}J_{C\text{-}F}$ = 4.0 Hz), 130.0 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.2 Hz), 61.3, 55.4, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 277 (1), 276 (4) [M^+], 203 (100), 201 (27), 183 (46). IR (NaCl): $\tilde{\nu}$ = 2983 (vs), 1734(vs), 1604 (vs), 1508 (vs), 1368 (s), 1228 (s), 1157 (s), 1028 (vs), 837 (vs) cm^{-1}. Anal. Calcd. for $C_{16}H_{14}F_2O_2$: C 69.56, H 5.11; found: C 69.74, H 5.27.



Ethyl 2,2-bis(4-chlorophenyl)acetate (3.2-6ag) [CAS-No. 30738-51-3]

Compound **3.2-6ag** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 1-bromo-4-chlorobenzene (191 mg, 1.0 mmol). After distillation, **3.2-6ag** (100 mg, 65 %) was obtained as a white solid, m.p. 86 °C.

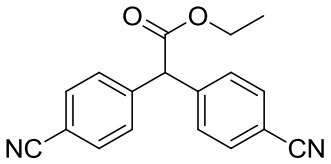
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.0 Hz, 4H), 7.22 (d, *J* = 8.0 Hz, 4H), 4.93 (s, 1H), 4.20 (q, *J* = 8.0 Hz, 2H), 1.25 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.8, 136.8, 133.4, 129.8, 128.8, 61.5, 55.7, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 310 (4) [M^+, ^{37}Cl], 308 (8) [M^+, ^{35}Cl], 237 (66), 235 (100), 202 (7), 200 (21), 165 (58). IR (KBr): $\tilde{\nu}$ = 2981 (m), 1733 (vs), 1489 (vs), 1408 (s), 1368 (s), 1297 (s), 1270 (s), 1190 (s), 1155 (vs), 1091 (s), 1015 (s), 851 (s), 805 (s), 776 (s) cm^{-1}. Anal. Calcd. for $C_{16}H_{14}Cl_2O_2$: C 62.15, H 4.56; found: C 62.34, H 4.78.



Diethyl 4,4'-(2-ethoxy-2-oxoethane-1,1-diyl)dibenzoate (3.2-6ah)

Compound **3.2-6ah** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and ethyl 4-bromobenzoate (229 mg, 160 µL, 1.0 mmol). After distillation, **3.2-6ah** (168 mg, 87 %) was obtained as colorless oil.

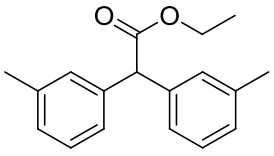
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.0 Hz, 4H), 7.49 (d, *J* = 8.0 Hz, 4H), 4.36 (m, 7H), 1.37 (t, *J* = 8.0 Hz, 6H), 1.26 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.3, 166.1, 146.1, 130.3, 129.4, 127.3, 80.5, 63.4, 61.1, 14.3, 13.9 ppm. EI-MS (70 eV), *m/z* (%): 384 (1) [M^+], 339 (12), 312 (29), 311 (100), 283 (8), 165 (21). IR (NaCl): $\tilde{\nu}$ = 2980 (s), 1732 (s), 1718 (vs), 1607 (s), 1445 (m), 1417 (m), 1367 (s), 1275 (vs), 1105 (vs), 1021 (vs), 863 (m), 759 (s), 711 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{22}H_{24}O_6$: 384.1573, *m/z* found: 384.1554.



Ethyl 2,2-bis(4-cyanophenyl)acetate (3.2-6ai)

Compound **3.2-6ai** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 4-bromobenzonitrile (182 mg, 1.0 mmol). After purification by column chromatography, **3.2-6ai** (80 mg, 55 %) was obtained as a white solid, m.p. 94 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.0 Hz, 4H), 7.40 (d, *J* = 8.0 Hz, 4H), 5.07 (s, 1H), 4.22 (q, *J* = 8.0 Hz, 2H), 1.24 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.4, 142.5, 132.5, 129.3, 118.3, 111.8, 62.0, 56.7, 14.0 ppm. EI-MS (70 eV), *m/z* (%): 290 (3) [M^+], 246 (5), 218 (53), 217 (100), 190 (35). IR (KBr): $\tilde{\nu}$ = 2982 (m), 2229 (vs), 1736 (vs), 1603 (s), 1499 (s), 1416 (m), 1334 (s), 1204 (s), 1161 (s), 1028 (s), 853 (s), 817 (s), 791 (s) cm^{-1}. Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C 74.47, H 4.86, N 9.65; found: C 74.09, H 4.95, N 9.61.

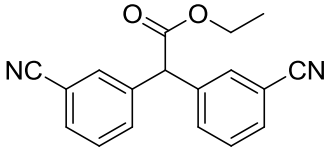


Ethyl 2,2-di(*m*-tolyl)acetate (3.2-6aj)

Compound **3.2-6aj** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 3-bromotoluene (171 mg, 121 µL, 1.0 mmol). After distillation, **3.2-6aj** (121 mg, 90 %) was obtained as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.13 (t, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 4H), 6.99 (d, *J* = 8.0 Hz, 2H), 4.87 (s, 1H), 4.13 (q, *J* = 8.0 Hz, 2H), 2.25 (s, 6H), 1.18 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.6, 138.7, 138.1, 129.2, 128.4, 127.9, 125.6,

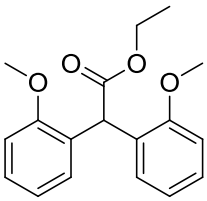
61.1, 57.0, 21.4, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 268 (8) [M^+], 196 (17), 195 (100), 180 (29), 165 (27). IR (NaCl): $\tilde{\nu}$ = 2980 (m), 1735 (vs), 1605 (s), 1458 (m), 1157 (vs), 1032 (s), 741 (m), 700 (m) cm^{-1}. Anal. Calcd. for $C_{16}H_{14}F_2O_2$: C 80.56, H 7.51; found: C 80.22, H 7.49.



Ethyl 2,2-bis(3-cyanophenyl)acetate (3.2-6ak)

Compound **3.2-6ak** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 3-bromobenzonitrile (182 mg, 1.0 mmol). After purification by column chromatography, **3.2-6ak** (100 mg, 69 %) was obtained as colorless oil.

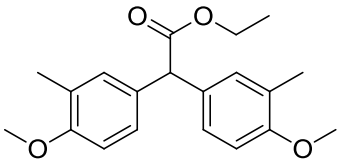
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60-7.50 (m, 6H), 7.47 (t, *J* = 8.0 Hz, 2H), 5.03 (s, 1H), 4.23 (q, *J* = 8.0 Hz, 2H), 1.25 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.5, 138.9, 132.9, 132.0, 131.4, 129.7, 118.2, 113.0, 62.0, 55.7, 14.0 ppm. EI-MS (70 eV), *m/z* (%): 291 (2) [M^+], 246 (14), 218 (100), 217 (100), 191 (18), 190 (62). IR (NaCl): $\tilde{\nu}$ = 2983 (s), 2230 (vs), 1732 (vs), 1601 (s), 1582 (s), 1482 (vs), 1176 (vs), 1027 (vs), 807 (s), 737 (s), 687 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{18}H_{14}N_2O_2$: 290.1055, *m/z* found: 290.1041.



Ethyl 2,2-bis(2-methoxyphenyl)acetate (3.2-6al)

Compound **3.2-6al** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 2-bromoanisole (187 mg, 125 µL, 1.0 mmol). After purification by column chromatography, **3.2-6al** (105 mg, 70 %) was obtained as a white solid, m.p. 87 °C.

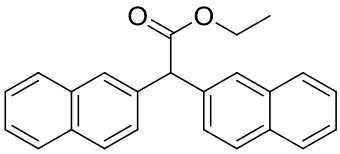
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (t, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.92-6.88 (m, 4H), 5.63 (s, 1H), 4.21 (q, *J* = 8.0 Hz, 2H), 3.81 (s, 6H), 1.25 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.3, 157.1, 129.2, 128.2, 126.8, 120.4, 110.4, 60.6, 55.4, 44.8, 14.2 ppm. EI-MS (70 eV), *m/z* (%): 310 (6), 300 (32) [M^+], 254 (16), 227 (61), 181 (24), 165 (8), 121 (100), 91 (20). IR (KBr): $\tilde{\nu}$ = 2936 (m), 2837 (s), 1734 (vs), 1600 (s), 1587 (m), 1491 (s), 1462 (s), 1438 (m), 1245 (s), 1182 (m), 1153 (m), 1029 (s), 753 (vs) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{18}H_{20}O_4$: 300.1362, *m/z* found: 300.1358.



Ethyl 2,2-bis(4-methoxy-3-methylphenyl)acetate (3.2-6am)

Compound **3.2-6am** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 4-bromo-1-methoxy-2-methylbenzene (201 mg, 1.0 mmol). After purification by column chromatography, **3.2-6am** (135 mg, 82 %) was obtained as colorless oil.

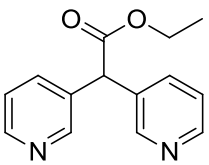
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.16-7.09 (m, 4H), 6.79 (d, *J* = 8.0 Hz, 2H), 4.88 (s, 1H), 4.22 (q, *J* = 8.0 Hz, 2H), 3.82 (s, 6H), 2.22 (s, 6H), 1.28 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.2, 156.8, 130.8, 130.7, 126.6, 109.8, 60.9, 55.5, 55.2, 16.3, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 328 (13) [M^+], 256 (23), 255 (100), 240 (5), 225 (5). IR (NaCl): $\tilde{\nu}$ = 2949 (m), 2834 (s), 1731 (vs), 1609 (s), 1503 (vs), 1463 (m), 1254 (s), 1154 (m), 1134 (s), 1033 (m), 888 (m), 815 (m) 750 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{24}O_4$: 328.1675, *m/z* found: 328.1661.



Ethyl 2,2-di(2-naphthyl)acetate (3.2-6an)

Compound **3.2-6an** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 2-bromonaphthaline (207 mg, 1.0 mmol). After purification by column chromatography, **3.2-6an** (140 mg, 82 %) was obtained as a white solid, m.p. 81 °C.

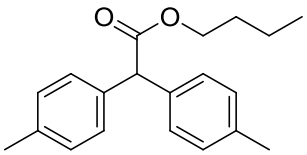
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.90-7.80 (m, 8H), 7.53-7.45 (m, 6H), 5.39 (s, 1H), 4.31 (q, *J* = 8.0 Hz, 2H), 1.32 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.4, 136.1, 133.3, 132.5, 128.3, 128.0, 127.6, 127.3, 126.8, 126.2, 126.0, 61.3, 57.3, 14.1 ppm. EI-MS (70 eV), *m/z* (%): 341 (13), 340 (44) [M^+], 268 (23), 267 (100), 126 (5). IR (KBr): $\tilde{\nu}$ = 2982 (w), 1728, 1596 (m), 1508 (s), 1448 (m),1363 (m), 1303 (s), 1179 (m), 1153 (m), 1031 (s), 896 (s), 868 (s), 761 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{24}H_{20}O_2$: 340.1463, *m/z* found: 300.1454.



Ethyl 2,2-di(3-pyridinyl)acetate (3.2-6ao)

Compound **3.2-6ao** was synthesized according to the general procedure from ethyl acetate (441 mg, 0.49 mL, 5.0 mmol) and 3-bromopyridine (158 mg, 97 µL, 1.0 mmol). After distillation, **3.2-6ao** (90 mg, 74 %) was obtained as colorless oil.

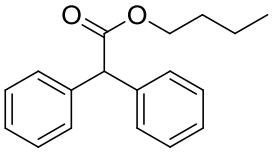
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.56 (s, sH), 8.53 (d, *J* = 4.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.27 (dd, *J* = 8.0, 4.0 Hz, 2H), 5.00 (s, 1H), 4.22 (q, *J* = 8.0 Hz, 2H), 1.25 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.9, 149.7, 149.0, 135.8, 133.6, 123.6, 61.9, 52.2, 14.0 ppm. EI-MS (70 eV), *m/z* (%): 243 (2), 242 (7) [M^+], 169 (100). IR (NaCl): $\tilde{\nu}$ = 2980 (m), 1734 (vs), 1575 (s), 1478 (s), 1425 (s), 1312 (m), 1156 (s), 1025 (vs), 713 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{14}H_{14}N_2O_2$: 242.1055, *m/z* found: 242.1046.



Butyl 2,2-di(*p*-tolyl)acetate (3.2-6ba)

Compound **3.2-6ba** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 4-bromotoluene (171 mg, 126 µL, 1.0 mmol). After distillation, **3.2-6ba** (120 mg, 81 %) was obtained as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.0 Hz, 4H), 7.29 (d, *J* = 8.0 Hz, 4H), 5.13 (s, 1H), 4.31 (t, *J* = 8.0 Hz, 2H), 2.49 (s, 6H), 1.77 (quin, *J* = 8.0 Hz, 2H), 1.49 (sext, *J* = 8.0 Hz, 2H), 1.06 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.8, 136.7, 136.0, 129.2, 128.4, 64.9, 56.4, 30.5, 21.0, 19.0, 13.6 ppm. EI-MS (70 eV), *m/z* (%): 296 (3) [M^+], 196 (17), 195 (100), 180 (23), 165 (21). IR (NaCl): $\tilde{\nu}$ = 2959 (s), 2930 (m), 2872 (m), 1736 (vs), 1512 (s), 1458 (m), 1307 (m), 1183 (m), 1150 (s), 1021 (s), 806 (m), 773 (m), 753 (m) cm^{-1}. Anal. Calcd. for $C_{20}H_{24}O_2$: C 81.04, H 8.16; found: C 81.43, H 7.94.

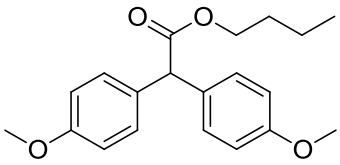


Butyl 2,2-diphenylacetate (3.2-6bb) [CAS-No. 58538-94-6]

Compound **6bb** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 4-bromobenzene (157 mg, 105 µL, 1.0 mmol). After distillation, **6bb** (120 mg, 89 %) was obtained as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.30-7.15 (m, 10H), 4.98 (s, 1H), 4.11 (t, *J* = 8.0 Hz, 2H), 1.56 (quin, *J* = 8.0 Hz, 2H), 1.27 (sext, *J* = 8.0 Hz, 2H), 0.84 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.5, 138.7, 128.6, 128.5, 127.1, 65.0, 57.2, 30.5, 19.0, 13.6 ppm. EI-MS (70 eV), *m/z* (%): 268 (2) [M^+], 168 (15), 167 (100). IR (NaCl): $\tilde{\nu}$ = 2958 (s),

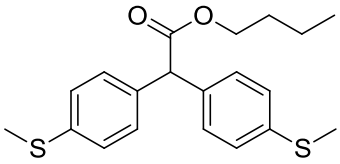
2871 (m), 1733 (vs), 1599 (s), 1584 (m), 1495 (s), 1453 (s), 1306 (m), 1188 (m), 1149 (m), 743 (s), 700 (vs) cm^{-1}. Anal. Calcd. for $C_{18}H_{20}O_2$: C 80.56, H 7.51; found: C 80.51, H 7.23.



Butyl 2,2-bis(4-methoxyphenyl)acetate (3.2-6bc)

Compound **3.2-6bc** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 4-bromoanisole (187 mg, 126 µL, 1.0 mmol). After distillation, **3.2-6bc** (140 mg, 85 %) was obtained as light yellow oil.

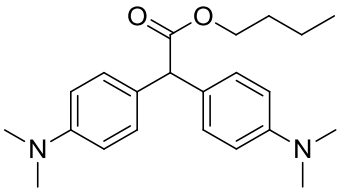
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 12.0 Hz, 4H), 6.77 (d, *J* = 8.0 Hz, 4H), 4.84 (s, 1H), 4.06 (t, *J* = 8.0 Hz, 2H), 3.69 (s, 6H), 1.52 (quin, *J* = 8.0 Hz, 2H), 1.24 (sext, *J* = 8.0 Hz, 2H), 0.81 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.0, 158.6, 131.2, 129.5, 113.8, 64.9, 55.5, 55.1, 30.5, 19.0, 13.6 ppm. EI-MS (70 eV), *m/z* (%): 328 (2) [M^+], 228 (16), 227 (100), 196 (5). IR (NaCl): $\tilde{\nu}$ = 2958 (s), 2836 (m), 1731 (vs), 1609 (s), 1583 (m), 1510 (vs), 1463 (m), 1249 (vs), 1177 (m), 1152 (m), 1034 (s), 831 (s) cm^{-1}. Anal. Calcd. for $C_{20}H_{24}O_4$: C 73.15, H 7.37; found: C 73.21, H 7.25.



Butyl 2,2-bis(4-(methylthio)phenyl)acetate (3.2-6bd)

Compound **3.2-6bd** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 4-bromothioanisole (203 mg, 1.0 mmol). After purification by column chromatography, **3.2-6bd** (150 mg, 83 %) was obtained as light yellow oil.

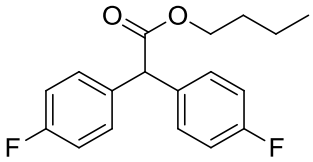
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.25-7.18 (m, 8H), 4.91 (s, 1H), 4.14 (t, *J* = 8.0 Hz, 2H), 2.45 (s, 6H), 1.59 (quin, *J* = 8.0 Hz, 2H), 1.30 (sext, *J* = 8.0 Hz, 2H), 0.88 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.4, 137.4, 135.5, 128.9, 126.7, 65.1, 56.0, 30.5, 19.0, 15.8, 13.6 ppm. EI-MS (70 eV), *m/z* (%): 361 (4), 360 (16) [M^+], 260 (18), 259 (100), 244 (5), 197 (6), 165 (16). IR (NaCl): $\tilde{\nu}$ = 2957 (m), 2920 (m), 2870 (m), 1731 (vs), 1593 (s), 1493 (s), 1436 (vs), 1189 (m), 1153 (m), 1093 (s), 1015 (s), 806 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{24}O_2S_2$: 360.1218, *m/z* found: 360.1210.



Butyl 2,2-bis(4-(dimethylamino)phenyl)acetate (3.2-6be)

Compound **3.2-6be** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 4-bromo-*N*,*N*-dimethylaniline (200 mg, 1.0 mmol). After purification by column chromatography, **3.2-6be** (90 mg, 51 %) was obtained as a yellow solid, m.p. 55 °C.

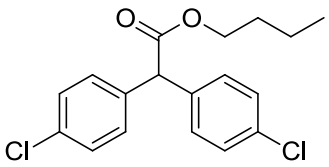
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.0 Hz, 4H), 6.69 (d, *J* = 8.0 Hz, 4H), 4.85 (s, 1H), 4.13 (t, *J* = 8.0 Hz, 2H), 2.92 (s, 12H), 1.61 (quin, *J* = 8.0 Hz, 2H), 1.34 (sext, *J* = 8.0 Hz, 2H), 0.90 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.6, 149.5, 129.1, 127.5, 112.6, 64.6, 55.4, 40.6, 30.6, 19.1, 13.7 ppm. EI-MS (70 eV), *m/z* (%): 355 (3), 354 (13) [M^+], 254 (20), 253 (100), 237 (16), 118 (4). IR (KBr): $\tilde{\nu}$ = 2928 (m), 1726 (vs), 1611 (s), 1518 (s), 1443 (m), 1340 (s), 1144 (m), 1019 (s), 832 (s), 798 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{22}H_{30}N_2O_2$: 354.2307, *m/z* found: 354.2310.



Butyl 2,2-bis(4-fluorophenyl)acetate (3.2-6bf)

Compound **3.2-6bf** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 1-bromo-4-fluorobenzene (175 mg, 110 µL, 1.0 mmol). After distillation, **3.2-6bf** (133 mg, 87 %) was obtained as colourless oil.

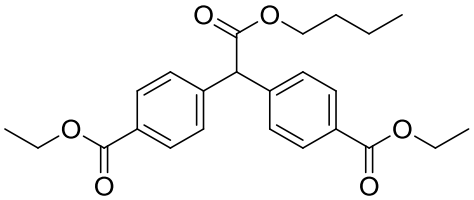
^{19}F-NMR (376 MHz, $CDCl_3$): δ = -115.2 (m, Ar-F) ppm. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29-7.24 (m, 4H), 7.01 (t, *J* = 8.0 Hz, 4H), 4.98 (s, 1H), 4.16 (t, *J* = 8.0 Hz, 2H), 1.60 (quin, *J* = 8.0 Hz, 2H), 1.31 (sext, *J* = 8.0 Hz, 2H), 0.89 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.3, 162.0 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 134.4 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 130.1 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz), 115.5 (d, $^{2}J_{C\text{-}F}$ = 22.2 Hz), 65.2, 55.5, 30.5, 19.0, 13.6 ppm. EI-MS (70 eV), *m/z* (%): 304 (1) [M^+], 203 (100), 184 (35). IR (NaCl): $\tilde{\nu}$ = 2960 (s), 2934 (m), 2873 (m), 1735 (vs), 1604 (vs), 1508 (vs), 1465 (m), 1228 (m), 1190 (m), 1157 (m), 1016 (s), 836 (s), 788 (m), 765 (m) cm^{-1}. Anal. Calcd. for $C_{18}H_{18}F_2O_2$: C 71.04, H 5.96; found: C 70.77, H 5.95.



Butyl 2,2-bis(4-chlorophenyl)acetate (3.2-6bg) [CAS-No. 42991-55-9]

Compound **3.2-6bg** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 1-bromo-4-chlorobenzene (191 mg, 1.0 mmol). After distillation, **3.2-6bg** (130 mg, 77 %) was obtained as light yellow oil.

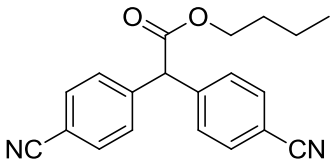
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.0 Hz, 4H), 7.21 (d, *J* = 8.0 Hz, 4H), 4.94 (s, 1H), 4.15 (t, *J* = 8.0 Hz, 2H), 1.59 (quin, *J* = 8.0 Hz, 2H), 1.31 (sext, *J* = 8.0 Hz, 2H), 0.89 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.8, 136.8, 133.4, 129.8, 128.8, 65.4, 55.8, 30.5, 19.0, 13.6 ppm. EI-MS (70 eV), *m/z* (%): 310 (4), 309 (2) [M^+], 308 (8), 237 (66), 235 (100), 200 (21), 165 (58). IR (NaCl): $\tilde{\nu}$ = 2960 (vs), 2873 (m), 1732 (vs), 1595 (m), 1491 (vs), 1465 (m), 1410 (s), 1300 (m), 1191 (s), 1154 (s), 1092 (vs), 1015 (vs), 800 (s), 775 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{18}H_{18}Cl_2O_2$: 336.0684, *m/z* found: 336.0673.



Diethyl 4,4'-(2-butoxy-2-oxoethane-1,1-diyl)dibenzoate (3.2-6bh)

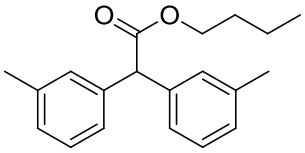
Compound **3.2-6bh** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and ethyl 4-bromobenzoate (229 mg, 160 µL, 1.0 mmol). After purification by column chromatography, **3.2-6bh** (102 mg, 50 %) was obtained as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.0 Hz, 4H), 7.36 (d, *J* = 8.0 Hz, 4H), 5.10 (s, 1H), 4.35 (q, *J* = 8.0 Hz, 4H) , 4.15 (t, *J* = 8.0 Hz, 2H), 1.58 (quin, *J* = 8.0 Hz, 2H), 1.36 (t, *J* = 8.0 Hz, 6H), 1.33-1.22 (m, 2H), 0.87 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 171.3, 166.1, 142.9, 129.9, 129.7, 128.6, 65.4, 61.0, 57.0, 30.4, 19.0, 14.3, 13.6 ppm. EI-MS (70 eV), *m/z* (%): 412 (2) [M^+], 367 (11), 312 (38), 311 (100), 283 (18), 238 (10), 165 (30). IR (NaCl): $\tilde{\nu}$ = 2960 (s), 1718 (vs), 1608 (s), 1275 (vs), 1105 (vs), 1021 (s), 759 (s), 711 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{24}H_{28}O_6$: 412.1886, *m/z* found: 412.1865.



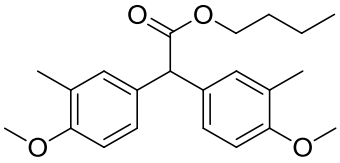
Butyl 2,2-bis(4-cyanophenyl)acetate (3.2-6bi)

Compound **3.2-6bi** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 4-bromobenzonitrile (182 mg, 1.0 mmol). After purification by column chromatography, **3.2-6bi** (90 mg, 57 %) was obtained as colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.0 Hz, 4H), 7.40 (d, *J* = 8.0 Hz, 4H), 5.08 (s, 1H), 4.16 (t, *J* = 8.0 Hz, 2H), 1.58 (quin, *J* = 8.0 Hz, 2H), 1.26 (sext, *J* = 8.0 Hz, 2H), 0.87 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.4, 142.5, 132.5, 129.3, 118.3, 111.8, 65.9, 56.8, 30.3, 18.9, 13.5 ppm. EI-MS (70 eV), *m/z* (%): 318 (1) [M^+], 218 (100), 190 (35). IR (NaCl): $\tilde{\nu}$ = 2960 (s), 2229 (vs), 1731 (vs), 1605 (s), 1503 (s), 1158 (s), 1020 (s), 820 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{18}N_2O_2$: 318.1368, *m/z* found: 318.1360.



Butyl 2,2-di(*m*-tolyl)acetate (3.2-6bj)

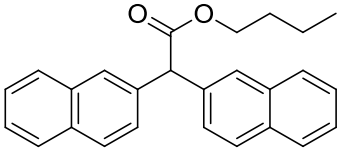
Compound **3.2-6bj** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 3-bromotoluene (171 mg, 121 µL, 1.0 mmol). After distillation, **3.2-6bj** (135 mg, 91 %) was obtained as colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.14 (t, *J* = 8.0 Hz, 2H), 7.08-6.98 (m, 6H), 4.88 (s, 1H), 4.09 (t, *J* = 8.0 Hz, 2H), 2.26 (s, 6H), 1.55 (quin, *J* = 8.0 Hz, 2H), 1.26 (sext, *J* = 8.0 Hz, 2H), 0.83 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.3, 138.7, 138.1, 129.3, 128.3, 127.9, 125.6, 64.9, 57.1, 30.5, 21.4, 19.0, 13.6 ppm. EI-MS (70 eV), *m/z* (%): 297 (3), 296 (15) [M^+], 196 (16), 195 (100), 180 (16), 165 (19). IR (NaCl): $\tilde{\nu}$ = 2959 (s), 2871 (m), 1735 (vs), 1605 (s), 1588 (m), 1489 (m), 1458 (m), 1241 (m), 1162 (s), 741 (m), 699 (s) cm^{-1}. Anal. Calcd. for $C_{20}H_{24}O_2$: C 81.04, H 8.16; found: C 80.74, H 7.77.



Butyl 2,2-bis(4-methoxy-3-methylphenyl)acetate (3.2-6bm)

Compound **3.2-6bm** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 4-bromo-1-methoxy-2-methylbenzene (201 mg, 1.0 mmol). After distillation, **3.2-6bm** (130 mg, 73 %) was obtained as colorless oil.
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.12-7.06 (m, 4H), 6.76 (d, *J* = 8.0 Hz, 2H), 4.86 (s, 1H), 4.14 (t, *J* = 8.0 Hz, 2H), 3.80 (s, 6H), 2.19 (s, 6H), 1.61 (quin, *J* = 8.0 Hz, 2H), 1.33 (sext, *J* = 8.0 Hz, 2H), 0.90 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 173.3, 156.8, 130.9, 130.8, 126.7, 126.6, 109.8, 64.8, 55.6, 55.3, 30.6, 19.0, 16.3, 13.6 ppm. EI-MS (70 eV),

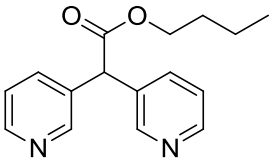
m/z (%): 356 (6) [M^+], 256 (19), 255 (100), 240 (4), 225 (4). IR (NaCl): $\tilde{\nu}$ = 2958 (m), 2931 (m), 2836 (m), 1733 (vs), 1609 (s), 1505 (vs), 1464 (s), 1255 (s), 1134 (m), 1034 (m), 887 (m), 813 (m) 750 (m) cm^{-1}. EI-HRMS *m/z* calcd. for for $C_{22}H_{28}O_4$: 356.1988; found: 356.1982.



Butyl 2,2-di(2-naphthyl)acetate (3.2-6bn)

Compound **3.2-6bn** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 2-bromonaphthaline (207 mg, 1.0 mmol). After distillation, **3.2-6bn** (150 mg, 81 %) was obtained as a light yellow solid, m.p. 86 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.90-7.80 (m, 8H), 7.54-7.44 (m, 6H), 5.4 (s, 1H), 4.27 (t, *J* = 8.0 Hz, 2H), 1.67 (quin, *J* = 8.0 Hz, 2H), 1.38 (sext, *J* = 8.0 Hz, 2H), 0.92 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.5, 136.1, 133.3, 132.5, 128.3, 127.9, 127.6, 127.3, 126.9, 126.2, 126.0, 65.2, 57.4, 30.5, 19.0, 13.6 ppm. EI-MS (70 eV), *m/z* (%): 369 (5), 368 (17) [M^+], 268 (23), 267 (100). IR (KBr): $\tilde{\nu}$ = 2954 (m), 1717 (v)s, 1596 (s), 1507 (s), 1458 (m), `1222 (vs), 1160 (m), 1059 (s), 1023 (s), 862 (s), 791 (m), 751 (s), 738 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{26}H_{24}O_2$: 368.1776, *m/z* found: 368.1778.



Butyl 2,2-di(3-pyridyl)acetate (3.2-6bo)

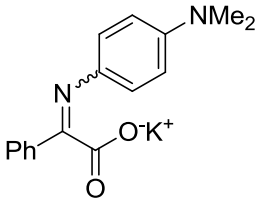
Compound **3.2-6bo** was synthesized according to the general procedure from *n*-butyl acetate (581 mg, 0.66 mL, 5.0 mmol) and 3-bromopyridine (158 mg, 97 µL, 1.0 mmol). After distillation, **3.2-6bo** (100 mg, 74 %) was obtained as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.54 (s, 2H), 8.51 (d, *J* = 4.0 Hz, 2H), 7.64 (d, *J* = 4.0 Hz, 2H), 7.25 (dd, *J* = 4.0, 8.0 Hz, 2H), 5.00 (s, 1H), 4.14 (t, *J* = 8.0 Hz, 2H), 1.57 (quin, *J* = 8.0 Hz, 2H), 1.27 (sext, *J* = 8.0 Hz, 2H), 0.85 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 170.9, 149.7, 149.0, 135.8, 133.5, 123.5, 65.7, 52.2, 30.3, 18.9, 13.5 ppm. EI-MS (70 eV), *m/z* (%): 270 (16) [M^+], 226 (8), 170 (93), 169 (100). IR (NaCl): $\tilde{\nu}$ = 3032 (m), 2959 (s), 2933 (m), 2873 (m), 1732 (vs), 1575 (s), 1479 (s), 1424 (vs), 1312 (s), 1190 (m), 1158 (m), 1026 (s), 714 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{16}H_{18}N_2O_2$: 270.1368, *m/z* found: 270.1371.

8.7 Development of Decarboxylative Coupling Processes for the Synthesis of Azomethines and Ketones

Synthesis of the potassium oxocarboxylates

Potassium phenyloxoacetate, potassium (4-cyanophenyl)oxoacetate, potassium 2-furyloxoacetate, potassium 2-thiophenyloxoacetate, potassium trimethylpyruvate and potassium 3-methyl-2-oxobutanoate were obtained by reaction of the commercially available carboxylic acids with potassium *tert*-butoxide in 2-propanol. Potassium (4-methylphenyl)oxoacetate, potassium (4-chlorophenyl)oxoacetate, potassium (4-methoxyphenyl)oxoacetate and potassium (2,5-dimethylphenyl)oxoacetate were obtained by Friedel-Crafts acylation of the corresponding commercially available arenes with ethyl oxalyl chloride in DCM, followed by ester hydrolysis with potassium hydroxide in 2-propanol. These starting materials were prepared by Dr. Felix Rudolph.



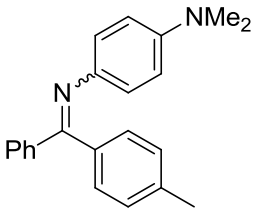
Potassium (*N*-[4-(dimethylamino)phenyl]imino)-phenylacetate (4.2-5a)

A mixture of phenyloxoacetic acid (751 mg, 5 mmol) and *N*,*N*-dimethyl-*p*-phenylendiamine (613 mg, 4.5 mmol) in 20 mL methanol was stirred for 16 h at 25 °C, filtered and washed with 5 mL of diethyl ether, yielding an orange solid (1178 mg). The solid was stirred with potassium *tert*-butoxide (493 mg, 4.39 mmol) in diethyl ether (20 mL) for 1 h at 25 °C, filtered and washed with diethyl ether (5 mL), affording potassium (*N*-[4-(dimethylamino)-phenyl]imino)-phenylacetate (**4.2-5a**) as a yellow solid (1.29 g, 94 %). M.p. 220 °C (dcomposition)

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.85-7.91 (m, 2H), 7.32-7.37 (m, 3H), 7.12-7.17 (m, 2H), 6.61-6.66 (m, 2H), 2.85 (s, 6H) ppm. ^{13}C-NMR (151 MHz, DMSO-d_6): δ = 169.2, 166.5, 147.5, 140.9, 137.8, 129.2, 127.9, 127.7, 122.8, 112.5, 40.6 ppm. IR (KBr): $\tilde{\nu}$ = 3356 (m, br), 1597 (vs), 1509 (vs), 1395 (s), 1338 (m), 1316 (m), 1214 (s), 1134 (w), 1056 (w), 1012 (w), 946 (w), 852 (m), 838 (m), 706 (m), 572 (w) cm^{-1}. Anal. Calcd. for $C_{16}H_{15}KN_2O_2$: C 62.72, H 4.93, N 9.14; found: C 61.98, H 5.04, N 9.14.

8.7.1 General Procedure for the Decarboxylative Cross-Coupling Reactions from Preformed α-Iminocarboxylate

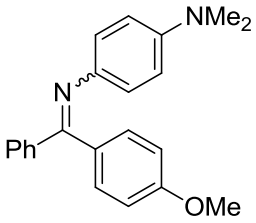
An oven-dried 20 mL reaction vial was charged with potassium phenyl(*N*-[4-(dimethylamino)phenyl]imino)acetate (**5a**, 1.2 mmol), copper (I) bromide (21.5 mg, 150 µmol), palladium(II)-1,1,1,3,3,3-hexafluoroacetylacetonate (5.2 mg, 10 µmol), 1,1'-bis-(diphenylphosphino)-ferrocene (5.7 mg, 10 µmol), magnesium trifluoromethane sulfonate (16.1 mg, 50 µmol) and ground 3 Å molecular sieves (200 mg). The reaction vessel was evacuated and flushed with nitrogen three times. Subsequently, a solution of the corresponding aryl halide (1.0 mmol) and the internal standard *n*-tetradecane (50 µL) in NMP (2 mL) was added *via* syringe. The resulting mixture was stirred at 130 °C for 16 h, diluted with saturated sodium bicarbonate solution (20 mL) and extracted repeatedly with 20 mL portions of ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate solution, water and brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced vacuum. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate gradient).



***N*,*N*-Dimethyl-*N'*-[(phenyl)-(4-tolyl)-methylene]-*p*-phenylenediamine (4.2-4aaa)**

Compound **4.2-4aaa** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 4-bromotoluene (171 mg, 122 µl, 1.00 mmol). After purification by column chromatography (hexane/ethyl acetate 90:10), **4.2-4aaa** (290 mg, 85 %) was obtained as orange solid, m.p. 99 °C.

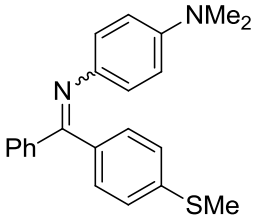
^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers, approx. ratio 1.2:1): $\delta =$ 7.58-7.62 and 7.68-7.72 (2 m, 2H), 7.26-7.30 and 7.33-7.42 (2 m, 3H), 7.02-7.11 and 7.12-7.20 (2 m, 4H), 6.65-6.72 (m, 2H), 6.51-6.60 (m, 2H), 2.87 and 2.85 (2 s, 6H), 2.38 and 2.34 (2 s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers): $\delta =$ 166.3 and 166.0, 147.26 and 147.22, 141.1,140.9, 140.8, 140.3, 138.1, 137.8, 137.4, 134.1, 130.0, 129.7, 129.6, 129.07, 129.00, 128.77, 128.73, 128.1, 128.0, 123.14 and 123.08, 112.74 and 112.70, 40.86 and 40.85, 21.38 and 21.37 ppm. EI-MS (70 eV): *m/z* (%): 343 (28), 342 (100) [M^+], 341 (57), 325 (22), 207 (30), 192 (20), 77 (23). IR (KBr): $\tilde{\nu}$ = 1607 (s), 1509 (vs), 1441 (m), 1351 (m), 1226 (m), 1176 (m), 1166 (m), 1064 (w), 944 (m), 820 (vs), 776 (m), 704 (vs), 670 (m) cm^{-1}. Anal. Calcd. for $C_{22}H_{22}N_2$: C 84.04, H 7.05, N 8.91; found: C 83.94, H 7.15, N 8.93.



***N*,*N*-Dimethyl-*N'*-[(4-methoxyphenyl)-(phenyl)-methylene]-*p*-phenylenediamine (4.2-4aab)**

Compound **4.2-4aab** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 2-bromoanisole (187 mg, 126 µl, 1.00 mmol). After purification by column chromatography (hexane/ethyl acetate 80:20), **4.2-4aab** (270 mg, 82 %) was obtained as orange solid, m.p. 119 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers, approx. 1.7:1): $\delta =$ 7.66-7.78 (m, 2H), 7.36-7.49 (m, 1H), 7.26-7.48 (m, 2H), 7.08-7.23 (m, 2H), 6.80-6.97 (m, 2H), 6.66-6.78 (m, 2H), 6.53-6.65 (m, 2H), 3.83 and 3.87 (s, 3H), 2.88 and 2.91 (2 s, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers): $\delta =$ 165.6 and 165.9, 161.3, 159.4, 147.1 and 147.2, 141.0 and 141.2, 137.3, 133.2, 131.4, 130.6, 130.0, 129.6, 129.21, 129.15, 128.1, 128.0, 123.0 and 123.1, 113.4, 112.7 and 112.8, 55.1 and 55.3, 40.9 ppm. EI-MS (70 eV): *m/z* (%): 332 (31), 331 (100), 330 (15) [M^+], 254 (38), 208 (13), 77 (19), 40 (14). IR (KBr): $\tilde{\nu} =$ 1653 (m), 1607 (s), 1559 (s), 1507 (vs), 1437 (m), 1260 (s), 1228 (s), 1166 (s), 1064 (m), 1030 (s), 816 (vs), 702 (s), 670 (s), 662 (m), 540 (m) cm^{-1}. Anal. Calcd. for $C_{22}H_{22}N_2O$: C 79.97, H 6.71, N 8.48; found: C 79.88, H 6.82, N 8.64.

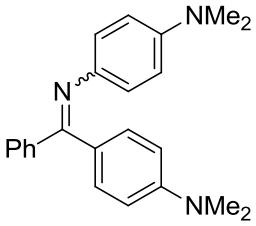


***N*,*N*-Dimethyl-*N'*-[(4-methylsulfanylphenyl)-(phenyl)-methylene]-*p*-phenylenediamine (4.2-4aac)**

Compound **4.2-4aac** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 2-bromothioanisole (203 mg, 1.00 mmol). After purification by column chromatography (hexane/ethyl acetate 85:15), **4.2-4aac** (220 mg, 64 %) was obtained as orange solid, m.p. 110 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers): $\delta =$ 7.64-7.69 and 7.69-7.75 (2 m, 2H), 7.26-7.36 and 7.37-7.47 (2 m, 3H), 7.08-7.13 and 7.23-7.26 (2 m, 2H), 7.14-7.21 (m, 2H), 6.68-6.76 (m, 2H), 6.54-6.63 (m, 2H), 2.89 and 2.91 (2 s, 6H), 2.50 and 2.52 (2 s,

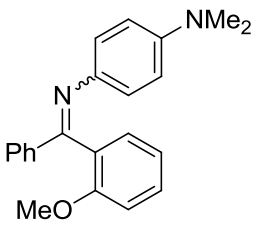
3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers): $\delta =$ 165.2 and 165.5, 147.3, 141.4, 140.9, 140.7, 140.6, 139.1, 137.15, 137.11, 133.45, 130.2, 130.1, 129.5, 129.3, 129.1, 128.2, 128.10, 128.05, 125.3, 123.3, 123.1, 112.6 and 112.8, 40.8, 15.1 and 15.3 ppm. EI-MS (70 eV): *m/z* (%): 347 (33), 346 (100) [M^+], 345 (11), 269 (23), 223 (12), 135 (19), 77 (17). IR (KBr): $\tilde{\nu}$ = 1605 (s), 1549 (m), 1507 (vs), 1441 (m), 1338 (m), 1226 (m), 1164 (m), 1122 (m), 1090 (s), 958 (m), 820 (vs), 702 (vs), 670 (w) cm^{-1}. Anal. Calcd. for $C_{22}H_{22}N_2S$: C 76.26, H 6.40, N 8.08, S 9.25; found: C 76.09, H 6.24, N 8.15, S 9.18.



***N*,*N*-Dimethyl-*N'*-[(4-(dimethylamino)phenyl)-(phenyl)-methylene]-*p*-phenylenediamine (4.2-4aad)**

Compound **4.2-4aad** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 2-bromo-N,N-dimethylaniline (**3**200 mg, 1.00 mmol) After purification by column chromatography (hexane/ethyl acetate 80:20), **4.2-4aad** (170 mg, 50 %) was obtained as orange solid, m.p. 173 °C.

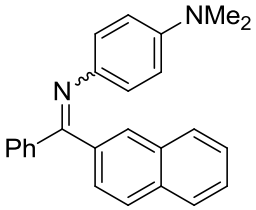
^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers, approx. 2.1:1): $\delta =$ 7.61-7.69 and 7.71-7.76 (2 m, 2H), 7.26-7.34 and 7.36-7.47 (2 m, 3H), 7.03-7.10 and 7.16-7.23 (2 m, 2H), 6.52-6.84 (m, 6H), 2.99 and 3.04 (2 s, 6H), 2.87 and 2.91 (2 s, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers): $\delta =$ 166.1 and 166.7, 151.7, 150.1, 146.8 and 147.0, 142.1, 141.8, 141.6, 137.8, 131.5, 130.4, 129.7, 129.6, 129.4, 128.2, 127.9, 127.8, 124.0, 123.1, 122.9, 112.9 and 113.1, 111.0 and 111.1, 41.0, 40.1 and 40.2 ppm. EI-MS (70 eV): *m/z* (%): 344 (31), 343 (100) [M^+], 342 (21), 328 (12), 266 (19), 208 (22), 77 (15). IR (KBr): $\tilde{\nu}$ = 1617 (m), 1583 (s), 1507 (s), 1441 (m), 1369 (m), 1343 (m), 1320 (m), 1224 (s), 1198 (m), 1164 (m), 1142 (m), 1058 (m), 942 (m), 914 (w), 816 (vs), 700 (s), 670 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{23}H_{25}N_3$: 343.2048; *m/z* found 343.2051.



***N*,*N*-Dimethyl-*N'*-[(2-methoxyphenyl)-(phenyl)-methylene]-*p*-phenylenediamine (4.2-4aae)**

Compound **4.2-4aae** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 2-bromoanisole (187 mg, 125 µl, 1.00 mmol). After purification by column chromatography (hexane/ethyl acetate 80:20), **4.2-4aae** (190 mg, 58 %) was obtained as orange solid, m.p. 93 °C.

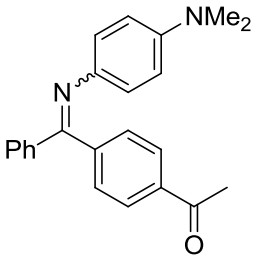
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.72-7.77 (m, 2H), 7.26-7.41 (m, 4H), 6.97-7.02 (m, 1H), 6.83-6.92 (m, 2H), 6.71-6.76 (m, 2H), 6.51-6.57 (m, 2H), 3.59 (s, 3H), 2.84 (s, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 163.8, 156.9, 147.4, 141.3, 140.0, 130.0, 129.9, 129.6, 128.2, 126.7, 122.2, 120.4, 112.5, 110.9, 55.3, 40.9 ppm. EI-MS (70 eV): *m/z* (%): 331 (25), 330 (97) [M^+], 167 (21), 136 (100), 135 (69), 121 (23), 77 (25). IR (KBr): $\tilde{\nu}$ = 1605 (s), 1509 (vs), 1485 (s), 1443 (s), 1345 (m), 1248 (s), 1228 (s), 1166 (m), 1108 (m), 1046 (w), 1022 (m), 956 (m), 816 (m), 754 (s), 698 (s) cm^{-1}. Anal. Calcd. for $C_{22}H_{22}N_2O$: C 79.97, H 6.71, N 8.48; found: C 80.05, H 6.69, N 8.49.



***N*,*N*-Dimethyl-*N'*-[(2-naphthyl)-(phenyl)-methylene]-*p*-phenylenediamine (4.2-4aaf)**

Compound **4.2-4aaf** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 2-bromonaphthalene (207 mg, 1.00 mmol). After purification by column chromatography (hexane/ethyl acetate 85:15), **4.2-4aaf** (185 mg, 53 %) was obtained as orange solid, m.p. 119 °C.

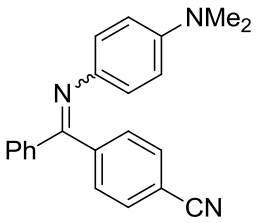
^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers, approx. 1.2:1): δ = 7.99-8.02 and 8.11-8.15 (2m, 1H), 7.35-7.56 and 7.71-7.93 (2m, 5H), 6.73-6.82 and 7.23-7.29 (2m, 2H), 6.49-6.56 and 6.56-6.63 (2m, 1H), 2.86 and 2.91 (2 s, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers): δ = 165.7 and 165.8, 147.4, 140.8, 140.7, 140.6, 138.0, 137.3, 134.9, 134.3, 132.9, 132.8, 130.1, 129.9, 129.7, 129.3, 129.2, 128.9, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.1, 127.0, 126.6, 126.2, 126.1, 125.6, 123.3 and 123.4, 112.6 and 112.7, 40.7 and 40.8 ppm. Ei-MS (70 eV): *m/z* (%): 352 (36), 351 (100), 349 (13) [M^+], 274 (19), 224 (16), 208 (15), 136 (30), 77 (20). IR (KBr): $\tilde{\nu}$ = 1605 (m), 1507 (s), 1441 (m), 1347 (m), 1226 (m), 1180 (m), 1166 (w), 1116 (w), 1060 (w), 936 (w), 896 (w), 818 (vs), 750 (m), 704 (vs) cm^{-1}. Anal. Calcd. for $C_{25}H_{22}N_2$: C 85.68, H 6.33, N 7.99; found: C 85.52, H 6.13, N 7.96.



***N*,*N*-Dimethyl-*N'*-[(4-acetylphenyl)-(phenyl)-methylen]-*p*-phenylenediamine (4.2-4aag)**

Compound **4aag** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 1-bromo-4-chlorobenzene (199 mg, 1.00 mmol). After purification by column chromatography (hexane/ethyl acetate 80:20), **4aag** (195 mg, 57 %) was obtained as reddish-brown solid, m.p. 111 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers, approx. 1.1:1): $\delta =$ 7.89-7.99 (m, 2H), 7.67-7.74 and 7.80-7.85 (2 m, 2H), 7.27-7.47 (m, 4H), 7.15-7.19 (m, 1H), 6.66-7.76 (m, 2H), 6.52-6.58 (m, 2H), 2.90 and 2.91 (2 s, 6H), 2.62 and 2.65 (2 s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers): $\delta =$ 197.6 and 197.8, 164.2 and 164.7, 147.5 and 147.7, 144.7, 142.3, 140.1, 140.0, 139.8, 137.8, 136.8, 136.5, 130.4, 129.9, 129.4, 129.0, 128.8, 128.6, 128.4, 128.2, 128.1, 128.0, 123.1 and 123.6, 112.4 and 112.6, 40.6 and 40.7, 26.6 and 26.8 ppm. EI-MS (70 eV): *m/z* (%): 344 (35), 343 (100) [M^+], 342 (19), 282 (19), 266 (23), 224 (24), 208 (35). IR (KBr): $\tilde{\nu}$ = 1683 (vs), 1607 (vs), 1511 (vs), 1443 (m), 1399 (m), 1355 (s), 1264 (vs), 1230 (s), 1184 (m), 1062 (m), 954 (m), 822 (s), 708 (vs), 670 (m), 604 (w), 592 (w) cm^{-1}. Anal. Calcd. for $C_{23}H_{22}N_2O$: C 80.67, H 6.48, N 8.18; found: C 80.19, H 6.55, N 8.65. EI-HRMS *m/z* calcd. for $C_{23}H_{22}N_2O$: 342.1732; *m/z* found: 342.1720.

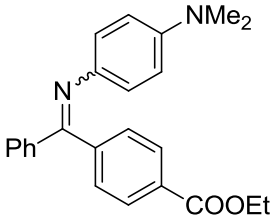


***N*,*N*-Dimethyl-*N'*-[(4-cyanophenyl)-(phenyl)-methylene]-*p*-phenylenediamine (4.2-4aah)**

Compound **4.2-4aah** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 4-bromobenzonitrile (182 mg, 110 µl, 1.00 mmol). After purification by column chromatography (hexane/ethyl acetate 80:20), **4.2-4aah** (250 mg, 77 %) was obtained as red solid, m.p. 148 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers): $\delta =$ 7.61-7.65 and 7.82-7.87 (2 m, 2H), 7.65-7.70 (m, 2H), 7.35-7.49 (m, 3H), 7.14-7.19 and 7.27-7.33 (2 m, 2H), 6.63-6.68 and 6.71-6.76 (2 m, 2H), 6.52-6.58 (m, 2H), 2.92 (s, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers): $\delta =$ 162.9 and 163.6, 147.7 and 148.0, 144.6, 142.2, 139.7, 139.4,

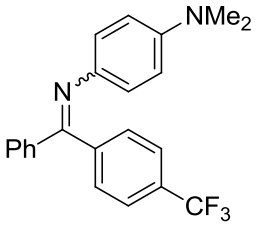
139.3, 136.4, 132.0, 131.8, 130.6, 130.3, 129.3, 129.2, 128.7, 128.6, 128.3, 123.8, 123.1, 118.8, 118.4, 113.0, 112.5, 112.2, 112.0. 40.56 and 40.62 ppm. EI-MS (70 eV): *m/z* (%): 327 (35), 326 (100), 325 (12) [M^+], 249 (16), 224 (34), 208 (18), 77 (26), 51 (14). IR (KBr): $\tilde{\nu}$ = 2227 (m), 1609 (s), 1513 (vs), 1443 (s), 1359 (s), 1318 (m), 1284 (w), 1230 (m), 1170 (m), 1066 (w), 950 (m), 814 (s), 782 (m), 698 (s). Anal. Calcd. for $C_{22}H_{19}N_3$: C 81.20, H 5.89, N 12.91; found: C 81.24, H 5.85, N 12.97.



***N*,*N*-Dimethyl-*N'*-[(4-(ethoxycarbonyl)phenyl)-(phenyl)-methylene]-*p*-phenylenediamine (4.2-4aai)**

Compound **4.2-4aai** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and ethyl 4-bromobenzoate (229 mg, 160 µl, 1.00 mmol). After purification by column chromatography (hexane/ethyl acetate 80:20), **4.2-4aai** (260 mg, 70 %) was obtained as red solid, m.p. 81 °C.

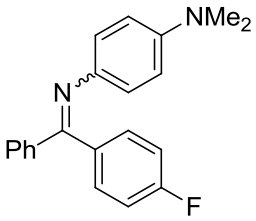
^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): δ = 7.96-8.11 (m, 2H), 7.67-7.82 (m, 2H), 7.15-7.48 (m, 5H), 6.66-6.78 (m, 2H), 6.52-6.60 (m, 2H), 4.36-4.47 (m, 2H), 2.895 and 2.905 (2 s, 6H), 1.38-1.47 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): δ = 166.2 and 166.3, 164.5 and 164.9, 147.5 and 147.7 142.0, 140.2, 140.1, 139.9, 136.9, 131.4, 130.3, 130.1, 129.6, 129.4, 129.3, 129.2, 128.84, 128.82, 128.5, 128.3, 128.2, 123.1 and 123.5, 112.4 and 112.6, 61.05 and 61.09, 40.67 and 40.70, 14.3 ppm. EI-MS (70 eV): *m/z* (%): 373 (35), 372 (100) [M^+], 344 (31), 299 (13), 223 (21), 135 (14), 77 (15).IR (KBr): $\tilde{\nu}$ = 2793 (w), 1719 (s), 1607 (m), 1507 (s), 1443 (m), 1272 (vs), 1228 (s), 1100 (vs), 1014 (m), 958 (m), 820 (s), 782 (m), 710 (s) cm^{-1}. Anal. Calcd. for $C_{24}H_{24}N_2O_2$: C 77.39, H 6.49, N 7.52; found: C 77.37, H 6.48, N 7.51.



***N*,*N*-Dimethyl-*N'*-[(4-(trifluoromethyl)phenyl)-(phenyl)-methylene)-*p*-phenylenediamine (4.2-4aaj)**

Compound **4.2-4aaj** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and ethyl 4-bromo-4-(trifluoromethyl)benzene (227 mg, 142 µl, 1.00 mmol). After purification by column chromatography (hexane/ethyl acetate 85:15), **4.2-4aaj** (303 mg, 82 %) was obtained as red solid, m.p. 117 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): $\delta =$ 7.69-7.74 and 7.84-7.89 (2 m, 2H), 7.58-7.68 (m, 2H), 7.27-7.52 (m, 4H), 7.16-7.22 (m, 1H), 6.67-6.78 (m, 2H), 6.54-6.61 (m, 2H), 2.92 (s, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers): $\delta =$ 163.9 and 164.2, 147.6 and 147.8, 141.0, 140.0, 139.9, 139.8, 133.5 (q, ^{1}J (C,F)=approx. 630 Hz), 130.2 and 131.5 (q, ^{2}J (C,F)=32.7 and 32.1 Hz), 130.0, 129.4, 129.2, 128.8, 128.6, 128.4, 128.2, 125.0 and 125.1 (q, ^{3}J (C,F)=3.69 Hz), 123.1 and 123.5, 122.5 and 122.7, 112.4 and 112.6, 40.6 and 40.7 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): $\delta =$ -62.6 (s, 3F) ppm. EI-MS (70 eV): *m/z* (%): 369 (35), 368 (100) [M^+], 291 (15), 223 (28), 135 (14), 77 (19), 42 (10). IR (KBr): $\tilde{\nu}$ = 1609 (s), 1507 (vs), 1443 (m), 1407 (m), 1351 (m), 1320 (vs), 1166 (s), 1128 (vs), 1108 (s), 1064 (vs), 1014 (m), 960 (w), 948 (w), 860 (m), 818 (m), 706 (m), 678 (w) cm^{-1}. Anal. Calcd. for $C_{22}H_{19}F_3N_2$: C 71.73, H 5.20, N 7.60; found: C 71.75, H 5.26, N 7.69.

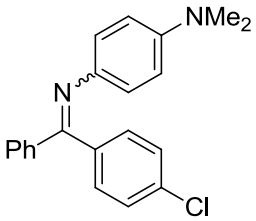


***N*,*N*-Dimethyl-*N'*-[(4-fluorophenyl)-(phenyl)-methylene]-*p*-phenylenediamine (4.2-4aak)**

Compound **4.2-4aak** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 1-bromo-4-fluorobenzene (175 mg, 110 µl, 1.00 mmol). After purification by column chromatography (hexane/ethyl acetate 85:15), **4.2-4aak** (240 mg, 75 %) was obtained as orange solid, m.p. 95 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers, approx. 1.1:1): $\delta =$ 7.66-7.75 (m, 2H), 7.26-7.35 and 7.35-7.46 (2m, 3H), 6.95-7.09 and 7.10-7.19 (2m, 4H), 6.64-6.72 (m, 2H), 6.49-6.60 (m, 2H), 2.86 and 2.88 (2s, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): $\delta =$ 164.6 and 165.0, 162.3 and 164.1 (d, ^{1}J (C,F)=248.8 and 250.6 Hz), 147.4, 140.6, 140.5, 140.4, 137.0, 133.1 and 136.7 (d, ^{4}J (C,F)=3.7 and 2.8 Hz), 131.0 and 131.6 (2 d, ^{3}J (C,F)=8.3 Hz), 130.2, 129.5, 129.0, 128.4, 128.1 and 128.2, 123.0 and 123.2, 115.0 and 115.2 (2 d, ^{2}J (C,F)=21.3 and 22.2 Hz), 112.6 and 112.7, 40.8 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers): $\delta =$ -110.8 and -112.1 (s, 1F) ppm. EI-MS (70 eV): *m/z* (%): 319 (29), 318 (100) [M^+], 317 (15), 241 (28), 223 (19), 135 (23), 77 (22). IR (KBr): $\tilde{\nu}$ = 1611 (m), 1595 (m), 1507 (vs), 1441 (m), 1353 (m), 1288 (m), 1224 (s), 1166 (m), 1064 (m),

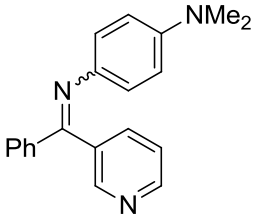
958 (m), 846 (m), 806 (s), 690 (s), 534 (m) cm^{-1}. Anal. Calcd. for $C_{21}H_{19}FN_2$: C 79.22, H 6.01, N 8.80; found: C 79.22, H 6.39, N 8.90.



***N*,*N*-Dimethyl-*N'*-[(4-chlorophenyl)-(phenyl)-methylene]-*p*-phenylenediamine (4.2-4aal)**

Compound **4.2-4aal** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 1-bromo-4-chlorobenzene (175 mg, 110 µl, 1.00 mmol). After purification by column chromatography (hexane/ethyl acetate 80:20), **4.2-4aal** (298 mg, 86 %) was obtained as orange solid, m.p. 127 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): $\delta =$ 7.66-7.74 (m, 2H), 7.26-7.48 (m, 5H), 7.11-7.19 (m, 2H), 6.67-6.74 (m, 2H), 6.52-6.62 (m, 2H), 2.90 and 2.92 (2s, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): $\delta =$ 164.5 and 164.7, 147.4 and 147.5, 140.4, 140.3, 140.2, 139.0, 136.8, 136.1, 135.6, 134.2, 131.1, 130.3, 129.4, 128.9, 128.4, 128.3, 128.1, 123.1 and 123.3, 112.5 and 112.7, 40.7 and 40.8 ppm. EI-MS (70 eV): *m/z* (%): 337 (35), 336 (36), 335 (100), 334 (12) [M^+], 258 (24), 224 (26), 136 (23), 77 (29). IR (KBr): $\tilde{\nu}$ = 1607 (m), 1507 (s), 1441 (m), 1339 (m), 1262 (vs), 1104 (vs), 1086 (vs), 1026 (s), 820 (vs), 802 (vs), 708 (m). Anal. Calcd. for $C_{21}H_{19}ClN_2$: C 75.33, H 5.72, N 8.37; found: C 75.01, H 5.82, N 8.46.

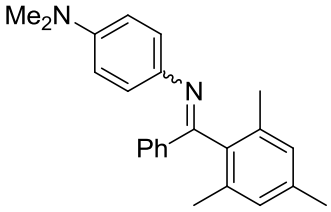


***N*,*N*-Dimethyl-*N'*-[(phenyl)-(3-pyridyl)-methylene]-*p*-phenylenediamine (4.2-4aam)**

Compound **4.2-4aam** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 3-bromopyridine (158 mg, 96.3 µl, 1.00 mmol). The crude product was purified by Kugelrohr distillation *in vacuo* (> 250 °C, 2.4×10^{-2} mbar), affording **4.2-4aam** (254 mg, 84 %) as red oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): δ = 8.60-8.64 and 8.81-8.85 (2m, 1H), 8.38-8.42 and 8.51-8.54 (2m, 1H), 7.65-7.72 (m, 1H), 7.35-7.49 (m, 2H), 7.27-7.35 (m, 2H), 7.20-7.24 and 8.03-8.08 (2m, 1H), 7.12-7.18 (m, 1H), 6.61-6.75 (m, 2H), 6.48-6.55 (m, 2H), 2.86 and 2.87 (2s, 6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers):

δ = 162.9 and 163.0, 150.6, 150.4, 150.2, 149.2, 147.6 and 147.7, 140.1, 139.8, 139.7, 137.1, 136.2, 136.2, 135.9, 133.0, 130.5, 129.3, 128.8, 128.7, 128.6, 128.4, 128.3, 123.5, 122.96 and 123.00, 112.4 and 112.7, 40.6 and 40.7 ppm. EI-MS (70 eV): *m/z* (%): 302 (27), 301 (100) [M^+], 300 (21), 224 (21), 223 (31), 135 (29), 77 (30). IR (NaCl): $\tilde{\nu}$ = 1659 (s), 1613 (vs), 1503 (vs), 1443 (vs), 1413 (s), 1351 (vs), 1228 (s), 1166 (s), 1062 (m), 1026 (m), 948 (s), 822 (s), 752 (m), 706 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{19}N_3$: 301.1579; *m/z* found: 301.1594.

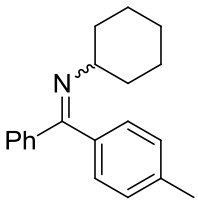


***N*,*N*-Dimethyl-*N'*-[(2-mesityl)-(phenyl)-methylene]-*p*-phenylenediamine (4.2-4aan)**

Compound **4.2-4aan** was synthesized at 130 °C according to the general procedure from **4.2-5a** (368 mg, 1.20 mmol) and 2-bromo-mesitylene (199 mg, 153 µl, 1.00 mmol). GC-Yield: 10 %. EI-MS (70 eV): *m/z* (%): 343 (27), 342 (100) [M^+], 341 (55), 325 (21), 207 (29), 192 (22), 77 (24).

8.7.2 General Procedure for The One-pot-azomethine Synthesis

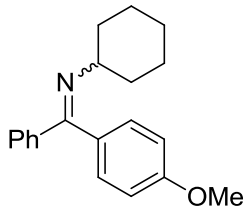
An oven-dried 20 mL vessel was charged with potassium aryloxoacetate (1.20 mmol), copper(I) bromide (21.5 mg, 0.15 mmol), palladium(II) 1,1,1,3,3,3-hexafluoroacetylacetonate (5.2 mg, 0.01 mmol), 1,10-phenanthroline (27.0 mg, 0.15 mmol), 1,1'-bis-(diphenylphosphino) ferrocene (5.7 mg, 0.01 mmol) and 3 Å molecular sieves (200 mg). The reaction vessel was evacuated and flushed with nitrogen three times. Subsequently, a solution of the corresponding aryl halide (1.00 mmol), the amine (1.20 mmol) and the internal standard *n*-tetradecane (50 µL) in NMP (2 mL) was added *via* syringe. The resulting mixture was stirred at 100 °C for 16 h, diluted with saturated sodium bicarbonate solution (20 mL) and extracted repeatedly with 20 mL portions of ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate solution, water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by Kugelrohr distillation *in vacuo*, yielding the corresponding azomethines.



***N*-(Phenyl-*p*-tolyl-methylene)-cyclohexylamine (4.2-4aba)**

Compound **4.2-4aba** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (171 mg, 122 µL, 1.00 mmol). After distillation, **4.2-4aba** (252 mg, 91 %) was obtained as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1:1): δ = 7.47-7.53 and 7.56-7.64 (2m, 2H), 7.28-7.37 and 7.38-7.47 (2m, 3H), 7.14-7.19 and 7.23-7.28 (2m, 2H), 7.04-7.09 and 7.10-7.14 (2m, 2H), 3.17-3.33 (m, 1H), 2.36 and 2.44 (2 s, 3H), 1.55-1.82 (m, 7H), 1.10-1.34 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 165.4 and 165.7, 140.6, 139.5, 137.6 and 137.7, 134.3, 129.4, 128.9, 128.6, 128.33, 128.26, 128.2, 127.8, 127.6, 61.2 and 61.3, 34.0, 25.7, 24.4, 21.2 and 21.3 ppm. EI-MS (70 eV): *m/z* (%): 278 (100), 277 (38) [M^+], 263 (21), 235 (21), 200 (30), 165 (36), 104 (29). IR (NaCl): $\tilde{\nu}$ = 3079 (m), 2923 (vs), 2851 (vs), 1659 (w), 1621 (s), 1607 (s), 1575 (m), 1567 (m), 1507 (m), 1489 (m), 1445 (s), 1312 (s), 1288 (s), 1256 (m), 1182 (m), 1070 (m), 1028 (m), 968 (s), 888 (m), 844 (w), 824 (m), 774 (m), 758 (m), 728 (m), 698 (s), 632 (w) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{23}N$: 277.1830; *m/z* found: 277.1819.

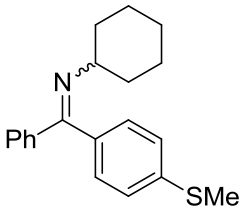


***N*-((4-Methoxyphenyl)-phenyl-methylene)-cyclohexylamine (4.2-4abb)**

Compound **4.2-4abb** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromoanisol (187 mg, 126 µL, 1.00 mmol). After distillation, **4.2-4abb** (263 mg, 90 %) was obtained as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1.6:1): δ = 7.54-7.59 and 7.59-7.64 (2m, 2H), 7.29-7.40 and 7.40-7.51 (2m, 3H), 7.09-7.15 and 7.15-7.21 (2m, 2H), 6.83-6.88 and 6.97-7.03 (2m, 2H), 3.82 and 3.90 (2s, 3H), 3.20 and 3.33 (2 qui, ^3J (H,H)=7.1 Hz, 1H), 1.55-1.83 (m, 7H), 1.10-1.35 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 164.8 and 165.4, 159.2 and 160.8, 140.9, 137.6, 133.2, 129.8, 129.5, 129.4, 129.1, 128.4, 128.2, 127.9, 127.6, 113.2 and 113.6, 61.2 and 61.3, 33.98 and 34.02, 25.7, 24.4 ppm. EI-MS (70 eV): *m/z* (%): 294 (37), 293 (31), 292 (100) [M^+], 264 (22), 250 (32), 216 (69), 77 (24). IR (NaCl): $\tilde{\nu}$ = 2927 (vs), 2853 (s), 1651 (vs), 1599 (vs), 1573 (s), 1507 (s), 1445 (s), 1417 (m), 1312 (s), 1282 (vs), 1256 (vs), 1172 (s), 1150 (s), 1072

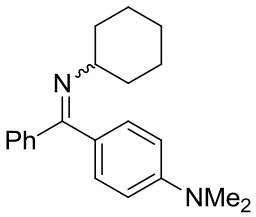
(w), 1032 (s), 922 (m), 842 (m), 792 (w), 742 (m), 702 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{23}NO$: 293.1780; *m/z* found: 293.1762.



***N*-((4-Methylsulfanylphenyl)-phenyl-methylene)-cyclohexylamine (4.2-4abc)**

Compound **4.2-4abc** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromothioanisol (203 mg, 1.00 mmol). After distillation, **4.2-4abc** (285 mg, 92 %) was obtained as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1.3:1): δ = 7.58-7.64 and 7.50-7.55 (2m, 2H), 7.37-7.48 (m, 2H), 7.27-7.37 (m, 2H), 7.06-7.12 and 7.12-7.19 (2m, 3H), 3.16-3.32 (m, 1H), 2.44 and 2.53 (2 s, 3H), 1.54-1.85 (m, 7H), 1.09-1.35 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 164.7 and 164.8, 140.2 and 140.5, 138.6, 136.9 and 137.1, 133.6, 129.4, 128.5, 128.2, 128.1, 127.8, 127.5, 125.3 and 125.7, 61.1 and 61.2, 33.8, 25.6, 24.3, 15.24 and 15.17 ppm. EI-MS (70 eV): *m/z* (%): 310 (51), 309 (41) [M^+], 308 (100), 266 (34), 262 (35), 254 (35), 165 (48). IR (NaCl): $\tilde{\nu}$ = 3077 (m), 2923 (vs), 2851 (vs), 2791 (w), 1619 (s), 1589 (s), 1551 (m), 1489 (s), 1445 (s), 1397 (m), 1306 (m), 1286 (s), 1188 (m), 1112 (w), 1092 (s), 1068 (m), 1028 (w), 1014 (w), 968 (m), 888 (w), 822 (m), 774 (m), 702 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{23}NS$: 309.1551; *m/z* found: 309.1552.

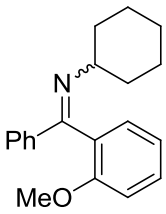


***N*-((4-(Dimethylamino)phenyl)-phenyl-methylene)-cyclohexylamine (4.2-4abd)**

Compound **4.2-4abd** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-brom-*N*,*N*-dimethylaniline (200 mg, 1.00 mmol). After distillation, **4.2-4abd** (260 mg, 85 %) was obtained as orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 2:1): δ = 7.48-7.55 and 7.62-7.67 (2m, 2H), 7.28-7.36 and 7.37-7.48 (2m, 3H), 7.05-7.11 and 7.15-7.21 (2m, 2H), 6.60-6.67 and 6.74-6.80 (2m, 2H), 3.18 and 3.46 (2qui, ^3J (H,H)=7.1 Hz, 1H), 2.97 and 3.03

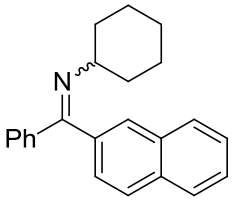
(2s, 6H), 1.54-1.84 (m, 7H), 1.09-1.36 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): $\delta =$ 165.1 and 166.0, 149.9 and 151.2, 141.5, 138.0, 129.4, 129.1, 129.0, 128.5, 128.4, 128.0, 127.7, 127.54, 127.48, 124.7, 111.1 and 111.4, 60.9 and 61.1, 40.1, 34.1, 25.6 and 25.7, 24.40 and 24.43 ppm. EI-MS (70 eV): *m/z* (%): 307 (46), 306 (100) [M^+], 251 (48), 223 (55), 209 (46), 185 (69), 104 (55). IR (NaCl): $\tilde{\nu}$ = 2925 (vs), 2851 (s), 1593 (vs), 1519 (s), 1481 (m), 1445 (m), 1357 (m), 1312 (m), 1292 (m), 1228 (m), 1218 (m), 1198 (m), 1156 (m), 1066 (m), 968 (w), 948 (w), 908 (w), 888 (w), 822 (m), 756 (m), 704 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{21}H_{26}N_2$: 306.2096; *m/z* found: 306.2090.



***N*-((2-Methoxyphenyl)-phenyl-methylene)-cyclohexylamine (4.2-4abe)**

Compound **4.2-4abe** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 2-bromoanisol (187 mg, 125 µL, 1.00 mmol). After distillation, **4.2-4abe** (251 mg, 86 %) was obtained as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): $\delta =$ 7.63-7.68 (m, 2H), 7.37-7.44 (m, 1H), 7.28-7.36 (m, 3H), 7.02-7.06 (m, 1H), 6.96-7.02 (m, 1H), 3.72 (s, 3H), 3.14 (m, 1H), 1.54-1.85 (m, 7H), 1.10-1.36 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, additional signals for cyclohexane conformers): $\delta =$ 162.4, 156.1, 140.0, 129.4, 129.3, 128.6, 127.8, 127.7, 126.3, 120.4, 110.8, 62.0, 55.3, 33.7 and 33.4, 25.7, 24.4 ppm. EI-MS (70 eV): *m/z* (%): 294 (82), 293 (36), 292 (100) [M^+], 262 (48), 210 (41), 195 (42), 104 (35). IR (NaCl): $\tilde{\nu}$ = 2927 (vs), 2853 (vs), 1625 (s), 1597 (s), 1579 (m), 1487 (s), 1461 (s), 1445 (s), 1290 (m), 1248 (s), 1180 (m), 1114 (m), 1028 (s), 968 (m), 754 (s), 696 (s), 646 (w) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{23}NO$: 293.1780; *m/z* found: 293.1778.

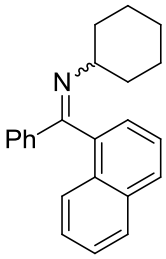


***N*-(2-Naphthyl-phenyl-methylene)-cyclohexylamine (4.2-4abf)**

Compound **4.2-4abf** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and

2-bromonaphthalene (207 mg, 1.00 mmol). After distillation, **4.2-4abf** (292 mg, 93 %) was obtained as yellow oil.

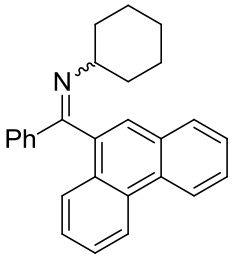
^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1.7:1): δ = 8.09-8.17 and 8.29-8.35 (2m, 2H), 7.41-7.56 and 7.72-7.80 (2m, 4H), 7.10-7.16 and 7.27-7.41 (2m, 3H), 3.03-3.11 and 3.27 (m and qui, ^3J (H,H)=7.0 Hz, 1H), 1.53-1.81 (m, 7H), 1.05-1.33 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 163.7 and 163.1, 148.3, 147.6, 145.8, 144.2, 138.9, 136.0, 132.5, 130.3, 130.1, 129.1, 128.7, 128.2, 128.0, 127.4, 126.7, 124.9, 123.7, 123.1, 61.8 and 61.7, 34.3, 33.8 and 33.7, 25.53 and 25.47, 24.7, 24.1 ppm. EI-MS (70 eV): *m/z* (%): 314 (36), 313 (80) [M^+], 312 (100), 256 (40), 230 (25), 215 (39), 127 (30). IR (NaCl): $\tilde{\nu}$ = 3055 (m), 2925 (vs), 2851 (vs), 1657 (w), 1615 (s), 1595 (m), 1575 (w), 1503 (w), 1489 (w), 1445 (s), 1347 (m), 1294 (m), 1234 (m), 1216 (w), 1198 (w), 1118 (w), 1072 (w), 1028 (w), 966 (w), 900 (w), 862 (m), 820 (m), 752 (s), 706 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{23}H_{23}N$: 313.1830; *m/z* found: 313.1815.



***N*-[(1-Naphthyl)-(phenyl)-methylene]cyclohexylamine (4.2-4abo)**

Compound **4.2-4abo** was synthesized at 100 °C according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol), and 1-bromonaphthalene (**3o**, 207 mg, 140 µl, 1.00 mmol). After distillation, **4.2-4abo** (183 mg, 58 %) was obtained as orange oil.

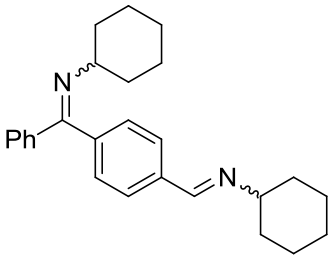
^{1}H-NMR (400 MHz, $CDCl_3$, some split signals for the cyclohexane ring): δ = 7.93-7.99 (m, 2H), 7.64-7.72 (m, 3H), 7.56-7.63 (m, 1H), 7.50-7.56 (m, 1H), 7.40-7.46 (m, 1H), 7.26-7.40 (m, 4H), 3.05-3.11 (m, 1H), 1.50-1.82 (m, 7H), 0.91-1.40 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, some split signals for the cyclohexane ring): δ = 164.5, 140.1, 135.6, 133.3, 130.8, 129.7, 128.3, 128.2, 128.1, 127.9, 126.5, 126.2, 125.6, 125.14, 125.08, 61.8, 33.8 and 33.7, 25.6, 24.3 and 24.1 ppm. EI-MS (70 eV): *m/z* (%): 315 (30), 314 (100), 313 (81) [M^+], 232 (17), 231 (44), 216 (36), 128 (23). IR (NaCl): $\tilde{\nu}$ = 3057 (m), 2927 (vs), 2853 (s), 1619 (m), 1505 (w), 1445 (m), 1286 (w), 1254 (w), 1214 (w), 1176 (w), 1026 (w), 960 (w), 800 (m), 758 (m), 694 (w) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{23}H_{23}N$: 313.1830; *m/z* found: 313.1819.



***N*-(9-Phenanthryl-phenyl-methylene)-cyclohexylamine (4.2-4abp)**

Compound **4.2-4abp** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 9-bromophenanthrene (257 mg, 1.00 mmol). After distillation, **4.2-4abp** (240 mg, 66 %) was obtained as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, some signals for the cyclohexane ring split): δ = 8.73-8.86 (m, 2H), 7.91-8.01 (m, 1H), 7.65-7.82 (m, 6H), 7.49-7.65 (m, 2H), 7.26-7.42 (m, 3H), 2.20-2.23 and 3.17-3.30 (m, 1H), 1.47-1.90 (m, 7H), 0.90-1.41 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, some signals for the cyclohexane ring split): δ = 164.2, 139.9, 134.4, 131.0, 130.2, 129.8, 129.7, 128.9, 128.1, 128.0, 127.03, 126.98, 126.5, 125.8, 123.0, 122.6, 61.9, 33.7 and 33.9, 25.6, 24.1 and 24.3 ppm. EI-MS (70 eV): *m/z* (%): 365 (42), 364 (100), 363 (90) [M^+], 282 (20), 281 (45), 266 (27), 55 (18). IR (NaCl): $\tilde{\nu}$ = 3059 (s), 2927 (vs), 2853 (s), 1621 (m), 1595 (m), 1491 (m), 1447 (m), 1371 (w), 1316 (w), 1264 (w), 1176 (w), 1026 (w), 914 (w), 886 (w), 848 (w), 748 (m), 722 (m), 694 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{27}H_{25}N$: 363.1987; *m/z* found: 363.1974.

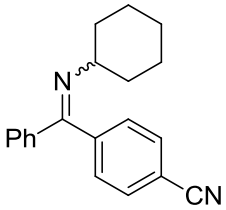


***N*-[4-(*N*-(Cyclohexylcarboximidoyl)phenyl)-(phenyl)-methylene]-cyclohexylamine (4.2-4abq)**

Compound **4.2-4abq** was synthesized at 100 °C according to the general procedure from **1a** (226 mg, 1.20 mmol), cyclohexylamine (218 mg, 252 µl, 2.20 mmol), and 4-bromobenzaldehyde (185 mg, 1.00 mmol). After distillation, **4.2-4abq** (200 mg, 54 %) was obtained as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers, approx. 1.3:1): δ = 8.29 and 8.38 (2s, 1H), 7.63-7.69 and 7.75-7.86 (2m, 2H), 7.54-7.63 (m, 2H), 7.24-7.37 and 7.38-7.54 (2m, 3H), 7.10-7.16 and 7.16-7.23 (2m, 2H), 3.12-3.29 (m, 2H), 1.50-1.89 (m, 14H), 1.05-1.45 (m,

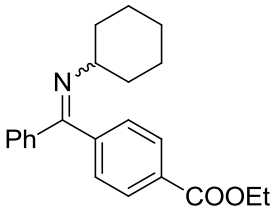
6H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, Signal sets for *E/Z*-isomers): δ = 164.9 and 165.0, 157.9 and 158.1, 142.0, 139.9, 139.4, 137.4, 137.1, 136.3, 129.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 69.9 and 70.0, 61.4 and 61.5, 34.2 and 34.3, 33.8, 25.55 and 25.58, 24.67 and 24.71, 24.3 ppm. EI-MS (70 eV): *m/z* (%): 374 (38), 372 (100) [M^+], 296 (90), 291 (29), 290 (97), 207 (29), 55 (60). IR (NaCl): $\tilde{\nu}$ = 2925 (vs), 2851 (s), 1641 (m), 1485 (w), 1447 (m), 1381 (w), 1345 (w), 1294 (w), 1148 (w), 1068 (m), 1010 (w), 966 (w), 888 (w), 854 (w), 830 (w), 820 (w), 776 (w), 756 (w), 696 (w) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{26}H_{32}N_2$: 372.2565; *m/z* found: 372.2545.



***N*-((4-Cyanophenyl)-phenyl-methylene)-cyclohexylamine (4.2-4abh)**

Compound **4.2-4abh** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromobenzonitrile (182 mg, 1.00 mmol). After distillation, **4.2-4abh** (274 mg, 95 %) was obtained as pale yellow oil.

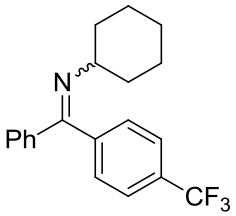
^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 2.2:1): δ = 7.72-7.79 and 7.65-7.71 (2m, 2H), 7.49-7.54 and 7.54-7.80 (2m, 2H), 7.41-7.49 (m, 2H), 7.09-7.15 and 7.26-7.38 (2m, 3H), 3.03-3.11 and 3.24 (qui and m, ^3J (H,H)=7.0 Hz, 1H), 1.51-1.80 (m, 7H), 1.06-1.32 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 163.3 and 163.9, 142.1 and 144.1, 136.0 and 139.0, 131.7 and 132.2, 130.0, 128.8, 128.63, 128.55, 128.4, 128.05 and 128.12, 127.4, 118.3 and 118.7, 112.2 and 112.8, 61.6 and 61.7, 33.7 and 33.8, 25.47 and 25.52, 24.1 and 24.2 ppm. EI-MS (70 eV): *m/z* (%): 289 (39), 288 (40) [M^+], 287 (100), 245 (35), 211 (47), 190 (61), 186 (84). IR (NaCl): $\tilde{\nu}$ = 3081 (m), 2927 (vs), 2853 (vs), 2227 (s), 1623 (m), 1491 (w), 1447 (m), 1405 (w), 1288 (m), 1068 (w), 968 (m), 850 (m), 756 (m), 706 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{20}N_2$: 288.1626; *m/z* found: 288.1629.



Ethyl 4-(Cyclohexylimino-*p*-tolyl-methyl)-benzoate (4.2-4abi)

Compound **4.2-4abi** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and ethyl 4-bromobenzoate (229 mg, 160 µL, 1.00 mmol). After distillation, **4.2-4abi** (277 mg, 83 %) was obtained as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1:1): δ = 7.96-8.02 and 8.13-8.20 (2m, 2H), 7.54-7.60 and 7.61-7.69 (2m, 2H), 7.30-7.41 and 7.41-7.51 (2m, 3H), 7.12-7.20 and 7.24-7.30 (2m, 2H), 4.39 and 4.45 (2q, ^{3}J (H,H)=7.2 Hz, 2H), 3.11-3.20 and 3.23-3.32 (2m, 1H), 1.55-1.85 (m, 7H), 1.40 and 1.45 (2t, ^{3}J (H,H)=7.2 Hz, 3H), 1.08-1.35 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 166.2, 164.6, 144.3, 142.1, 139.6, 136.8, 131.1, 130.2, 129.8, 129.7, 129.2, 128.5, 128.3, 128.2, 128.1, 127.7, 127.6, 61.7 and 61.6, 61.2 and 61.0, 33.8, 25.62 and 25.58, 24.3, 14.4 and 14.3 ppm. EI-MS (70 eV): *m/z* (%): 336 (53), 335 (41) [M^+], 334 (96), 306 (63), 280 (31), 259 (100), 104 (35). IR (NaCl): $\tilde{\nu}$ = 3079 (w), 2979 (m), 2927 (vs), 2853 (s), 1715 (vs), 1621 (m), 1445 (m), 1403 (m), 1274 (vs), 1176 (m), 1102 (s), 1076 (w), 1022 (m), 968 (m), 852 (w), 780 (m), 756 (m), 712 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{22}H_{25}NO_2$: 335.1885; *m/z* found: 335.1886.

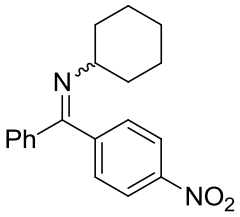


***N*-(Phenyl-(4-trifluoromethylphenyl)-methylene)-cyclohexylamine (4.2-4abj)**

Compound **4.2-4abj** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromobenzotrifluoride (227 mg, 142 µL, 1.00 mmol). After distillation, **4.2-4abj** (215 mg, 65 %) was obtained as red oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1.4:1): δ = 7.70-7.80 (m, 2H), 7.54-7.63 (m, 2H), 7.43-7.51 (m, 2H), 7.13-7.21 and 7.28-7.41 (2m, 3H), 3.11-3.20 and 3.30 (m and qui, ^{3}J (H,H)=7.1 Hz, 1H), 1.56-1.84 (m, 7H), 1.13-1.36 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 163.9 and 164.2, 143.5, 139.5, 132.5 (q, ^{1}J (C,F) ca. 220 Hz), 131.2 (q, ^{2}J (C,F)=32.4 Hz), 128.6, 128.4, 128.2, 128.1, 127.5, 125.4 and 128.9 (2 q, ^{3}J (C,F)=3.7 Hz), 61.5 and 61.6, 33.81 and 33.85, 25.57 and 25.61, 24.20 and 24.23 ppm. ^{19}F-NMR (376 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = -62.7 and -62.6 (2 s, 3F) ppm. EI-MS (70 eV): *m/z* (%): 332 (100), 331 (27) [M^+], 330 (68), 288 (33), 276 (26), 254 (65), 165 (42). IR (NaCl): $\tilde{\nu}$ = 3081 (s), 2923 (vs), 2855 (vs), 1667 (w), 1625 (s), 1615 (s), 1573 (m), 1447 (s), 1407 (s), 1326 (s), 1288 (s), 1170 (s), 1122

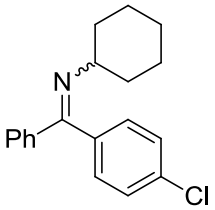
(s), 1066 (s), 1018 (s), 970 (m), 890 (w), 852 (m), 772 (m), 722 (m), 702 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{20}F_3N$: 331.1548; *m/z* found: 331.1530.



***N*-((4-Nitrophenyl)-phenyl-methylene)-cyclohexylamine (4.2-4abr)**

Compound **4.2-4abr** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and bromo-4-nitrobenzene (202 mg, 1.00 mmol). After distillation, **4.2-4abr** (175 mg, 57 %) was obtained as orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 2:1): δ = 8.06-8.17 and 8.29-8.38 (2m, 2H), 7.40-7.58 and 7.65-7.80 (2m, 4H), 7.10-7.19 and 7.28-7.40 (2m, 3H), 3.00-3.12 and 3.26 (qui and m, ^3J (H,H)=7.1 Hz, 1H), 1.52-1.86 (m, 7H), 1.05-1.45 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 163.1 and 163.7, 147.6 and 148.3, 144.2 and 145.8, 136.0 and 138.7, 130.1 and 132.5, 129.1, 128.7, 128.2, 128.0, 127.4, 123.7, 123.1, 61.7 and 61.8, 33.70 and 33.74, 25.46 and 25.52, 24.1 ppm. EI-MS (70 eV): *m/z* (%): 308 (40) [M^+], 307 (100), 265 (57), 253 (44), 231 (93), 165 (51), 117 (44), 55 (55). IR (NaCl): $\tilde{\nu}$ = 3077 (m), 2929 (vs), 2853 (vs), 1621 (m), 1599 (s), 1519 (s), 1487 (m), 1447 (m), 1347 (s), 1314 (m), 1108 (m), 1068 (w), 1014 (w), 968 (m), 852 (m), 776 (w), 736 (w), 704 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{19}H_{20}N_2O_2$: 308.1525; *m/z* found: 308.1523.

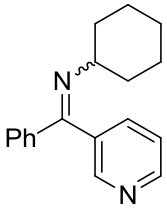


***N*-((4-Chlorophenyl)-phenyl-methylene)-cyclohexylamine (4.2-4abl)**

Compound **4.2-4abl** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and bromo-4-chlorobenzene (175 mg, 110 µL, 1.00 mmol). After distillation, **4.2-4abl** (280 mg, 94 %) was obtained as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.52-7.64 (m, 2H), 7.38-7.50 (m, 3H), 7.25-7.37 (m, 2H), 7.09-7.19 (m, 2H), 3.16-3.30 (m, 1H), 1.54-1.84 (m, 7H), 1.10-1.35 ppm (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 164.1 and 164.2, 139.8, 138.7, 136.7,

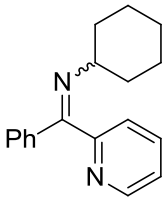
135.5, 134.0, 131.3, 129.8, 129.6, 129.5, 129.0, 128.6, 128.4, 128.2, 128.0, 127.9, 127.4, 61.4 and 61.3, 33.8, 25.6, 24.2 ppm. EI-MS (70 eV): *m/z* (%): 298 (73), 297 (38) [M^+], 296 (100), 254 (42), 220 (49), 165 (76), 104 (36). IR (NaCl): $\tilde{\nu}$ = 3079 (w), 2927 (vs), 2853 (vs), 1661 (w), 1619 (s), 1589 (s), 1485 (s), 1445 (s), 1397 (m), 1286 (s), 1176 (w), 1090 (s), 1014 (m), 968 (m), 888 (w), 838 (m), 774 (m), 746 (m), 728 (m), 704 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{19}H_{20}ClN$: 297.1284; *m/z* found: 297.1280.



***N*-(Phenyl-(3-pyridyl)-methylene)-cyclohexylamine (4.2-4abm)**

Compound **4.2-4abm** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 3-bromopyridine (158 mg, 96 µL, 1.00 mmol). After distillation, **4.2-4abm** (240 mg, 91 %) was obtained as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1.5:1): δ = 8.64-8.70 (m, 1H), 8.42-8.46 and 8.52-8.57 (2m, 1H), 7.27-7.57 and 7.90-7.96 (2m, 5H), 7.10-7.15 and 7.18-7.24 (2m, 2H), 3.11-3.19 and 3.27 (m and qui, ^3J (H,H)=7.0 Hz, 1H), 1.50-1.80 (m, 7H), 1.06-1.31 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 162.1 and 163.3, 150.3, 149.9, 149.5, 148.3, 139.7, 136.1, 135.7, 135.4, 135.2, 132.9, 129.9, 128.6, 128.5, 128.2, 128.1, 127.5, 122.8 and 123.3, 61.3 and 61.6, 33.79 and 33.85, 25.50 and 25.55, 24.2 ppm. EI-MS (70 eV): *m/z* (%): 264 (35) [M^+], 263 (95), 221 (50), 187 (64), 186 (100), 167 (43), 104 (35), 51 (35). IR (NaCl): $\tilde{\nu}$ = 2925 (vs), 2853 (vs), 1665 (w), 1621 (m), 1585 (m), 1447 (m), 1413 (m), 1290 (m), 1194 (w), 1066 (w), 970 (w), 890 (w), 774 (w), 756 (w), 706 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{18}H_{20}N_2$: 264.1626; *m/z* found: 264.1626.

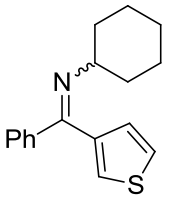


***N*-[(Phenyl)-(2-pyridyl)-methylene]cyclohexylamine (4.2-4abs)**

Compound **4.2-4abs** was synthesized at 100 °C according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL,

1.20 mmol), and 1-bromopyridine (158 mg, 96 µl, 1.00 mmol). After distillation, **4.2-4abs** (123 mg, 47 %) was obtained as light yellow oil.

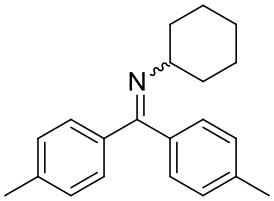
^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers, approx. 1.3:1): δ = 8.53-8.60 and 8.69-8.76 (2m, 1H), 7.85-7.95 and 8.00-8.09 (2 m, 1H), 7.63-7.81 (m, 1H), 7.50-7.61 (m, 1H), 7.36-7.50 (m, 2H), 7.12-7.24 and 7.26-7.36 (2 m, 3H), 3.07-3.18 and 3.25-3.37 (2 m, 1H), 1.50-1.81 (m, 7H), 1.02-1.31 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): δ = 163.9 and 165.8, 156.3 and 157.8, 149.8, 149.0, 136.6, 136.1, 136.0, 130.9, 129.7, 128.2, 128.11, 128.06, 128.0, 127.7, 123.6, 123.0, 122.9, 122.7, 61.4 and 61.6, 33.7, 25.5, 24.29 and 24.33 ppm. EI-MS (70 eV): *m/z* (%): 264 (35) [M^+], 222 (20), 221 (100), 208 (23), 207 (19), 168 (21), 167 (17). IR (NaCl): $\tilde{\nu}$ = 2927 (vs), 2853 (s), 1665 (s), 1579 (m), 1445 (m), 1433 (m), 1304 (m), 1282 (m), 1246 (m), 1162 (m), 994 (m), 970 (w), 940 (m), 744 (w), 696 (m), 652 (w) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{18}H_{20}N_2$: 264.1626; *m/z* found: 264.1622.



***N*-(Phenyl-(3-thienyl)-methylene)-cyclohexylamine (4.2-4abt)**

Compound **4.2-4abt** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 3-bromothiophene (163 mg, 94 µL, 1.00 mmol). After distillation, **4.2-4abt** (230 mg, 85 %) was obtained as pale yellow oil.

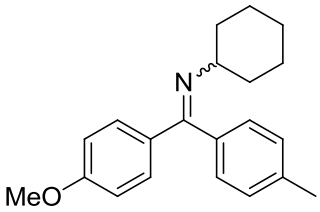
^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 2:1): δ = 7.41-7.52 and 7.60-7.69 (2 m, 4H), 7.31-7.41 (m, 1H), 7.19-7.31 (m, 2H), 6.97-7.02 and 7.02-7.10 (2m, 1H), 3.17-3.30 and 3.32-3.45 (2m, 1H), 1.55-1.91 (m, 7H), 1.10-1.39 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 161.0 and 161.1, 144.6, 140.5, 137.7 and 137.0, 130.2, 129.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.2, 126.9, 125.5, 125.2, 123.9, 60.8 and 61.7, 33.9 and 34.0, 25.60 and 25.63, 24.3 and 24.4 ppm. EI-MS (70 eV): *m/z* (%): 270 (61), 269 (100) [M^+], 268 (89), 226 (28), 192 (41), 171 (61), 110 (26). IR (NaCl): $\tilde{\nu}$ = 3103 (w), 3079 (w), 3059 (m), 2923 (vs), 2853 (vs), 2791 (w), 2667 (w), 1613 (vs), 1597 (s), 1491 (m), 1445 (vs), 1347 (m), 1276 (vs), 1176 (m), 1070 (s), 1030 (m), 966 (m), 890 (m), 856 (s), 798 (s), 772 (s), 704 (vs) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{17}H_{19}NS$: 269.1238; *m/z* found: 269.1240.



***N*-[Bis-(4-tolyl)-methylene]-cyclohexylamine (4.2-4bba)**

Compound **4.2-4bba** was synthesized at 100 °C according to the general procedure from potassium oxocarboxylate (243 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol), and 1-bromotoluene (171 mg, 123 µl, 1.00 mmol). After distillation, **4.2-4bba** (80 mg, 62 %) was obtained as red oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.51-7.57 (m, 2H), 7.23-7.30 (m, 2H), 7.05-7.11 (m, 2H), 7.11-7.17 (m, 2H), 3.30 (quint, ^{3}J (H,H)=7.1 Hz, 1H), 2.44 (s, 3H), 2.36 (s, 3H), 1.57-1.84 (m, 7H), 1.14-1.39(m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 165.4, 139.3, 137.9, 137.5, 134.5, 128.8, 128.5, 128.2, 127.5, 61.1, 33.9, 25.6, 24.3, 21.2, 21.1 ppm. EI-MS (70 eV): *m/z* (%): 292 (32), 291 (39) [M^+], 290 (100), 200 (85), 179 (34), 118 (37), 91 (31). IR (NaCl): $\tilde{\nu}$ = 2919 (vs), 2853 (vs), 1659 (m), 1621 (s), 1605 (s), 1505 (s), 1447 (s), 1405 (m), 1310 (s), 1292 (s), 1256 (m), 1180 (s), 1112 (m), 1068 (m), 1038 (w), 1020 (m), 968 (m), 932 (w), 890 (w), 822 (m), 778 (m), 756 (m), 732 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{21}H_{25}N$: 291.1987; *m/z* found: 291.1977.

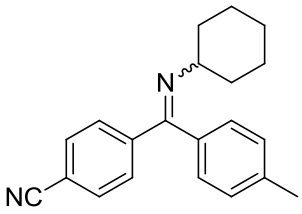


***N*-((4-Methoxyphenyl)-*p*-tolyl-methylene)-cyclohexylamine (4.2-4cba)**

Compound **4.2-4cba** was synthesized according to the general procedure from potassium (4-methoxyphenyl)oxoacetate (262 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (171 mg, 123 µL, 1.00 mmol). After distillation, **4.2-4cba** (105 mg, 34 %) was obtained as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1.4:1): δ = 7.49-7.54 and 7.54-7.60 (2m, 2H), 7.04-7.17 and 7.24-7.30 (2m, 4H), 6.82-6.88 and 6.96-7.03 (2m, 2H), 3.82 and 3.89 (2s, 3H), 3.21-3.35 (m, 1H), 2.37 and 2.46 (2s, 3H), 1.55-1.85 (m, 7H), 1.13-1.36 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 165.0 and 165.2, 160.7, 159.1, 139.4, 138.2, 137.5, 134.6, 133.5, 129.8, 129.7, 129.0, 128.9, 128.5, 128.3, 127.6, 113.1 and 113.6, 61.1 and 61.2, 55.1 and 55.2, 33.99 and 34.04, 25.7, 24.4, 21.2 and 21.3 ppm. EI-MS (70 eV): *m/z* (%): 308 (41), 307 (40) [M^+], 306 (100),

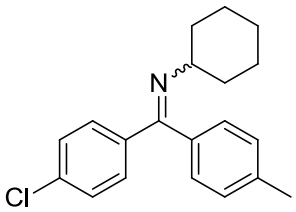
264 (31), 252 (31), 250 (25), 91 (26). IR (NaCl): $\tilde{\nu}$ = 2925 (vs), 2851 (vs), 2053 (w), 1911 (w), 1601 (vs), 1573 (s), 1505 (vs), 1447 (s), 1415 (m), 1310 (s), 1292 (s), 1248 (vs), 1176 (s), 1158 (s), 1110 (m), 1068 (m), 1034 (s), 968 (s), 888 (m), 836 (s), 742 (m), 730 (m), 686 (w), 630 (w) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{21}H_{25}NO$: 307.1936; *m/z* found: 307.1931.



4-(Cyclohexylimino-*p*-tolyl-methyl)-benzonitrile (4.2-4dba)

Compound **4.2-4dba** was synthesized according to the general procedure from potassium (4-cyanophenyl)oxoacetate (256 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (171 mg, 123 µL, 1.00 mmol). After distillation, **4.2-4dba** (285 mg, 94 %) was obtained as colorless solid, m.p. 112.2 °C.

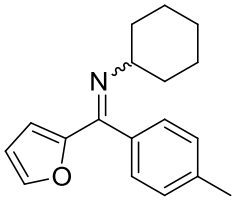
^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 3.4:1): δ = 7.65-7.71 and 7.71-7.78 (2m, 2H), 7.36-7.42 and 7.54-7.59 (2 m, 2H), 7.23-7.29 (m, 2H), 6.97-7.03 and 7.09-7.15 (2m, 2H), 2.98-3.08 and 3.27 (m and qui, ^{3}J (H,H)=7.0 Hz, 1H), 2.34 and 2.42 (2s, 3H), 1.50-1.79 (m, 7H), 1.05-1.30 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 163.2 and 164.1, 144.5, 142.4, 140.3, 138.5, 136.4, 133.0, 132.2, 131.8, 129.3, 128.9, 128.5, 128.1, 127.5, 118.4 and 118.8, 112.1 and 112.7, 61.56 and 61.65, 33.80 and 33.84, 25.5 and 25.6, 24.19 and 24.23, 21.27 and 21.33 ppm. EI-MS (70 eV): *m/z* (%): 305 (25), 303 (100), 302 (46) [M^+], 288 (16), 202 (12), 201 (51), 132 (11). IR (NaCl): $\tilde{\nu}$ = 2927 (vs), 2853 (vs), 2227 (s), 1659 (w), 1621 (s), 1603 (m), 1507 (m), 1447 (m), 1403 (m), 1310 (m), 1290 (m), 1198 (w), 1184 (w), 1112 (w), 1066 (w), 1020 (w), 968 (m), 910 (m), 850 (m), 822 (m), 732 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{21}H_{22}N_2$: 302.1783; *m/z* found: 302.1775.



***N*-[(4-Chlorophenyl)-(4-tolyl)-methylene]cyclohexylamine (4.2-4eba)**

Compound **4.2-4eba** was synthesized at 100 °C according to the general procedure from potassium oxocarboxylate (267 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol), and 4-bromotoluene (171 mg, 123 µl, 1.00 mmol). After distillation, **4.2-4eba** (276 mg, 89 %) was obtained as colorless oil.

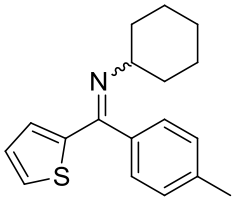
^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers, approx. 1.6:1): δ = 7.44-7.48 and 7.50-7.56 (2m, 2H), 7.25-7.28 and 7.40-7.44 (2m, 2H), 7.00-7.05 and 7.07-7.15 und 7.22-7.25 (3m, 4H), 3.13-3.30 (m, 1H), 2.35 and 2.43 (2s, 3H), 1.54-1.79 (m, 7H), 1.10-1.33 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): δ = 164.1 and 164.5, 139.1 and 139.8, 137.3 and 138.0, 135.5 and 135.9, 133.8 and 133.9, 129.6, 129.1, 128.7, 128.6, 128.2, 128.0, 127.5, 61.3 and 61.4, 33.9, 25.6, 24.3, 21.2 and 21.3 ppm. EI-MS (70 eV): *m/z* (%): 312 (100), 311 (36), 310 (82) [M^+], 268 (33), 256 (43), 200 (56), 179 (31). IR (NaCl): $\tilde{\nu}$ = 2927 (vs), 2853 (vs), 1659 (w), 1619 (s), 1589 (m), 1567 (m), 1509 (m), 1485 (s), 1447 (m), 1397 (m), 1288 (m), 1174 (w), 1090 (m), 1068 (w), 1014 (m), 968 (m), 888 (w), 824 (m), 792 (w), 756 (m), 732 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{22}ClN$: 311.1441; *m/z* found: 311.1422.



***N*-((2-Furyl)-*p*-tolyl-methylene)-cyclohexylamine (4.2-4fba)**

Compound **4.2-4fba** was synthesized according to the general procedure from potassium 2-furyloxoacetate (214 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (171 mg, 123 µL, 1.00 mmol). After distillation, **4.2-4fba** (230 mg, 85 %) was obtained as brown oil.

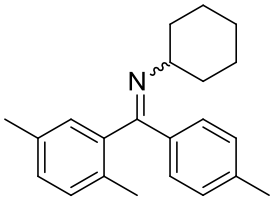
^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 2.7:1): δ = 7.47-7.50 (m, 1H), 7.16-7.23 and 7.40-7.45 (2m, 2H), 7.05-7.11 and 7.11-7.14 (2m, 2H), 6.05-6.11, 6.29-6.33 and 6.43-6.48 (3m, 2H), 3.13-3.24 and 3.63-3.75 (2m, 1H), 2.32 and 2.38 (2s, 3H), 1.50-1.83 (m, 7H), 1.02-1.42 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 156.6, 155.0, 153.7, 146.2, 144.3, 142.8, 139.4, 138.2, 137.4, 132.5, 128.8, 128.5, 128.4, 127.5, 115.0, 113.4, 111.0, 110.4, 60.8 and 61.8, 33.8 and 34.1, 25.4 and 25.6, 24.47 and 24.51, 21.16 and 21.21 ppm. EI-MS (70 eV): *m/z* (%): 267 (55) [M^+], 266 (89), 238 (51), 224 (47), 176 (100), 142 (51), 115 (67). IR (NaCl): $\tilde{\nu}$ = 2925 (vs), 2851 (vs), 1649 (m), 1643 (m), 1605 (s), 1509 (m), 1481 (m), 1463 (m), 1447 (s), 1302 (m), 1224 (w), 1182 (m), 1152 (w), 1112 (w), 1066 (w), 1016 (m), 970 (m), 886 (m), 874 (w), 820 (m), 782 (m), 748 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{18}H_{21}NO$: 267.1623; *m/z* found: 267.1617.



***N*-[(2-Thienyl)-(4-tolyl)-methylene]cyclohexylamine (4.2-4gba)**

Compound **4.2-4gba** was synthesized at 100 °C according to the general procedure from potassium oxocarboxylate (233 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol), and 4-bromotoluene (171 mg, 123 µl, 1.00 mmol). After distillation, **4.2-4gba** (150 mg, 53 %) was obtained as brown solid, m.p. 78 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers, approx. 9:1): δ = 7.31-7.37 and 7.50-7.56 (2 m, 1H), 7.24-7.39 and 7.44-7.48 (2 m, 2H), 7.10-7.16 (m, 2H), 6.90-6.95 and 7.00-7.02 (2 m, 1H), 6.70-6.75 (m, 1H), 3.21 and 3.44-3.53 (qui and m, ^{3}J (H,H)=7.1 Hz, 1H), 2.37 and 2.44 (2s, 3H), 1.53-1.80 (m, 7H), 1.10-1.30 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): δ = 160.5, 147.9, 138.1, 133.6, 129.7, 128.9, 128.7, 128.3, 127.5, 126.9, 60.7, 33.8 und 34.1, 25.6 und 25.7, 24.3 und 24.4, 21.3 ppm. EI-MS (70 eV): *m/z* (%): 283 (74) [M^+], 282 (99), 250 (100), 240 (36), 192 (46), 186 (41), 171 (47). IR (NaCl): $\tilde{\nu}$ = 2921 (s), 2849 (s), 1601 (vs), 1445 (vs), 1429 (vs), 1290 (s), 1260 (s), 1230 (s), 1108 (s), 1068 (vs), 1046 (s), 1018 (s), 842 (s), 818 (s), 804 (s), 780 (m), 700 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{18}H_{21}NS$: 283.1395; *m/z* found: 283.1391.

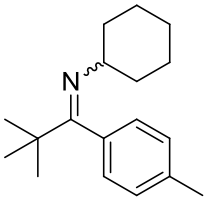


***N*-((2,5-Dimethylphenyl)-*p*-tolyl-methylene)-cyclohexylamine (4.2-4hba)**

Compound **4.2-4hba** was synthesized according to the general procedure from potassium (2,5-dimethylphenyl)oxoacetate (260 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (171 mg, 123 µL, 1.00 mmol). After distillation, **4.2-4hba** (200 mg, 66 %) was obtained as colorless solid, M.p. 87 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.45-7.51 (m, 2H), 7.08-7.17 (m, 4H), 6.81-6.84 (m, 1H), 3.02-3.11 (m, 1H), 2.34 (s, 6H), 2.04 (s, 3H), 1.51-1.80 (m, 7H), 1.08-1.31 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, some signals for the cyclohexane ring split): δ = 165.4, 139.5, 137.4, 137.1, 135.0, 131.7, 129.8, 128.8, 128.7, 127.9, 127.8, 61.4, 33.7 and 33.8, 25.7, 24.37 and 24.43, 21.0 and 21.3, 19.1 ppm. EI-MS (70 eV): *m/z* (%): 306 (52), 305 (13) [M^+], 304 (76), 292 (27), 291 (14), 290 (100), 55 (11). IR (NaCl): $\tilde{\nu}$ = 2919 (vs), 2855 (vs), 1667 (m), 1621

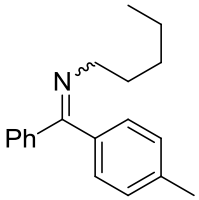
(s), 1605 (s), 1567 (m), 1503 (m), 1493 (m), 1447 (s), 1310 (m), 1296 (m), 1276 (m), 1258 (m), 1178 (m), 1150 (m), 1066 (m), 1020 (w), 968 (m), 890 (w), 858 (w), 828 (m), 812 (m), 786 (w), 760 (w) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{22}H_{27}N$: 305.2144; *m/z* found: 305.2131.



***N*-(*tert*-Butyl-*p*-tolyl-methylene)-pentylamine (4.2-4ica)**

Compound **4.2-4ica** was synthesized within 36 h according to the general procedure from potassium trimethylpyruvate (202 mg, 1.20 mmol), pentylamine (106 mg, 140 µL, 1.20 mmol) and 4-bromotoluene (171 mg, 123 µL, 1.00 mmol). After distillation, **4.2-4ica** (63.0 mg, 26 %) was obtained as pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.14-7.18 (m, 2H), 6.81-6.86 (m, 2H), 2.97 (t, ^3J (H,H)=7.2 Hz, 2H), 2.37 (s, 3H), 1.44-1.54 (m, 2H), 1.16-1.29 (m, 4H), 1.13 (s, 9H), 0.85 (t, ^3J (H,H)=7.2 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 178.1, 136.6, 134.9, 128.5, 127.1, 55.2, 39.7, 30.7, 29.6, 28.5, 22.5, 21.2, 14.0 ppm. EI-MS (70 eV): *m/z* (%): 247 (30), 245 (8) [M^+], 188 (51), 119 (10), 118 (100), 91 (9), 41 (12). IR (NaCl): $\tilde{\nu}$ = 2953 (vs), 2927 (vs), 2859 (s), 1637 (s), 1477 (m), 1461 (m), 1389 (w), 1359 (m), 1224 (w), 1196 (m), 1184 (w), 1110 (w), 1040 (w), 990 (w), 972 (w), 824 (m), 786 (w), 730 (w) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{18}H_{27}N$: 245.2144; *m/z* found: 245.2130.

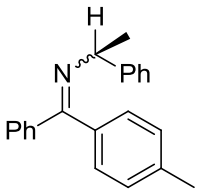


***N*-(Phenyl-*p*-tolyl-methylene)-pentylamine (4.2-4aca)**

Compound **4.2-4aca** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), pentylamine (106 mg, 140 µL, 1.20 mmol) and 4-bromotoluene (171 mg, 123 µL, 1.00 mmol). After distillation, **4.2-4aca** (232 mg, 87 %) was obtained as orange-yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 7.48-7.53 and 7.59-7.64 (2m, 2H), 7.24-7.48 (m, 4H), 7.04-7.16 (m, 3H), 3.36 and 3.40 (2t, ^3J (H,H)=7.0 and 7.2 Hz, 2H), 2.35 and 2.42 (2s, 3H), 1.64-1.75 (m, 2H), 1.25-1.36 (m, 4H), 0.85-0.94 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 167.5 and 167.8, 139.8 and 140.3, 137.9, 137.4, 137.2, 134.0, 129.9, 129.5, 129.0, 128.7, 128.3, 128.2, 128.0, 127.9,

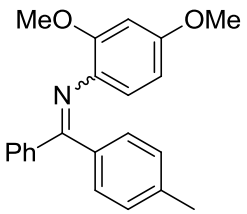
127.79, 127.75, 53.8 and 53.9, 31.0, 29.7, 22.5, 21.2 and 21.3, 14.0 and 14.1 ppm. EI-MS (70 eV): *m/z* (%): 266 (32), 265 (100) [M^+], 223 (20), 209 (74), 105 (71), 91 (45), 77 (22). IR (NaCl): $\tilde{\nu}$ = 2953 (s), 2927 (vs), 2857 (s), 1659 (w), 1621 (m), 1607 (m), 1445 (m), 1312 (m), 1292 (m), 1182 (w), 1112 (w), 1072 (w), 1018 (w), 1002 (w), 938 (w), 924 (w), 824 (w), 776 (w), 728 (w), 698 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{19}H_{23}N$: 265.1830; *m/z* found: 265.1811.



(+)-*S*-1-Phenyl-*N*-(phenyl-*p*-tolyl-methylene)-ethylamine (4.2-4aga)

Compound **4.2-4aga** was synthesized according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), L(–)-α-methylbenzylamine (147 mg, 94 µL, 1.20 mmol) and 4-bromotoluene (171 mg, 123 µL, 1.00 mmol). After distillation, **4.2-4aga** (191 mg, 64 %) was obtained as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1:1): δ = 7.72-7.79 and 7.82-7.90 (2m, 2H), 7.42-7.50 and 7.50-7.62 (2 m, 7H), 7.31-7.42 (m, 2H), 7.23-7.31 (m, 2H), 7.15-7.22 (m, 1H), 4.66-4.81 (2q, ^3J (H,H)=6.4°Hz, 1H), 2.49 and 2.57 (2s, 2H), 1.70-1.61 (q, ^3J (H,H)=3.3 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 165.8 and 166.1, 146.2, 140.2, 139.9, 138.0, 137.3, 137.1, 133.9, 129.7, 129.0, 128.6, 128.5, 128.4, 128.3, 128.21, 128.19, 128.1, 127.9, 127.6, 127.5, 126.6, 126.41, 126.39, 61.2 and 61.3, 25.0, 21.2 and 21.3 ppm. EI-MS (70 eV): *m/z* (%): 300 (46), 299 (100) [M^+], 285 (77), 181 (36), 165 (33), 105 (100), 77 (45). IR (NaCl): $\tilde{\nu}$ = 3025 (s), 2969 (s), 2923 (m), 2889 (m), 2863 (m), 1737 (w), 1621 (vs), 1605 (s), 1491 (m), 1445 (s), 1312 (m), 1290 (s), 1182 (m), 1114 (w), 1074 (m), 1030 (m), 1010 (m), 910 (m), 824 (m), 760 (m), 730 (m), 698 (m) cm^{-1}. Anal. Calcd. for $C_{22}H_{21}N$: C 88.25, H 7.07, N 4.68; found: C 87.97, H 6.94, N 4.70. $[\alpha]_{589}^{24}$ = 18° (ethyl acetate).

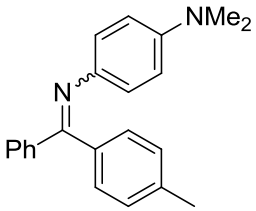


2,4-Dimethoxy-*N*-(phenyl-*p*-tolyl-methylene)-aniline (4.2-4aha)

Compound **4.2-4aha** was synthesized at 130 °C according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), 2,4-dimethoxyaniline (184 mg, 171 µL,

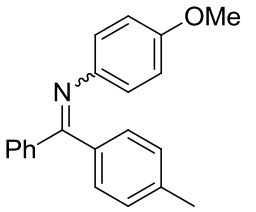
1.20 mmol) and 4-bromotoluene (171 mg, 123 µL, 1.00 mmol). After distillation, **4.2-4aha** (312 mg, 94 %) was obtained as brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1.2:1): δ = 7.64-7.71 and 7.74-7.81 (2 m, 2H), 7.00-7.07, 7.12-7.27 and 7.33-7.46 (3 m, 7H), 6.49 and 6.51 (2 s, 1H), 6.23-6.30 and 6.33-6.40 (2 m, 2H), 3.65, 3.67, 3.69, 3.71 (4 s, 6H), 2.30 and 2.39 (2 s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 169.3 and 169.6, 156.57 and 156.60, 150.5 and 150.6, 140.6, 139.9, 138.1, 137.2, 136.9, 134.8, 134.6, 134.0, 130.2, 129.3, 129.2, 128.8, 128.7, 128.6, 128.2, 128.1, 127.8, 127.4, 121.1 and 121.3, 103.6 and 103.7, 98.9 and 99.0, 55.13, 55.15, 55.16 and 55.24, 21.2 and 21.3 ppm. EI-MS (70 eV): *m/z* (%): 333 (40), 332 (100), 331 (4) [M^+], 317 (20), 302 (12), 255 (22), 241 (11), 182 (17). IR (NaCl): $\tilde{\nu}$ = 2870 (s), 2833 (vs), 1605 (vs), 1503 (vs), 1453 (vs), 1445 (s), 1306 (s), 1258 (s), 1208 (s), 1158 (s), 1122 (s), 1036 (s), 960 (m), 828 (m), 700 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{22}H_{21}NO_2$: 331.1572; *m/z* found: 331.1568.



***N*,*N*-Dimethyl-*N'*-(phenyl-*p*-tolyl-methylene)-*p*-phenylendiamine (4.2-4aaa)**

Compound **4aaa** was synthesized at 130 °C according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), *N*,*N*-*d*imethyl-*p*-phenylendiamine (163 mg, 1.20 mmol) and 4-bromotoluene (171 mg, 123 µL, 1.00 mmol). After distillation, **4aaa** (190 mg, 60 %) was obtained as orange solid, M.p. 99 °C. The spectroscopic data correspond with those reported above.

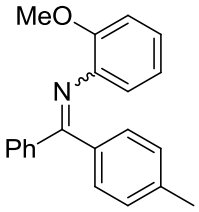


***N*-[(Phenyl)-(4-tolyl)-methylene]-*p*-anisidine (4.2-4ada)**

Compound **4.2-4ada** was synthesized at 130 °C according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), *p*-anisidine (148 mg, 1.20 mmol), and 4-bromotoluene (171 mg, 123 µl, 1.00 mmol). After distillation, **4.2-4ada** (165 mg, 55 %) was obtained as orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers, approx. 1.1:1): δ = 7.62-7.68 and 7.73-7.78 (2m, 2H), 7.18-7.31 and 7.36-7.48 (2m, 4H), 7.01-7.17 (m, 3H), 6.67-6.75 (m, 4H),

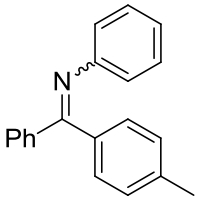
3.71 and 3.73 (2s, 2H), 2.34 and 2.41 (2s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): δ = 167.6 and 167.8, 155.6 and 155.7, 144.4 and 144.5, 140.7, 140.2, 138.3, 137.2, 136.7, 133.5, 130.3, 129.5, 129.4, 129.14, 129.08, 128.8, 128.6, 128.3, 128.0, 127.9, 122.5, 122.4, 113.6 and 113.7, 55.2, 21.27 and 21.33 ppm. EI-MS (70 eV): *m/z* (%): 302 (38), 301 (100) [M^+], 287 (16), 225 (8), 224 (17), 210 (11), 179 (8). IR (NaCl): $\tilde{\nu}$ = 2929 (m), 2833 (m), 1605 (vs), 1567 (s), 1503 (vs), 1443 (s), 1290 (s), 1242 (vs), 1220 (s), 1180 (m), 1106 (m), 1036 (s), 960 (m), 832 (m), 778 (m), 700 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{21}H_{19}NO$: 301.1467; *m/z* found: 301.1469.



***N*-(Phenyl-*p*-tolyl-methylene)-*o*-anisidine (4.2-4aia)**

Compound **4.2-4aia** was synthesized at 130 °C according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), *o-a*nisidine (148 mg, 135 µL, 1.20 mmol) and 4-bromotoluene (171 mg, 123 µL, 1.00 mmol). After distillation, **4.2-4aia** (220 mg, 73 %) was obtained as yellow-orange oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1.2:1): δ = 7.73-7.79 and 7.82-7.88 (2 m, 2H), 7.16-7.23, 7.23-7.32 and 7.40-7.54 (3m, 5H), 7.06-7.14 (m, 2H), 6.91-7.01 (m, 1H), 6.75-6.85 (m, 2H), 6.62-6.70 (m, 1H), 3.73 and 3.75 (2s, 3H), 2.34 and 2.46 (2s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 169.6 and 169.3, 149.5, 149.4, 141.2, 141.1, 140.8, 139.6, 138.4, 136.9, 136.6, 133.8, 130.4, 129.3, 128.7, 128.5, 128.2, 127.4, 123.7, 121.0, 120.8, 120.4, 120.3, 110.9, 110.8, 55.2, 55.1, 21.3, 21.2 ppm. EI-MS (70 eV): *m/z* (%): 303 (51), 302 (100), 301 (9) [M^+], 287 (17), 271 (14), 225 (17), 182 (40), 51 (15). IR (NaCl): $\tilde{\nu}$ = 2983 (m), 1731 (vs), 1607 (m), 1489 (m), 1373 (m), 1246 (vs), 1112 (m), 1046 (s), 910 (m), 758 (s), 734 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{21}H_{19}NO$: 301.1467; *m/z* found: 301.1472.

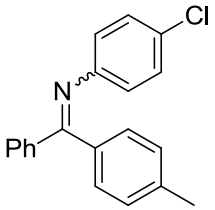


***N*-(Phenyl-*p*-tolyl-methylene)-aniline (4.2-4aea)**

Compound **4.2-4aea** was synthesized at 130 °C according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), aniline (112 mg, 109 µL, 1.20 mmol) and

4-bromotoluene (171 mg, 123 µL, 1.00 mmol). After distillation, **4.2-4aea** (144 mg, 53 %) was obtained as yellow oil.

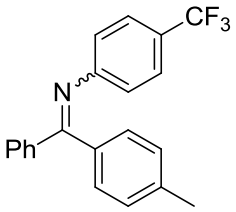
^{1}H-NMR (400 MHz, $CDCl_3$, 2 signal sets for stereoisomers, approx. ratio 1.2:1): δ = 7.69-7.75 and 7.79-7.86 (2 m, 2H), 7.14-7.24, 7.24-7.35 and 7.41-7.55 (3 m, 7H), 6.92-7.01 and 7.04-7.13 (2 m, 3H), 6.75-6.83 (m, 2H), 2.35 and 2.45 (2 s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 signal sets for stereoisomers): δ = 168.0 and 168.2, 151.3 and 151.4, 140.9, 139.9, 138.4, 136.9, 136.3, 133.1, 130.5, 129.5, 129.4, 129.3, 129.2, 128.8, 128.5, 128.4, 128.3, 128.0, 127.7, 122.89 and 122.91, 120.8 and 120.9, 21.3 and 21.4 ppm. EI-MS (70 eV): *m/z* (%): 272 (100), 271 (30) [M^+], 257 (41), 195 (53), 181 (35), 180 (30), 77 (37). IR (NaCl): $\tilde{\nu}$ = 3055 (s), 3025 (s), 2919 (m), 1617 (s), 1591 (vs), 1481 (m), 1445 (m), 1316 (m), 1292 (m), 1220 (m), 1180 (w), 1142 (m), 1072 (w), 1026 (w), 958 (w), 832 (w), 764 (w), 696 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{17}N$: 271.1361; *m/z* found: 271.1350.



4-chloro-*N*-[phenyl-(4-tolyl)-methylene]aniline (4.2-4afa)

Compound **4.2-4afa** was synthesized at 130 °C according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), *p*-anisidine (156 mg, 1.20 mmol), and 4-bromotoluene (171 mg, 123 µl, 1.00 mmol). After distillation, **4.2-4afa** (229 mg, 75 %) was obtained as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$, 2 Signal sets for E/Z-isomers, approx. 1.2:1): δ = 7.61-7.68 and 7.71-7.79 (2 m, 2H), 7.17-7.34 and 7.36-7.51 (2 m, 2H), 7.05-7.15 (m, 4H), 6.96-7.03 (m, 1H), 6.61-6.71 (m, 2H), 2.33 and 2.41 (2 s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$, 2 Signal sets for *E/Z*-isomers): δ = 168.8 and 169.0, 149.8 and 149.9, 141.3, 139.6, 138.8, 136.6, 136.0, 132.8, 130.8, 129.5, 129.32, 129.28, 128.9, 128.7, 128.6, 128.52, 128.46, 128.25, 128.21, 128.1, 128.0, 122.3 und 122.4, 21.3 and 21.4 ppm. EI-MS (70 eV): *m/z* (%): 307 (36), 306 (33), 305 (100) [M^+], 290 (34), 228 (42), 179 (41), 75 (43). IR (NaCl): $\tilde{\nu}$ = 3079 (m), 3055 (m), 3025 (m), 2919 (m), 1605 (vs), 1481 (vs), 1445 (m), 1314 (s), 1296 (s), 1222 (s), 1182 (m), 1142 (s), 1092 (s), 1010 (m), 960 (m), 834 (s), 774 (m), 722 (m), 702 (s), 670 (w) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{16}ClN$: 305.0971; *m/z* found: 305.0951.

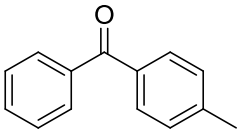


***N*-(Phenyl-*p*-tolyl-methylene)-4-trifluoromethylaniline (4.2-4aja)**

Compound **4.2-4aja** was synthesized at 130 °C according to the general procedure from potassium phenyloxoacetate (226 mg, 1.20 mmol), 4-trifluoroaniline (193 mg, 149 µL, 1.20 mmol) and 4-bromotoluene (171 mg, 123 µL, 1.00 mmol). GC yield: 16 %. EI-MS (70 eV): *m/z* (%): 341 (38), 340 (100), 339 (22) [M^+], 325 (33), 263 (57), 249 (22), 180 (45).

8.7.3 General Procedure for the One-pot Ketone Synthesis

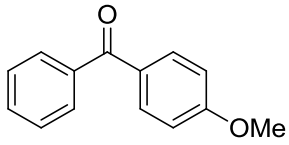
An oven-dried 20 mL vessel was charged with potassium aryloxoacetate (1.20 mmol), copper(I) bromide (21.5 mg, 0.15 mmol), palladium(II) 1,1,1,3,3,3-hexafluoroacetylacetonate (5.2 mg, 0.01 mmol), 1,10-phenanthroline (27.0 mg, 0.15 mmol), 1,1'-bis-(diphenylphosphino) ferrocene (5.7 mg, 0.01 mmol) and 3 Å molecular sieves (200 mg). The reaction vessel was evacuated and flushed with nitrogen three times. Subsequently, a degassed solution of the corresponding aryl halide (1.00 mmol), the amine (1.20 mmol) and the internal standard *n*-tetradecane (50 µL) in quinoline (2 mL) was added *via* syringe. The resulting mixture was stirred at 100 °C for 10 h. Then, 3 mL of a 2 M HCl / THF (1:1) solution were added *via* syringe and the mixture was stirred at 80 °C for 1 h. After addition of 20 mL of 6 M HCl solution, the mixture was extracted three times with 20 mL portions of ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate solution, water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate 80:20), affording the corresponding ketone.



4-Methylbenzophenone (4.2-6a) [CAS-No. 134-84-9]

The ketone **4.2-6a** was synthesized according to the general procedure, starting from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (175 mg, 126 µL, 1.00 mmol). 4-Methylbenzophenone **4.2-6a** was purified by column chromatography (SiO_2, hexane/ethyl acetate 90:10) and isolated as a pale yellow solid (190 mg, 97 %). M.p. 55 °C.

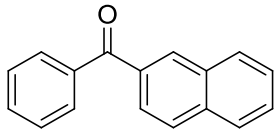
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75-7.81 (m, 2H), 7.71 (d, ^{3}J (H,H) = 8.2 Hz, 2H), 7.52-7.58 (m, 1H), 7.42-7.48 (m, 2H), 7.26 (d, ^{3}J (H,H) = 7.8 Hz, 2H), 2.42 ppm (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 196.2, 143.0, 137.9, 134.8, 132.0, 130.1, 129.7, 128.8, 128.1, 21.5 ppm. EI-MS (70 eV), *m/z* (%): 196 (55) [M+], 181 (19), 119 (100), 105 (23), 91 (28), 77 (24). IR (KBr): $\tilde{\nu}$ = 1654 (vs), 1604 (s), 1446 (m), 1408, 1317 (m), 1279 (s), 1176, 1149, 935 (m), 840 (m), 785 (m), 732 (m), 699 (m), 602 cm^{-1}. Anal. Calcd. for $C_{12}H_{14}O$: C 85.65, H 6.16; found: C 86.06, H 6.40.



4-Methoxybenzophenone (4.2-6b) [CAS-No. 611-94-9]

The ketone **4.2-6b** was synthesized according to the general procedure, starting from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromoanisole (187 mg, 126 µL, 1.00 mmol). 4-Methoxybenzophenone **4.2-6b** was purified by column chromatography (SiO_2, hexane/ethyl acetate 90:10) and isolated as a yellow oil (184 mg, 87 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, ^{3}J (H,H) = 8.9 Hz, 2H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 2H), 6.93 (d, 3*J* (H,H) = 8.9 Hz, 2H), 3.84 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 195.3, 163.2, 138.3, 132.4, 131.7, 130.1, 129.6, 128.1, 113.5, 55.3 ppm. EI–MS (70 eV), *m/z* (%): 212 (60) [M+], 136 (12), 135 (100), 105 (9), 77 (19), 51 (19). IR (NaCl): $\tilde{\nu}$ = 1654 (vs), 1599 (vs), 1508 (m), 1445 (m), 1317 (m), 1281 (s), 1257 (vs), 1172 (s), 1148 (s), 1028 (s), 922 (m), 844 (m), 741 (m), 701 (m) cm^{-1}. Anal. Calcd. for $C_{15}H_{14}O_2$: C 79.62, H 6.24; found: C 79.42, H 5.93.

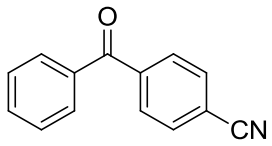


2-Benzoylnaphthalene (4.2-6c) [CAS-No. 644-13-3]

The ketone **4.2-6c** was synthesized according to the general procedure, starting from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 2-bromonaphthalene (207 mg, 1.00 mmol). 2-Benzoylnaphthalene **4.2-6c** was purified by column chromatography (SiO_2, hexane/ethyl acetate 90:10) and isolated as a pale yellow solid (220 mg, 95 %). M.p. 83-84 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 1H), 7.88-7.99 (m, 6H), 7.61-7.66 (m, 2H), 7.52-7.59 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 196.7, 137.9, 135.2, 134.8, 132.3,

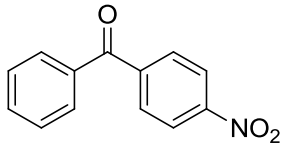
132.2, 131.8, 130.0, 129.4, 128.3, 128.3, 128.2, 127.8, 126.8, 125.7 ppm. EI-MS (70 eV), *m/z* (%): 232 (100) [M+], 231 (74), 155 (92), 127 (59), 105 (32), 77 (55), 51 (32). IR (KBr): $\tilde{\nu}$ = 1655 (vs), 1622 (m), 1598 (m), 1446 (m), 1277 (vs), 1269 (vs), 1234 (s), 1115 (m), 920 (m), 819 (s), 754 (vs), 696 (vs) cm^{-1}. Anal. Calcd. for $C_{17}H_{12}O$: C 87.90, H 5.21; found: C 88.02, H 4.96.



4-Benzoylbenzonitrile (4.2-6d) [CAS-No. 1503-49-7]

The ketone **4.2-6d** was synthesized according to the general procedure, starting from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromobenzonitrile (182 mg, 1.00 mmol). 4-Benzoylbenzonitrile **4.2-6d** was purified by column chromatography (SiO_2, hexane/ethyl acetate 80:20) and isolated as a white solid (195 mg, 94 %). M.p. 114-115 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, ^3J (H,H) = 8.0 Hz, 2H), 7.78-7.81 (m, 4H), 7.63-7.67 (m, 1H), 7.50-7.54 (m, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 195.0, 141.2, 136.3, 133.3, 132.1, 130.2, 130.0, 128.6, 118.0, 115.6 ppm. EI-MS (70 eV), *m/z* (%): 207 (49) [M+], 130 (23), 105 (100), 102 (21), 77 (50), 51 (28), 51 (21). IR (KBr): $\tilde{\nu}$ = 2227 (m), 1648 (vs), 1595 (m), 1403 (m), 1311 (s), 1279 (vs), 856 (s), 735 (s), 694 (vs) cm^{-1}. Anal. Calcd. for $C_{14}H_9NO$: C 81.14, H 4.38, N 6.76; found: C 81.39, H 4.21, N 6.74.

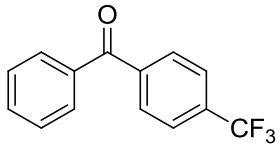


4-Nitrobenzophenone (4.2-6e) [CAS-No. 1144-74-7]

The ketone **4.2-6e** was synthesized according to the general procedure, starting from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 1-bromo-4-nitrobenzene (202 mg, 1.00 mmol). 4-Nitrobenzo phenone **4.2-6e** was purified by column chromatography (SiO_2, hexane/ethyl acetate 85:15) and isolated as a pale yellow solid (148 mg, 65 %). M.p. 138-139 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, ^3J (H,H) = 7.4 Hz, 2H), 7.94 (d, ^3J (H,H) = 7.4 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.64-7.68 (m, 1H), 7.52-7.55 (m, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 194.7, 149.8, 142.8, 136.2, 133.4, 130.6, 130.0, 128.6, 123.5 ppm. EI-MS (70 eV): *m/z* (%): 227 (26) [M^+], 150 (12), 105 (100), 77 (46), 76 (15), 51 (19), 50 (23). IR (KBr): $\tilde{\nu}$ = 1651 (s), 1594 (m), 1511 (vs), 1446 (m), 1357 (s), 1317 (s), 1276 (s), 1146 (w),

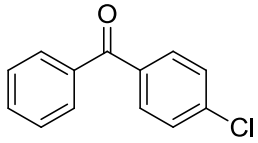
1104 (m), 929 (m), 872 (m), 851 (m), 705 (vs), 691 (vs) cm^{-1}. Anal. Calcd. for $C_{13}H_9NO_3$: C 68.72, H 3.99, N 6.16; found: C 68.72, H 3.67, N 6.15.



4-Trifluoromethylbenzophenone (4.2-6f) [CAS-No. 728-86-9]

The ketone **4.2-6f** was synthesized according to the general procedure, starting from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 1-bromo-4-trifluoromethylbenzene (227 mg, 142 µL, 1.00 mmol). 4-Trifluoromethylbenzophenone **4.2-6f** was purified by column chromatography (SiO_2, hexane/ethyl acetate 95:5) and isolated as a white solid (220 mg, 88 %). M.p. 116-117 °C.

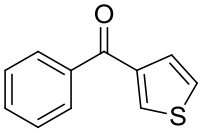
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, ^3J (H,H) = 8.2 Hz, 2H), 7.76 - 7.83 (m, 4H), 7.62-7.66 (m, 1H), 7.50 - 7.54 (m, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 195.5, 140.7 (d, J = 1.8 Hz), 136.7, 133.5, 133.1 (q, ^2J (C,F) = 32.7 Hz), 130.1, 130.0, 128.5, 125.3 (q, ^3J (C,F) = 3.7 Hz), 123.6 (q, ^1J (C,F) = 272.6 Hz) ppm. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -63.0 (s, 3F) ppm. EI-MS (70 eV), *m/z* (%): 250 (100) [M^+], 173 (32), 145 (27), 105 (92), 77 (24), 51 (11). IR (KBr): $\tilde{\nu}$ = 1651 (s), 1597 (m), 1448 (m), 1409 (s), 1330 (vs), 1281 (s), 1168 (vs), 1110 (vs), 1065 (vs), 1016 (s), 924 (s), 857 (vs), 715 (vs), 698 (vs) cm^{-1}. Anal. Calcd. for $C_{14}H_9F_3O$: C 67.20, H 3.63; found: C 66.93, H 3.58.



4-Chlorobenzophenone (4.2-6g) [CAS-No. 134-85-0]

The ketone **4.2-6g** was synthesized according to the general procedure, starting from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 1-bromo-4-chlorobenzene (191 mg, 116 µL, 1.00 mmol). 4-Chlorobenzophenone **4.2-6g** was purified by column chromatography (SiO_2, hexane/ethyl acetate 95:5) and isolated as a white solid (200 mg, 92 %). M.p. 76-77 °C.

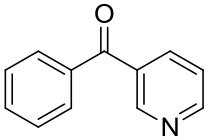
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.76-7.79 (m, 4H), 7.59-7.63 (m, 1H), 7.46-7.52 (m, 4H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 195.5, 138.9, 137.2, 135.8, 132.6, 131.4, 129.9, 128.6, 128.4 ppm. EI-MS (70 eV), *m/z* (%): 216 (93) [M^+], 139 (86), 111 (31), 105 (100), 77 (44), 51 (29), 50 (28). IR (KBr): $\tilde{\nu}$ = 1643 (vs), 1584 (m), 1483 (s), 1284 (m), 1089 (m), 854 (s), 748 (vs) cm^{-1}. Anal. Calcd. for $C_{13}H_9ClO$: C 72.07, H 4.19; found: C 71.81, H 4.16.



3-Benzoylthiophene (4.2-6h) [CAS-No. 6453-99-2]

The ketone **4.2-6h** was synthesized according to the general procedure, starting from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 3-bromothiophene (163 mg, 94 µL, 1.00 mmol). 3-Benzoylthiophene **4.2-6h** was purified by column chromatography (SiO_2, hexane/ethyl acetate 80:20) and isolated as yellow oil (182 mg, 97 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, ^4J (H,H) = 1.7 Hz, 1H), 7.83 (d, ^3J (H,H) = 7.2 Hz, 2H), 7.52-7.61 (m, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.36 ppm (dd, ^3J (H,H) = 5.1 Hz, ^4J (H,H) = 3.1 Hz, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 189.8, 141.3, 138.6 133.7, 132.2, 129.3, 128.5, 128.3, 126.1 ppm. EI-MS (70 eV), *m/z* (%): 188 (100) [M^+], 160 (7), 111 (96), 105 (43), 83(10), 77 (34), 51 (23). IR (NaCl): $\tilde{\nu}$ = 3106 (s)), 1648 (vs), 1597 (s), 1509 (s), 1446 (s), 1409 (s), 1387 (s), 1276 (vs), 1177 (m), 1137 (m), 1074 (m), 968 (m), 858 (s), 717 (vs), 671 (s) cm^{-1}.

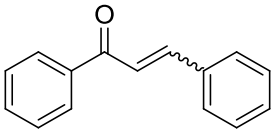


3-Benzoylpyridine (4.2-6i) [CAS-No. 5424-19-1]

The ketone **4.2-6i** was synthesized according to the general procedure, starting from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 3-bromopyridine (158 mg, 96 µL, 1.00 mmol). After addition of dilute sodium bicarbonate solution, the reaction mixture was extracted three times with 20 mL ethyl acetate. The combined organic layers were dried over magnesium sulfate, and the volatile components were removed at 130 °C and 2 x 10^{-2} mbar. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate 80:20) to afford 3-benzoylpyridine **4.2-6i** (166 mg, 91 %) as brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.92 (br s, 1H), 8.73 (br s, 1H), 8.02 (d, ^3J (H,H) = 7.8 Hz, 1H), 7.72 (d, ^3J (H,H) = 7.0 Hz, 2H), 7.52-7.55 (m, 1H), 7.32-7.44 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 194.7, 152.6, 150.7, 137.0, 136.5, 133.0, 129.9, 128.4, 123.3 ppm. EI-MS (70 eV), *m/z* (%):183 (84) [M^+], 182 (36), 106 (25), 105 (100), 77 (44), 51 (35). IR (NaCl): $\tilde{\nu}$ = 3057 (m), 1662 (vs), 1585 (vs), 1447 (s), 1415 (s), 1317 (m), 1284 (vs), 1026 (m),

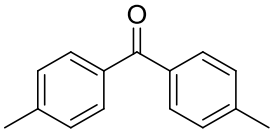
922 (m), 784 (w), 714 (m), 654 (m) cm^{-1}. Anal. Calcd. for $C_{12}H_9NO$: C 78.67, H 4.95, N 7.65; found: C 78.14, H 5.07, N 7.49.



1,3-Diphenylprop-2-en-1-one (chalcone) (4.2-6j) [CAS-No. 94-41-7]

The ketone **4.2-6j** was synthesized according to the general procedure, starting from potassium phenyloxoacetate (226 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 2-bromovinylbenzene (183 mg, 129 µL, 1.00 mmol). Chalcone **4.2-6j** was purified by column chromatography (SiO_2, hexane/ethyl acetate 90:10) and isolated as yellow oil (88 mg, 42 %).

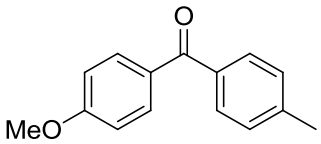
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, ^3J (H,H) = 7.8 Hz, 2H), 7.82 (d, ^3J (H,H) = 15.7 Hz, 1H), 7.62-7.65 (m, 2H), 7.48-7.60 (m, 4H), 7.40-7.42 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 190.4, 144.7, 138.1, 134.8, 132.7, 130.5, 128.9, 128.5, 128.4, 128.3, 122.0 ppm. EI-MS (70 eV): m/z (%): 208 (52) [M^+], 207 (100), 131 (35), 103 (46), 77 (90), 51 (54), 50 (33). IR (NaCl): $\tilde{\nu}$ = 1663 (s), 1605 (vs), 1573 (s), 1447 (m), 1336 (s), 1216 (s), 1016 (m), 988 (m), 748 (vs), 688 (m) cm^{-1}. CHN: C = 86.53 %, H = 6.00 %; calcd: C = 86.51 %, H = 5.81 %. Anal. Calcd. for $C_{15}H_{12}O$: C 86.51, H 5.81; found: C 86.53, H 6.00.



4,4'-Dimethylbenzophenone (4.2-6k) [CAS-No. 611-97-2]

The ketone **4.2-6k** was synthesized according to the general procedure, starting from potassium 4-methylphenyloxoacetate (243 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (175 mg, 126 µL, 1.00 mmol). 4,4'-Dimethylbenzophenone **4.2-6k** was purified by column chromatography (SiO_2, hexane/ethyl acetate 85:15) and isolated as a yellow solid (115 mg, 55 %). M.p. 72-73 °C.

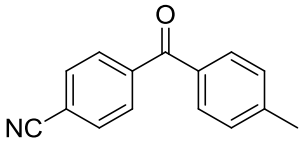
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, ^3J (H,H) = 8.0 Hz, 4H), 7.19 (d, ^3J (H,H) = 8.0 Hz, 4H), 2.36 ppm (s, 6H, CH_3). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 196.2, 142.9, 135.2, 130.1, 128.9, 21.6 ppm. EI-MS (70 eV): *m/z* (%): 210 (32) [M^+], 120 (9), 119 (12), 91 (7), 89 (6). IR (KBr): $\tilde{\nu}$ = 1645 (vs), 1605 (vs), 1312 (m), 1277 (s), 1175 (s), 1145, 926 (m), 842 (m), 820 (m), 747 (s), 680 (m), 577 (m) cm^{-1}. Anal. Calcd. for $C_{15}H_{14}O$: C 85.68, H 6.71; found: C 84.57, H 6.76.



4-Methoxy-4'-methylbenzophenone (4.2-6l) [CAS-No. 23886-71-7]

The ketone **4.2-6l** was synthesized according to the general procedure, starting from potassium 4-methoxyphenyloxoacetate (262 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (175 mg, 126 µL, 1.00 mmol). 4-Methoxy-4'-methylbenzophenone **4.2-6l** was purified by column chromatography (SiO_2, hexane/ethyl acetate 90:10) and isolated as a pale yellow solid (160 mg, 71 %). M.p. 89-90 °C.

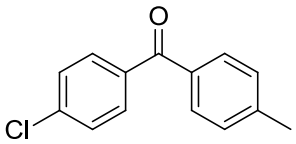
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.82 (d, ^3J (H,H) = 8.8 Hz, 2H), 7.69 (d, ^3J (H,H) = 8.1 Hz, 2H), 7.28 (d, ^3J (H,H) = 8.0 Hz, 2H), 6.97 (d, ^3J (H,H) = 8.8 Hz, 2H), 3.89 (s, 3 H), 2.44 (s, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 195.2, 162.9, 142.4, 135.4, 132.3, 130.4, 129.9, 128.8, 113.4, 55.4, 21.5 ppm. EI-MS (70 eV): *m/z* (%): 226 (63) [M^+], 211 (14), 135 (100), 119 (23), 91 (19), 77 (26). IR (KBr): $\tilde{\nu}$ = 1645 (s), 1596 (vs), 1505 (m), 1458 (m), 1315 (s), 1259 (vs), 1168 (s), 1146 (s), 1114 (m), 1022 (m), 929 (m), 849 (m), 760 (s), 682 (m), 577 (m) cm^{-1}. Anal. Calcd. for $C_{15}H_{14}O_2$: C 79.62, H 6.24; found: C 79.42, H 5.93.



(4-Methylbenzoyl)benzonitrile (4.2-6m) [CAS-No. 35776-95-5]

The ketone **4.2-6m** was synthesized according to the general procedure, starting from potassium 4-cyanophenyloxoacetate (256 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (175 mg, 126 µL, 1.00 mmol). (4-methylbenzoyl)benzonitrile **4.2-6m** was purified by column chromatography (SiO_2, hexane/ethyl acetate 90:10) and isolated as a white solid (132 mg, 60 %). M.p. 166-167 °C.

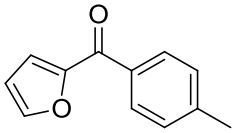
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, ^3J (H,H) = 8.0 Hz, 2H), 7.79 (d, ^3J (H,H) = 8.0 Hz, 2H), 7.70 (d, ^3J (H,H) = 8.0 Hz, 2H), 7.32 (d, ^3J (H,H) = 8.0 Hz, 2H), 2.46 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 194.7, 144.3, 141.6, 133.6, 2x 132.1, 2x 130.2, 2x 130.1, 2x 129.3, 118.0, 115.3, 21.7 ppm. EI-MS (70 eV): *m/z* (%): 221 (44) [M^+], 130 (10), 119 (100), 102 (14), 91 (23), 65 (14). IR (KBr): $\tilde{\nu}$ = 2229 (w), 1648 (vs), 1603 (m), 1404 (w), 1312 (m), 1282 (m), 1140 (w), 929 (w), 856 (m), 755 (s), 677 (m), 573 (w), 546 (w) cm^{-1}. Anal. Calcd. for $C_{15}H_{11}NO$: C 81.43, H 5.01, N 6.33; found: C 80.96, H 5.01, N 6.25.



4-Chloro-4'-methylbenzophenone (4.2-6n) [CAS-No. 5395-79-9]

The ketone **4.2-6n** was synthesized according to the general procedure, starting from potassium 4-chlorophenyloxoacetate (267 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (175 mg, 126 µL, 1.00 mmol). 4-Chloro-4'-methylbenzophenone **4.2-6n** was purified by column chromatography (SiO_2, hexane/ethyl acetate 95:5) and isolated as a white solid (69 mg, 30 %). M.p. 127-128 °C.

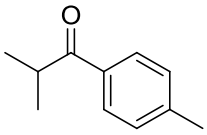
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60-7.67 (m, 4H), 7.37 (dd, ^3J (H,H) = 8.2 and 1.6 Hz, 2H), 7.21 (d, ^3J (H,H) = 7.4 Hz, 2H), 2.36 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 195.2, 143.5, 138.5, 136.2, 134.5, 131.3, 130.1, 129.0, 128.5, 21.6 ppm. EI-MS (70 eV): *m/z* (%): 230 (41) [M^+], 195 (16), 139 (23), 119 (100), 111 (19), 91 (31), 65 (18). IR (KBr): $\tilde{\nu}$ = 1643 (vs), 1605 (s), 1584 (m), 1286 (m), 1088 (m), 854 (s), 748 (vs) cm^{-1}.



2-Furyl-4-tolylketone (4.2-6o) [CAS-No. 13365-62-3]

The ketone **4.2-6o** was synthesized according to the general procedure, starting from potassium 2-furyloxoacetate (214 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (175 mg, 126 µL, 1.00 mmol). 2-Furyl-4-tolylketone **4.2-6o** was purified by column chromatography (SiO_2, hexane/ethyl acetate 90:10) and isolated as yellow oil (135 mg, 73 %).

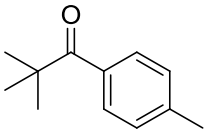
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, ^3J (H,H) = 8.12 Hz, 2H), 7.66 (s, 1H), 7.26 (d, ^3J (H,H) = 7.3 Hz, 2H), 7.18 (d, ^3J (H,H) = 3.4 Hz, 1H), 6.53-6.57 (m, 1H), 2.40 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 182.1, 152.2, 146.7, 143.2, 134.4, 129.3, 128.9, 120.0, 112.0, 21.5 ppm. EI-MS (70 eV): *m/z* (%): 186 (87) [M^+], 171 (21), 158 (27), 119 (100), 95 (17), 91 (45), 65 (24). IR (NaCl): $\tilde{\nu}$ = 3130 (w), 3031 (w), 2921 (w), 1643 (vs), 1607 (vs), 1561 (s), 1463 (vs), 1389 (s), 1314 (s), 1300 (vs), 1226 (w), 1176 (s), 1148 (w), 1082 (w), 1016 (m), 950 (m), 888 (m), 874 (s), 832 (w), 754 (s), 626 (w) cm^{-1}.



2,4'-Dimethylpropiophenone (4.2-6p) [CAS-No. 50390-51-7]

The ketone **4.2-6p** was synthesized according to the general procedure, starting from potassium isopropyloxoacetate (185 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (175 mg, 126 µL, 1.00 mmol) for 36 hours at 100 °C. 2,4'-Dimethylpropiophenone **4.2-6p** was purified by column chromatography (SiO_2, hexane/ethyl acetate 95:5) and isolated as colorless oil (138 mg, 85 %).

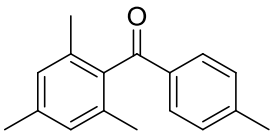
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, ^3J (H,H) = 8.0 Hz, 2H), 7.18 (d, ^3J (H,H) = 8.0 Hz, 2H), 3.43-3.50 (m, 1H), 2.33 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 204.1, 143.5, 133.6, 129.2, 128.4, 35.1, 21.5, 19.2 ppm. EI-MS (70 eV), *m/z* (%): 162 (1) [M^+], 119 (100), 91 (31), 65 (13).. IR (NaCl): $\tilde{\nu}$ = 2972 (s), 2931 (m), 1683 (vs), 1607 (s), 1466 (m), 1458 (m), 1382 (m), 1229 (s), 1209 (m), 1161 (m), 977 (s), 829 (s), 745 (s) cm^{-1}.



2,2,4'-Trimethylpropiophenone (4.2-6q) [CAS-No. 30314-44-4]

The ketone **4.2-6q** was synthesized according to the general procedure, starting from potassium 3,3,3-trimethyl pyruvate (202 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (175 mg, 126 µL, 1.00 mmol) for 36 hours at 100 °C. 2,2,4'-Trimethylpropiophenone **4.2-6q** was purified by column chromatography (SiO_2, hexane) and isolated as colorless oil (78 mg, 44 %).

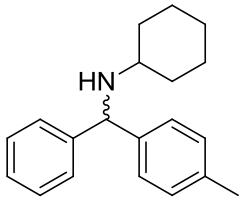
^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, ^3J (H,H) = 8.2 Hz, 2H), 7.11 (d, ^3J (H,H) = 8.2 Hz, 2H), 2.28 (s, 3H), 1.29 (s, 9H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 207.1, 140.9, 135.0, 128.3, 127.9, 43.5, 27.7, 20.9 ppm. EI-MS (70 eV), *m/z* (%): 176 (1) [M^+], 120 (10), 119 (100), 91 (8), 65 (6), 57 (5). IR (NaCl): $\tilde{\nu}$ = 1657 (vs), 1605 (vs), 1449 (m), 1310 (m), 1296 (s), 1272 (s), 1170 (m), 1038 (w), 948 (w), 898 (m), 840 (w), 820 (w), 760 (m), 686 (w), 588 (m), 562 (m) cm^{-1}.



2,4,4',6-Tetramethylbenzophenone (4.2-6r)

The ketone **4.2-6r** was synthesized according to the general procedure, starting from potassium 2,4,6-trimethylphenyloxoacetate (276 mg, 1.20 mmol), cyclohexylamine (119 mg, 137 µL, 1.20 mmol) and 4-bromotoluene (175 mg, 126 µL, 1.00 mmol). 2,4,4',6-Tetramethyl benzophenone **4.2-6r** was detected in 7 % yield (GC yield).

8.7.4 General Procedure for the Reduction of Azomethines to Amines



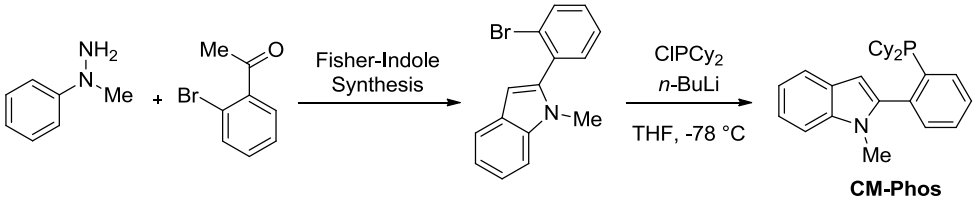
Synthesis of N-(phenyl(*p*-tolyl)methyl)cyclohexylamine (4.2-7a)

A 20 mL vessel was charged with *N*-(phenyl-*p*-tolyl-methylene)-cyclohexylamine (**4aba**) (277 mg, 1.00 mmol), lithium aluminum hydride (120 mg, 3.00 mmol) and THF (2 mL). The resulting mixture was stirred at 60 °C for 16 h, diluted with saturated sodium bicarbonate solution (20 mL) and extracted repeatedly with 20 mL portions of ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and the volatiles were removed *in vacuo*, yielding the product **4.2-7a** as yellowish oil (262 mg, 94 %).

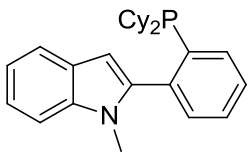
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23-7.30 (m, 2H), 7.12-7.20 (m, 4H), 7.03-7.09 (m, 1H), 6.95-7.01 (m, 2H), 4.89 (s, 1H), 2.24-2.34 (m, 1H), 2.18 (s, 3H), 1.79-1.88 (m, 2H), 1.37-1.65 (m, 3H), 1.20-1.36 (br, 1H), 0.91-1.13 (m, 5H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 144.9, 141.8, 136.2, 129.0, 128.3, 127.2, 126.6, 63.3, 53.9, 33.9, 26.2, 25.1, 21.0 ppm. EI-MS (70 eV): *m/z* (%): 279 (5) [M^+], 202 (29), 188 (14), 182 (23), 181 (100), 167 (17), 166 (26), 165 (28). IR (NaCl): $\tilde{\nu}$ = 3021 (m), 2923 (vs), 2849 (vs), 1601 (w), 1509 (m), 1491 (m), 1449 (s), 1339 (w), 1176 (w), 1110 (m), 1028 (w), 890 (w), 846 (w), 806 (m), 698 (m) cm^{-1}. Anal. Calcd. for $C_{20}H_{25}N$·HCl: C 76.05, H 8.30, N 4.43; found: C 75.91, H 8.39, N 4.32. EI-HRMS *m/z* calcd. for $C_{20}H_{25}N$: 279.1987; *m/z* found: 279.1976.

8.8 Decarboxylative Cross-Coupling of Mesylates Catalyzed by Copper/Palladium with Customized Imidazolyl Phosphine Ligands

8.8.1 Synthesis of Imidazolyl Ligands



CM-Phos

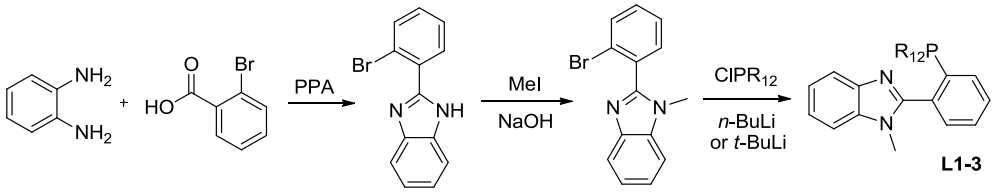


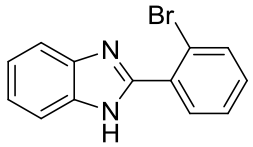
2-(2-(Dicyclohexylphosphino)phenyl)-1-methyl-1H-indole (CM-Phos)

CM-Phos was prepared according to the literature procedures.[5] The white solid was obtained by recrystalization from acetone, m.p. 184-185 ^{o}C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 6.0 Hz, 2H), 7.60-7.40 (m, 4H), 7.33 (d, *J* = 6.0 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 6.48 (s, 1H), 3.59 (s, 3H), 2.40-1.60 (m, 12H), 1.50-0.80 (m, 10H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 141.32, 141.27, 141.11, 140. 79, 137.23, 137.03, 136.65, 132.60. 132.56, 131.98, 131.93, 128.18, 127.81, 127.67, 121.04, 120.05, 119.30. 109.44, 103.28, 103.25, 30.83, 30.77, 27.27, 27.20, 26.38 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -10.09 ppm. IR (KBr): $\tilde{\nu}$ = 2923 (m), 2847 (m), 1467 (m), 1445 (s), 1385 (m), 1363 (w), 1339 (m), 1310 (m), 780 (m), 770 (vs), 748 (vs), 732 (m), 670 (w) cm^{-1}. Anal. Calcd. for $C_{27}H_{34}NP$: C 80.36, H 8.49, N 3.47; found: C 80.30, H 8.25, N 3.50.

Synthesis of 5.2-L1-3.



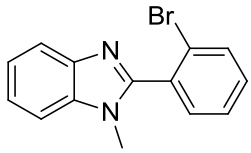


2-(2-Bromophenyl)-1H-benzimidazole [CAS No. 13275-42-8]

To a mixture of 2-bromobenzoic acid (8.04 g, 40 mmol) and 1,2-phenylenediamine (4.83 g, 44.7 mmol) were added polyphosphoric acid (56 g) and heated to 150 °C for 6 h. The reaction mixture was poured over crushed ice and kept in a refrigerator overnight. The resulting violet solid precipitate was filtered and added to 0.5 M Na_2CO_3 solution (500 mL), stirred for 30 min and filtered. The yellow solid was dissolved in warm methanol (100 mL) and water (100 mL) was added dropwise to the previous solution within 1h. A light yellow solid (9.4 g, 34.4 mmol, 86 %) was obtained after filteration and drying under vacuum overngiht. M.p. >300 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.81 (s, 1H), 7.82 (d, *J* = 4.0 Hz, 1H), 7.79 (d, *J* = 4.0 Hz, 1H), 7.73 (d, *J* = 4.0 Hz, 1H), 7.58 (d, *J* = 4.0 Hz, 1H), 7.54 (t, *J* = 4.0 Hz, 1H), 7.45 (t, *J* = 4.0 Hz, 1H), 7.26-7.23 (m, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 159.49, 143.26, 134.54, 133.43, 132.44, 132.30, 131.38, 127.81, 122.73, 121.68, 121.61, 119.15, 111.65 ppm. EI-MS (70 eV), *m/z* (%): 275 (17), 274 (100) [M^{+}], 273 (96), 272 (19), 193 (23), 166 (15). IR

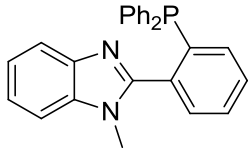
(KBr): $\tilde{\nu}$ = 3566 (m), 3079 (w), 1441 (vs), 1405 (s), 1026 (m), 762 (m), 742 (vs), 728 (m) cm^{-1}. Anal. Calcd. for $C_{13}H_9BrN_2$: C 57.17, H 3.32, N 10.26; found: C 57.14, H 3.43, N 10.25.



2-(2-Bromophenyl)-1-methyl-1H-benzimidazole [CAS No. 92152-36-8]

2-(2-Bromophenyl)-1H-benzoimidazole (4.1 g, 15.0 mmol) was dissolved in a aqeuous solution of sodium hydroxide (50 %, 15 mL), and iodomethane (2.3 g, 1.0 mL, 16.5 mmol) was added dropwise to the previous solution. The reaction mixture was heat to reflux for 1 h, then cooled to room temperature. The resulted soltuion was diluted with water (100 mL), and the mixture was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (40 % ethyl acetate in hexane) to give a brown solid (4.04 g, 14.1 mmol, 94 %). M.p. 94.7 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88-7.81 (m, 1H), 7.69 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.53 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.47-7.28 (m, 5H), 3.62 (s, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 152.33, 142.56, 135.29, 132.59, 132.17, 131.93, 131.25, 127.32, 123.59, 122.77, 122.18, 119.89, 109.51, 30.65 ppm. ESI-MS (70 eV), *m/z* (%): 287, 289 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 3041 (w), 2945 (w), 1643 (m), 1467 (s), 1449 (s), 1431 (s), 1387 (s), 1328 (m), 1284 (m), 1242 (m), 1024 (s), 766 (vs), 754 (s), 742 (vs), 728 (s) cm^{-1}. Anal. Calcd. for $C_{14}H_{11}BrN_2$: C 58.56, H 3.86, N 9.76; found: C 58.28, H 4.03, N 9.60.

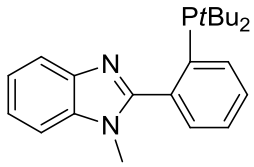


2-(2-(Diphenylphosphino)phenyl)-1-methyl-1H-benzimidazole (**5.2-L1**)

2-(2-Bromophenyl)-1-methyl-1H-benzoimidazole (718 mg, 2.5 mmol) was dissolved in freshly distilled THF (15 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in ethanol/liquid nitrogen bath. *n*-BuLi (1.6 mL, 1.6 M, 2.6 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodiphenylphosphine (0.47 mL, 2.6 mmol) in THF (5 mL) was added dropwise by syringe. The reaction was stirred for 40 min at -78 °C and warmed to room temperature within 2 h, and then kept stirring for another 0.5 h. The reaction mixture was passed through a pad of celite and silica gel and washed with ethyl acetate. After the solvent was removed

under reduced pressure, the obtained yellow solid was purified by recrystallization from acetonitile to give a white solid (600 mg, 1.53 mmol, 61 %). M.p. 178-179 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.84-7.74 (m, 1H), 7.51-7.42 (m, 3H), 7.34-7.20 (m, 14H), 3.38 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 153.15, 142.74, 140.21, 140.4, 136.39, 136.27, 135.93, 135.65, 135.25, 134.01, 133.81, 133.56, 130.78, 130.74, 129.74, 128.68, 128.55, 128.35, 128.28, 122.48, 121.99, 120.00, 109.30, 30.67; (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -11.04 ppm. ESI-MS (70 eV), *m/z* (%): 393.1 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 3064 (w), 3050 (w), 2940 (w), 1477 (w), 1458 (m), 1436 (w), 1421 (m), 1376 (w), 1326 (m), 1281 (w), 1264 (w), 1243 (w), 1091 (w), 1080 (w), 1069 (w), 1036 (w), 1025 (w), 819 (w), 739 (vs), 731 (s), 693 (vs) cm^{-1}. Anal. Calcd. for $C_{26}H_{21}N_2P$: C 79.58, H 5.39, N 7.14; found: C 79.33, H 5.59, N 7.18.

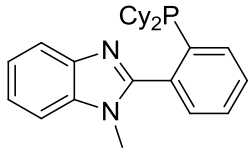


2-(2-(Di-*tert*-butylphosphino)phenyl)-1-methyl-1H-benzimidazole (**5.2-L2**)

2-(2-Bromophenyl)-1-methyl-1H-benzoimidazole (718 mg, 2.5 mmol) was dissolved in freshly distilled THF (15 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in ethanol/liquid nitrogen bath. *tert*-Butyllithium (3.1 mL, 1.6 M, 5.0 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, CuCl (247 mg, 2.5 mmol) was added in one portion, and di-*tert*-butylchlorophosphine (0.59 mL, 2.8 mmol) in THF (5 mL) was added dropwise by syringe. The reaction was stirred for 1 h at -78 °C and warmed to room temperature. The reaction mixture was treated with microwave in a sealed reaction vessel for 0.5 h at 140 °C. The resulted soltuion was diluted with ethyl acetate (50 mL), washed with ammonium solution (3 x 30 mL). The aqueous solution was extracted with ethyl acetate (2 x 30 mL), and the combined organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuum. The residue was purified by column chromatography on silica gel (30 % ethyl acetate in hexane) to give a white solid (375 mg, 1.06 mmol, 43 %). M.p. 184-185 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97-7.93 (m, 1H), 7.82-7.78 (m, 1H), 7.55-7.42 (m, 3H), 7.41-7.37 (m, 1H), 7.36-7.27 (m, 2H), 3.62 (s, 3H), 1.31-1.06 (m, 18H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 155.08, 155.03, 142.90, 139.61, 139.26, 138.80, 138.51, 135.24, 135.11, 135.08, 131.45, 131.37, 128.73, 128.37, 122.13, 121.71, 119.68, 109.44, 31.54, 31.39, 31.29, 31.23, 30.18, 30.02; (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = 24.19 ppm. ESI-MS (70 eV), *m/z* (%): 391.1 $[M+K]^+$. IR (KBr):

$\tilde{\nu}$ = 3049 (w), 2971 (w), 2948 (w), 2936 (w), 2888 (w), 2856 (w), 1469 (w), 1456 (w), 1446 (w), 1435 (w), 1422 (w), 1386 (w), 1366 (w), 1359 (w), 1328 (w), 1281 (w), 1255 (w), 1240 (w), 1174 (w), 1163 (w), 1124 (w), 1077 (w), 1040 (w), 780 (m), 738 (vs), 721 (w) cm^{-1}. Anal. Calcd. for $C_{22}H_{29}N_2P$: C 74.97, H 8.29, N 7.95; found: C 74.83, H 8.21, N 7.99.

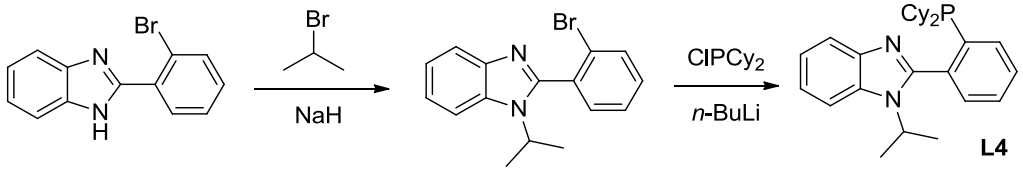


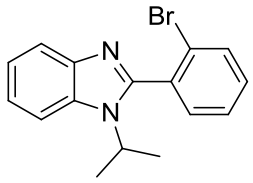
2-(2-(Dicyclohexylphosphino)phenyl)-1-methyl-1H-benzimidazole (**5.2-L3**)

2-(2-Bromophenyl)-1-methyl-1H-benzoimidazole (2.87 g, 10 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in ethanol/liquid nitrogen bath. *n*-BuLi (7.5 mL, 1.6 M, 12 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (2.6 mL, 12 mmol) in THF (10 mL) was added dropwise by syringe. The reaction was stirred for 40 min at -78 °C and warmed to room temperature in 2h, and then kept stirring for another 0.5 h. The reaction mixture was passed through a pad of celite and silica gel and washed with ethyl acetate. After the solvent was removed under reduced pressure, the obtained yellow oil was purified by column chromatography on silica gel (10% ethyl acetate in hexane) to give a white solid (3.63 g, 9.0 mmol, 90 %). M.p. 163-164 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.76-7.70 (m, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.48-7.34 (m, 3H), 7.32-7.26 (m, 1H), 7.25-7.16 (2H), 3.48 (s, 3H), 1.90-1.45 (m, 12H), 1.23-0.88 (m, 10H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 154.55, 154.52, 142.66, 138.75, 138.43, 136.58, 136.35, 135.13, 132.37, 132.35, 131.08, 131.01, 128.79, 128.65, 122.22, 121.70, 119.56, 109.46, 33.30, 33.20, 30.84, 30.75, 29.91, 29.75, 29.07, 29.00, 27.18, 27.09, 27.05, 27.02, 26.19 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -7.81 ppm. ESI-MS (70 eV), *m/z* (%): 405.2 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 3047 (w), 2918 (s), 2845 (m), 1446 (m), 1440 (m), 1426 (m), 1389 (w), 1327 (w), 1269 (w), 1232 (w), 1128 (w), 1042 (w), 1029 (w), 1002 (w), 883 (w), 849 (w), 818 (w), 776 (m), 765 (m), 755 (m), 747 (vs), 720 (w) cm^{-1}. Anal. Calcd. for $C_{26}H_{33}N_2P$: C 77.20, H 8.22, N 6.92; found: C 77.09, H 8.05, N 6.93.

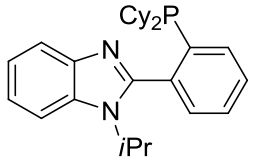
Synthesis of 5.2-L4





2-(2-bromophenyl)-1-isopropyl-1H-benzimidazole

2-(2-Bromophenyl)-1H-benzoimidazole (2.0 g, 7.3 mmol) was dissolved in THF (40 mL) and cooled to 0 °C. NaH (586 mg, 60 %, suspension in mineral oil, 14.6 mmol) was added to the previous solution in one portion under 0 °C. After the cease of the extursion of H_2, isopropyl bromide (1.8 mL, 19.3 mmol) was added dropwise and the reaction mixture was warmed to room temperature under kept stirring for another 1 h. The resulting mixture was washed with aqueous NaOH solution (10 %, 100 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (40 % ethyl acetate in hexane) to give a mixture of product and starting material (1.58 g). The starting material could be removed by recrystallization from acetone to give a yellow oil (1.05 g, 3.33 mmol, 46 %), which was directly used for the next step without further purification.



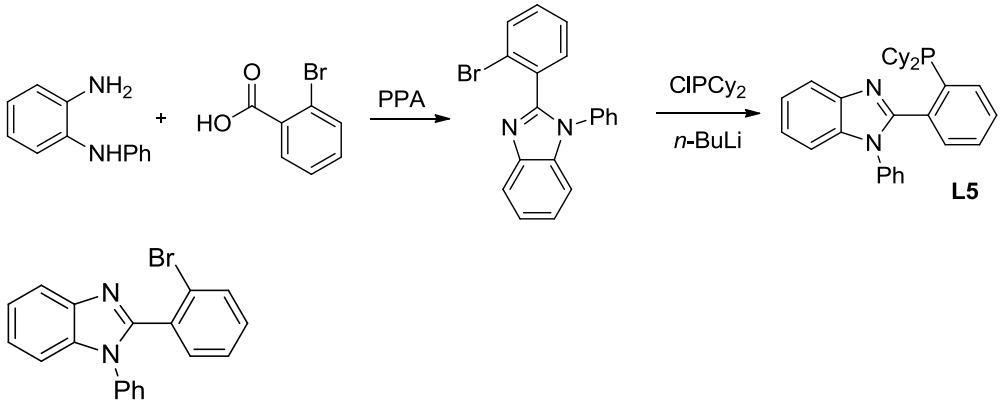
2-(2-(Dicyclohexylphosphino)phenyl)-1-isopropyl-1H-benzimidazole (5.2-L4)

2-(2-Bromophenyl)-1-isopropyl-1H-benzimidazole (501 mg, 1.6 mmol) was dissolved in freshly distilled THF (10 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in an ethanol/liquid nitrogen bath. *n*-Butyllithium (1.2 mL, 1.6 M, 1.9 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (0.4 mL, 1.75 mmol) in THF (5 mL) was added dropwise by syringe. The reaction was stirred for 1h at -78 °C and warmed to room temperature overnight. The reaction mixture was passed through a pad of celite and silica gel, and then washed with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (2 0% ethyl acetate in hexane) to give a light yellow solid, which was further purified by recrystallization from acetone giving a white solid (391 mg, 0.9 mmol, 57 %). M.p. 139-140 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.83-7.75 (m, 1H), 7.66-7.57 (m, 2H), 7.51 (dt, *J* = 4.0, 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.40-7.35 (m, 1H), 7.29-7.20 (m, 2H), 4.25 (heptet, *J* = 8.0 Hz, 1H), 2.25-2.10 (m, 1H), 1.85-1.51 (m, 14H), 1.48-0.97 (m, 13H) ppm. ^{13}C-NMR

(101 MHz, $CDCl_3$): δ = 153.80, 153.76, 143.70, 139.73, 139.40, 137.13, 136.91, 132.60, 132.51, 132.47, 130.68, 130.61, 128.72, 128.46, 121.81, 121.36, 120.15, 119.94, 48.62, 35.59, 35.42, 32.20, 32.09, 29.98, 29.81, 28.56, 27.51, 26.94, 26.45, 26.21, 21.55 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -9.67 ppm. ESI-MS (70 eV), *m/z* (%): 433.3 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 3053 (w), 2919 (m), 2846 (m), 1445 (m), 1427 (w), 1369 (m), 1282 (m), 1266 (w), 770 (m), 756 (w), 743 (vs), 724 (w) cm^{-1}.Anal. Calcd. for $C_{28}H_{37}N_2P$: C 77.74, H 8.62, N 6.48; found: C 77.36, H 8.32, N 6.40.

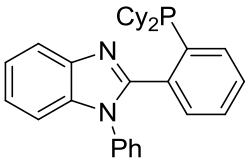
Synthesis of 5.2-L5.



2-(2-Bromophenyl)-1-phenyl-1H-benzimidazole [CAS No. 1173654-26-6]

2-Bromobenzoic acid (8.04 g, 40 mmol) and *N*-phenyl-*o*-phenylenediamine (8.65 g, 46 mmol) were dissolved in polyphosphoric acid (56 g) and heated to 150 °C for 6 h. The reaction mixture was poured over crushed ice and kept in a refrigerator overnight. The resulting dark solution was neutralized with KOH, stirred for 30 minutes, extracted with dichlormethane (3 x 100 mL), and the combined organic layers were washed with bine (200 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (30 % ethyl acetate in hexane) to give a white solid (570 mg, 1.63 mmol, 4 %). M.p. 168-169 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80-7.87 (m, 1H), 7.53 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.47 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.41-7.20 (m, 10H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 151.41, 142.68, 135.75, 135.51, 132.66, 132.38, 132.20, 130.93, 129.21, 128.00, 126.90, 126.57, 123.55, 123.50, 122.83, 120.15, 110.46 ppm. IR (KBr): $\tilde{\nu}$ = 3055 (w), 3013 (w), 1495 (s), 1457 (s), 1451 (s), 1427 (m), 1383 (s), 1324 (s), 1272 (m), 1262 (m), 1252 (m), 772 (s), 758 (vs), 742 (vs), 728 (m), 708 (m), 698 (s), 650 (w) cm^{-1}. Anal. Calcd. for $C_{19}H_{13}BrN_2$: C 65.35, H 3.75, N 8.02; found: C 65.27, H 3.73, N 8.08.

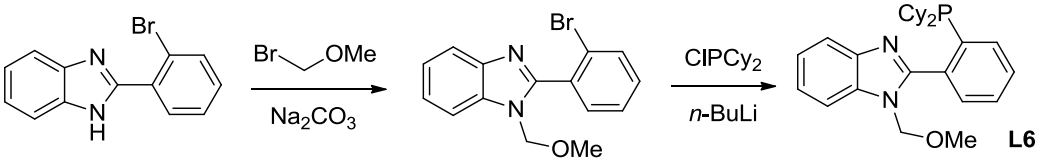


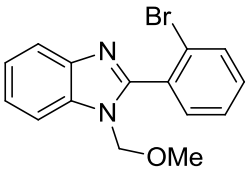
2-(2-(Dicyclohexylphosphino)phenyl)-1-phenyl-1H-benzimidazole (**5.2-L5**)

2-(2-Bromophenyl)-1-phenyl-1H-benzimidazole (419 mg, 1.2 mmol) was dissolved in freshly distilled THF (10 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in an ethanol/liquid nitrogen bath. *n*-BuLi (0.9 mL, 1.6 M, 1.44 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (0.3 mL, 1.32 mmol) in THF (5 mL) was added dropwise by syringe. The reaction was stirred for 1h at -78 °C and warmed to room temperature overnight. The reaction mixture was passed through a pad of celite and silica gel and washed with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (20 % ethyl acetate in hexane) to give a white solid (301 mg, 0.65 mmol, 54 %). M.p. 167-168 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.0 Hz, 1H), 7.54-7.48 (m, 1H), 7.36-7.30 (m, 4H), 7.28-7.13 (m, 7H), 1.69-1.43 (m, 10H), 1.14-0.90 (m, 10H), 0.50-0.38 (m, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 153.61, 153.58, 142.85, 139.02, 138.70, 136.55, 136.44, 136.33, 135.37, 132.48, 132.45, 131.53, 131.47, 128.91, 128.64, 128.26, 127.18, 122.96, 122.40, 119.87, 110.55, 33.75, 33.62, 30.09, 29.92, 28.48, 28.39, 27.23, 27.13, 27.11, 27.06, 26.24 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -8.06 ppm. ESI-MS (70 eV), *m/z* (%): 467.2 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 3071 (w), 3049 (w), 2925 (m), 2911 (m), 2837 (m), 1599 (w), 1582 (w), 1525 (w), 1502 (m), 1490 (w), 1447 (m), 1430 (w), 1373 (m), 1260 (m), 1250 (w), 1194 (w), 778 (m), 757 (s), 748 (m), 737 (vs) cm^{-1}. Anal. Calcd. for $C_{31}H_{35}N_2P$: C 79.80, H 7.56, N 6.00; found: C 79.31, H 7.24, N 6.03.

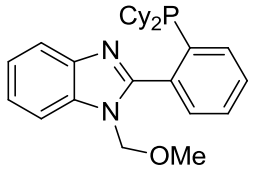
Synthesis of 5.2-L6





2-(2-Bromophenyl)-1-(methoxymethyl)-1H-benzimidazole

To a solution of 2-(2-bromophenyl)-1H-benzimidazole (2.7 g, 10 mmol) in acetone (40 mL), was added Na_2CO_3 (7.4 g, 70 mmol) and the suspension was kept stirring for 0.5 h under room temperature. Bromomethyl methyl ether (0.9 mL, 10 mmol) was added to the previous solution and the reaction mixture was heated to reflux for 2 h. After the reaction was cooled to room temperature, the solvent was removed under reduced pressure and the residue was diluted with ethyl acetate (50 mL), washed with water (100 mL). The aqueous phase was extracted with ethyl acetate (2 x 30 mL), and the conbined organic layers were washed with brine dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (40 % ethyl acetate in hexane) to give a yellow oil (2.86 g, 9 mmol, 90 %), which was directly used for the next step without further purification.

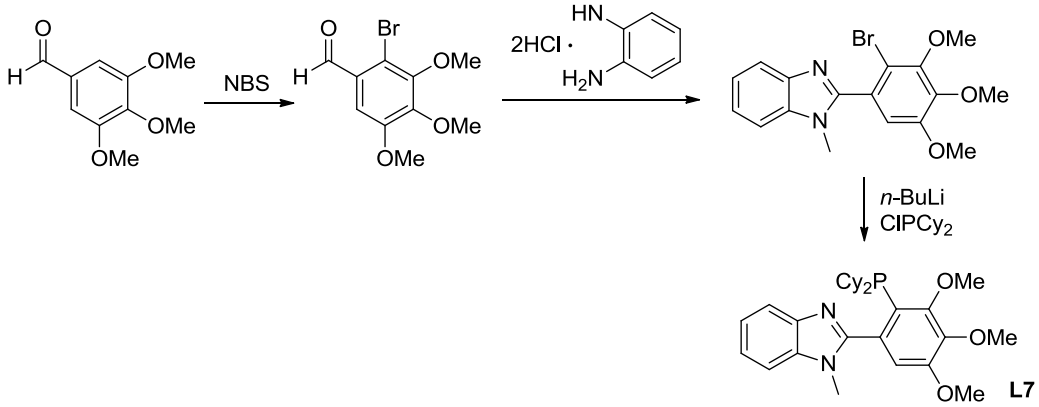


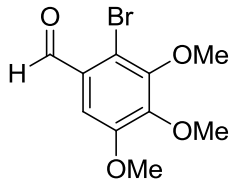
2-(2-(Dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-benzimidazole (5.2-L6)

2-(2-Bromophenyl)-1-(methoxymethyl)-1H-benzimidazole (758 mg, 2.4 mmol) was dissolved in freshly distilled THF (15 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in ethanol/liquid nitrogen bath. *n*-Butyllithium (1.8 mL, 1.6 M, 2.9 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (0.6 mL, 2.6 mmol) in THF (5 mL) was added dropwise by syringe. The reaction was stirred for 1h at -78 °C and warmed to room temperature overnight. The reaction mixture was passed through a pad of celite and silica gel and then washed with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (20 % ethyl acetate in hexane) to give a light yellow solid, which was further purified by recrystallization from acetonitrile giving a white solid (573 mg, 1.3 mmol, 55 %). M.p. 154-155 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85-7.78 (m, 1H), 7.66-7.61 (m, 1H), 7.60-7.45 (m, 4H), 7.37-7.28 (m, 2H), 5.33 (s, 2H), 3.06 (s, 3H), 1.88 (br. s, 2H), 1.76-1.60 (m, 10H), 1.27-0.98 (m, 10H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 154.29, 142.87, 138.28, 137.97, 136.71, 136.48, 134.23, 132.42, 132.39, 131.54, 131.48, 129.04, 128.68, 122.99, 122.43, 119.76, 110.72, 75.80, 75.71, 56.03, 33.35, 29.90, 29.74, 29.19, 27.23, 27.17, 27.10, 26.26 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -8.30 ppm. ESI-MS (70 eV), *m/z* (%): 435.3 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 2920 (m), 2844 (m), 1736 (w), 1447 (m), 1428 (w), 1377 (w), 1351 (m), 1096 (s), 917 (m), 781 (m), 747 (vs) cm^{-1}.Anal. Calcd. for $C_{27}H_{35}N_2OP$: C 74.63, H 8.12, N 6.45; found: C 74.16, H 7.97, N 6.44.

Synthesis of L7

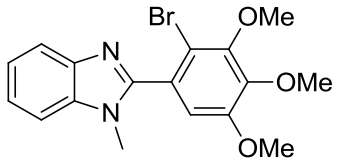




2-Bromo-3,4,5-trimethoxybenzaldehyde [CAS No. 35274-53-4]

N-Bromsuccinimide (9.0 g, 50.0 mmol) and 3,4,5-Trimethoxybenzaldehyde (9.8 g, 50.0 mmol) were dissolved in chloroform (150 mL). The reaction mixture was heated to reflux for 24 h under stirring. After the reaction was cooled to room temperature, saturated NaS_2O_3 solution (50 mL) was added to the reaction solution. The aqueous layer was extracted with diethyl ether (2 x 40 mL), and the conbined organic layer was washed with brine dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (40 % ethyl acetate in hexane) to give a white solid (12.0 g, 43.7 mmol, 88 %). M.p. 76-77 ^{o}C.

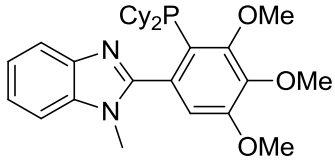
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 10.17 (s, 1H), 7.20 (s, 1H), 3.90 (s, 3H), 3.83 (s, 6H) ppm. ^{13}C-NMR (151 MHz, $CDCl_3$): δ = 190.58, 152.74, 150.48, 148.40, 128.49, 115.27, 107.16, 60.96, 60.89, 55.95 ppm. EI-MS (70 eV), *m/z* (%): 276 (99), 275 (100) [M^+], 274 (19), 262 (23), 260 (23), 124 (24). IR (KBr): $\tilde{\nu}$ = 3003 (w), 2943 (m), 2866 (m), 2836 (w), 1686 (s), 1578 (m), 1564 (m), 1472 (m), 1449 (s), 1426 (m), 1404 (m), 1383 (vs), 1326 (s), 1285 (m), 1244 (m), 1198 (vs), 1165 (s), 1105 (vs), 1044 (m), 1002 (s), 981 (vs), 920 (vs), 859 (s), 817 (m), 774 (m), 726 (m) cm^{-1}. Anal. Calcd. for $C_{10}H_{11}BrO_4$: C 43.66, H 4.03; found: C 43.85, H 4.24.



2-(2-Bromo-3,4,5-trimethoxyphenyl)-1-methyl-1H-benzimidazole

2-Bromo-3,4,5-trimethoxybenzaldehyde (5.2 g, 18.8 mmol) and *N*-methyl-1,2-phenylenediamine dihydrochloride (23.7 g, 18.8 mmol) was dissolved in acetonitrile (250 mL). 30 % H_2O_2 solution (1.88 mL, 132 mmol) was added to the previous solution and the reaction mixture was kept stirring for 24 h at room temperature. Saturated $Na_2S_2O_3$ solution (200 mL) was added into the resulted reaction mixture and the aqueous solution was extracted with diethyl ether (3 x 60 mL). The conbined organic layers were washed with brine dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (40 % ethyl acetate in hexane) to give a white solid (3.38 g, 8.96 mmol, 48 %). M.p. 126-127 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.0 Hz, 1H), 7.42-7.28 (m, 3H), 6.90 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3), 3.85 (s, 3H), 3.66 (s, 3H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 152.93, 152.37, 151.08, 144.55, 142.52, 135.37, 127.16, 122.86, 122.27, 119.87, 111.08, 110.54, 109.51. 61.03, 56.19, 30.74 ppm. ESI-MS (70 eV), *m/z* (%): 377, 379 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 3020 (w), 2936 (w), 2849 (w), 1564 (w), 1474 (m), 1466 (m), 1425 (s), 1393 (m), 1381 (s), 1320 (m), 1248 (m), 1102 (s), 1021 (w), 997 (s), 964 (w), 934 (w), 851 (w), 809 (m), 741 (vs), 730 (m) cm^{-1}. Anal. Calcd. for $C_{17}H_{17}BrN_2O_3$: C 54.13, H 4.54, N 7.43; found: C 54.20, H 4.56, N 7.40.

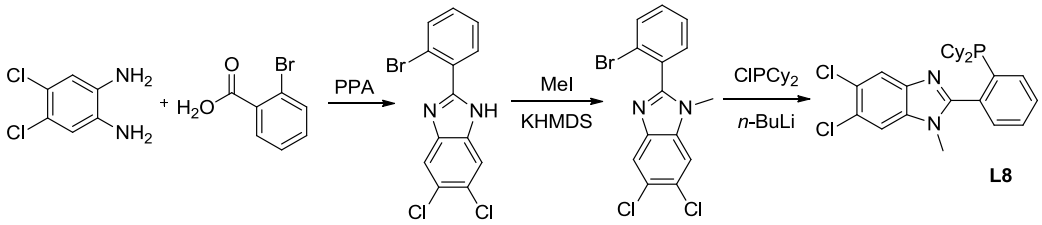


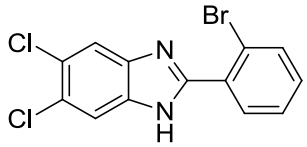
2-(2-(Dicyclohexylphosphino)-3,4,5-trimethoxyphenyl)-1-methyl-1H-benzimidazole (**5.2-L7**)

2-(2-Bromo-3,4,5-trimethoxyphenyl)-1-methyl-1H-benzoimidazole (377 mg, 1.0 mmol) was dissolved in freshly distilled THF (10 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in an ethanol/liquid nitrogen bath. *n*-Butyllithium (0.75 mL, 1.6 M, 1.2 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (0.25 mL, 1.1 mmol) in THF (5 mL) was added dropwise by syringe. The reaction was stirred for 1h at -78 °C and warmed to room temperature overnight. The reaction mixture was passed through a pad of celite and silica gel and washed with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (20 % ethyl acetate in hexane) to give a light yellow solid, which was further purified by recrystallization from acetonitrile giving a white solid (351 mg, 0.71 mmol, 71 %). M.p. 119-120 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.82-7.77 (m, 1H), 7.40-7.36 (m, 1H), 7.34-7.28 (m, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 4.04 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.62 (s, 3H), 1.90-0.90 (m, 22H) ppm; ^{13}C-NMR (151 MHz, $CDCl_3$): δ = 156.88, 156.86, 154.95, 154.91, 154.59, 142.50, 135.17, 134.92, 122.24, 122.06, 121.88, 121.81, 119.53, 109.51, 109.41, 109.36, 60.60, 60.45, 55.89, 36.48, 36.40, 34.36, 34.29, 32.57, 32.42, 32.06, 31.92, 31.25, 31.07, 31.03, 30.35, 27.23, 37.01, 26.91, 26.44, 26.10 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = 4.32 ppm. ESI-MS (70 eV), *m/z* (%): 495.3 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 2922 (m), 2846 (w), 1582 (w), 1556 (w), 1463 (m), 1445 (m), 1424 (m), 1365 (m), 1327 (w), 1310 (m), 1241 (m), 1193 (w), 1103 (vs), 1017 (m), 941 (m), 849 (w), 820 (w), 768 (w), 736 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{29}H_{39}N_2O_3P$: 494.2698, *m/z* found: 494.2709.

Synthesis of L8

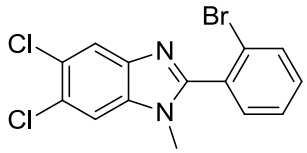




2-(2-Bromophenyl)-5,6-dichloro-1H-benzimidazole

2-Bromobenzoic acid (3.11 g, 15.0 mmol) and 4,5-dichloro-*o*-phenylenediamine (2.92 g, 16.5 mmol) were taken in polyphosphoric acid (21 g) and heated to 150 °C for 6 h. The reaction mixture was poured over crushed ice and kept in a refrigerator overnight. The resulting violet solid precipitate was filtered and added to 0.5 M Na_2CO_3 solution (300 mL), stirred for 30 min and filtered. The yellow solid was dissolved in warm methanol (100 mL), and water (100 mL) was added dropwise to the previous solution within 1 h. A white solid (4.5 g, 13.2 mmol, 88 %) was obtained after filtration and drying under vacuum overnight. M.p. 234-235 °C.

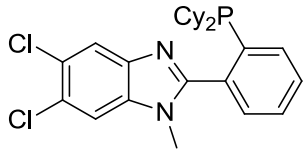
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 13.11 (br. s, 1H), 7.99 (s, 1H), 7.85-7.75 (m, 3H), 7.60-7.45 (m, 2H) ppm. ^{13}C-NMR (101 MHz, DMSO-d_6): δ = 152.98, 142.82, 133.99, 133.50, 132.30, 131.87, 131.49, 127.90, 125.09, 124.31, 121.46, 120.31, 113.06 ppm. EI-MS (70 eV), *m/z* (%):344 (49), 343 (16), 342 (100) $[M^+]$, 341 (11), 340 (61), 262 (9), 226 (29), 207 (23). IR (KBr): $\tilde{\nu}$ = 2920 (w), 2850 (w), 1445 (m), 1428 (s), 1387 (vs), 1296 (m), 762 (vs) cm^{-1}. Anal. Calcd. for $C_{13}H_7BrCl_2N_2$: C 45.65, H 2.06, N 8.19; found: C 45.40, H 2.26, N 8.19.



2-(2-Bromophenyl)-5,6-dichloro-1-methyl-1H-benzimidazole

To a solution of 2-(2-bromophenyl)-5,6-dichloro-1H-benzimidazole (2.4 g, 7.0 mmol) in THF (30 mL), KHMDS (0.5 M in toluene, 14.7 mL, 7.4 mmol) was added under nitrogen at 0 °C. After 5 min, the ice bath was removed, and the formed brown solution was stirred for 1.5 h at room temperature. The reaction mixture was cooled to 0 °C, and iodomethane (0.46 mL, 7.4 mmol) was added dropwise to the solution. The resulting suspension was stirred for 2 h at room temperature. Saturated ammonium chloride solution (50 mL) was added to the resulting reaction mixture, and the aqueous solution was extracted with ethyl acetate (3 x 30 mL). The conbined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of silica gel. After removing the solvent under reduced pressure, a light yellow solid (2.4 g, 6.74 mmol, 96 %) was obtained, which was pure enough for the next step. M.p. >300 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.56-7.39 (m, 4H), 3.83 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 154.43, 1412.00, 134.72, 132.93, 132.16, 131.83, 131.25, 127.65, 127.03, 126.50, 123.60, 121.28, 111.13, 31.11 ppm. EI-MS (70 eV), *m/z* (%):358 (43), 357 (40), 356 (100) [M^+], 355 (51), 354 (62), 353 (26), 277 (180), 276 (16), 275 (31), 207 (38). IR (KBr): $\tilde{\nu}$ = 2918 (m), 2850 (w), 1465 (s), 1451 (m), 1426 (s), 1382 (vs), 1311 (m), 1023 (m), 839 (m), 755 (s), 727 (m) cm^{-1}. Anal. Calcd. for $C_{13}H_9BrCl_2N_2$: C 47.23, H 2.55, N 7.87; found: C 47.35, H 2.72, N 7.75.



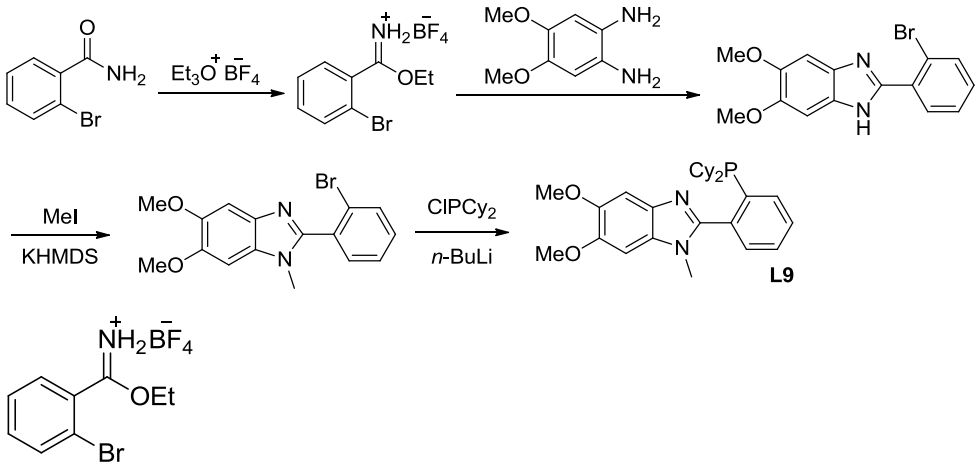
5,6-Dichloro-2-(2-(dicyclohexylphosphino)phenyl)-1-methyl-1H-benzimidazole (5.2-L8)

2-(2-Bromophenyl)-1-methyl-1H-benzoimidazole (2.63 g, 7.3 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in ethanol/liquid nitrogen bath. *n*-BuLi (4.8 mL, 1.6 M, 7.7 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (1.74 mL, 7.7 mmol) in THF (10 mL) was added dropwise by syringe. The reaction was stirred for 40 minutes at -78 °C and warmed to room temperature within 2 h, and then kept stirring for another 0.5 h. The reaction mixture was passed through a pad of celite and silica gel and washed with ethyl acetate. After the solvent was removed

under reduced pressure, the obtained yellow solid was purified by recrystallization from acetonitile to give a white solid (2.67 g, 5.64 mmol, 77 %). M.p. 160-161 °C.

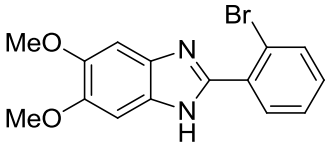
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.60-7.44 (m, 4H), 3.53 (s, 3H), 1.90-1.56 (m, 12H), 1.30-0.90 (m, 10H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 156.68, 156.65, 141.91, 137.75, 137.54, 136.59, 136.45, 134.44, 132.60, 132.58, 130.78, 130.73, 129.26, 128.89, 126.17, 125.73, 120.71, 111.01, 33.21, 31.14, 31.08, 29.93, 29.82, 29.06, 27.14, 27.06, 27.00, 26.18 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -7.35 ppm. ESI-MS (70 eV), *m/z* (%): 473.2 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 2925 (vs), 2845 (s), 1464 (m), 1446 (vs), 1421 (vs), 1375 (vs), 1304 (m), 1088 (m), 867 (m), 834 (m), 835 (m), 791 (m), 775 (m), 742 (m) cm^{-1}. Anal. Calcd. for $C_{26}H_{31}Cl_2N_2P$: C 65.96, H 6.60, N 5.92; found: C 65.99, H 6.71, N 5.85.

Synthesis of L9



Ethyl 2-bromobenzimidate tetrafluoroborate [CAS No. 77250-67-0]:

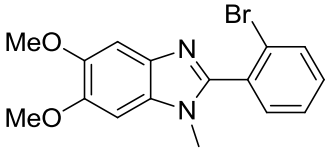
The solution of triethyloxonium tetrafluoroborate (1.0 M in dichloromethane, 24 mL, 24 mmol) was added dropwise to *ortho*-bromobenzamide (41.2 g, 20 mmol) within 20 min under N_2 at room temperature. The yellowish slurry solution was stirred for 24 h at room temperature. After the resulting suspension had been filtered, the filtrate was removed under reduced pressure and dried under vacuum overnight to yield a light yellow solid (6.32 g, 20 mmol, 100 %) quantatively, which was used directly for the next step without further purification.



2-(2-bromophenyl)-5,6-dimethoxy-1H-benzimidazole

A solution of the freshly prepared imidate (4.74 g, 15.0 mmol) and 4,5-dimethoxybenzene-1,2-diamine (2.68 g, 15.8 mmol) in anhydrous EtOH (40 mL) was stirred for 1 h at room

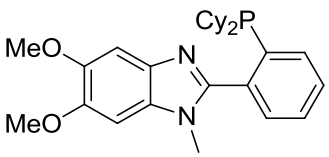
temperature and warmed to reflux overnight. After the evaporation of the solvent under reduced pressure, the residue was neutralized by 1M NaOH solution. The resulting mixture was extracted with dichloromethane (3 x 20 mL), and the combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. This crude product was purified by column chromatography on silica gel (ethyl acetate) giving a light yellow solid (4.47 g, 13.4 mmol, 90 %), which was pure enough for the next step.



2-(2-Bromophenyl)-5,6-dimethoxy-1-methyl-1H-benzimidazole

To a solution of 2-(2-bromophenyl)-5,6-dimethoxy-1H-benzimidazole (1.2 g, 3.6 mmol) in THF (10 mL), KHMDS (0.5 M in toluene, 7.6 mL, 3.8 mmol) was added under nitrogen at 0 °C. After 5 min, the ice bath was removed, and the formed brown solution was stirred for 1.5 h at room temperature. The reaction mixture was cooled to 0 °C, and iodomethane (0.24 mL, 3.8 mmol) was added dropwise to the solution. The resulting suspension was stirred for 2 h at room temperature. Saturated ammonium chloride solution (50 mL) was added to the resulted reaction mixture. The aqueous solution was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a thin pad of silica gel and washed with ethyl acetate. After removing the solvent under reduced pressure, a light yellow solid was obtained (1.1 g, 3.17 mmol, 88%), which was pure enough for the next step. M.p. 181-182 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.47 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.42-7.35 (m, 1H), 7.34-7.28 (m, 1H), 6.83 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.57 (s, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 150.69, 147.27, 146.62, 135.95, 132.49, 132.23, 132.07, 130.98, 128.97, 127.22, 123.78, 101.76, 92.31, 56.17, 56.07, 30.74 ppm; EI-MS (70 eV), *m/z* (%): 348 (100) [M^+], 346 (94) [M^+], 349 (17), 347 (16), 333 (43), 331 (41), 207 (30); IR (KBr): $\tilde{\nu}$ = 2937 (w), 2840 (w), 1485 (s), 1448 (m), 1428 (vs), 1390 (s), 1211 (s), 1200 (vs), 1154 (vs), 1090 (vs), 1002 (s), 855 (m), 809 (m), 761 (m), 729 (m) cm^{-1}; Anal. Calcd. for $C_{16}H_{15}Br\ N_2O_2$: C 55.35, H 4.35, N 8.07; found: C 55.70, H 4.68, N 7.96.

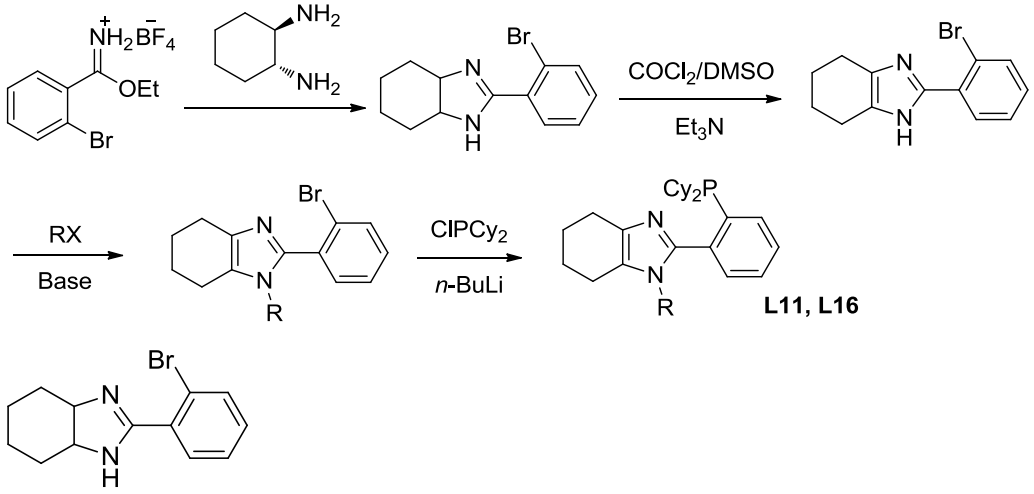


2-(2-(Dicyclohexylphosphino)phenyl)-5,6-dimethoxy-1-methyl-1H-benzimidazole (5.2-L9)

2-(2-Bromophenyl)-5,6-dimethoxy-1-methyl-1H-benzimidazole (552 mg, 1.59 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in an ethanol/liquid nitrogen bath. *n*-BuLi (1.1 mL, 1.6 M, 1.75 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (0.4 mL, 1.75 mmol) in THF (8 mL) was added dropwise by syringe. The reaction was stirred for 40 min at -78 °C and warmed to room temperature overnight. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate (20 mL), passed through a pad of celite and silica gel and washed with ethyl acetate. After the solvent was removed under reduced pressure, the obtained yellow solid was purified by recrystallization from hexane and diethyl ether to give a white solid (600 mg, 1.29 mmol, 81 %). M.p. 81-82 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.0 Hz, 1H), 7.55-7.42 (m, 3H), 7.32 (s, 1H), 6.84 (s, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.53 (s, 3H), 1.90-1.56 (m, 12H), 1.30-0.90 (m, 10H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 152.87, 147.12, 146.83, 136.79, 136.57, 132.46, 132.44, 131.33, 131.26, 128.81, 128.76, 128.68, 101.80, 92.73, 56.43, 56.33, 33.36, 31.11, 31.02, 30.01, 29.85, 29.06, 27.27, 27.18, 27.15, 27.11, 26.28 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -8.00 ppm. ESI-MS (70 eV), *m/z* (%): 465.3 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 3019 (w), 2940 (w), 1506 (m), 1361 (vs), 1329 (s), 1208 (s), 1175 (s), 1135 (m), 1112 (m), 820 (m), 809 (m), 751 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{28}H_{37}N_2O_2P$: 464.2593, *m/z* found: 464.2568.

Synthesis of 5.2-L11 and **L16.**

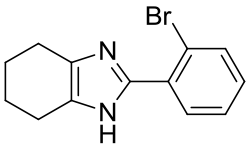


2-(2-Bromophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzimidazole

A solution of the freshly prepared imidate (11.1 g, 35.0 mmol) and (±)-trans-1,2-Diaminocyclohexane (4.24 g, 36.8 mmol) in anhydrous EtOH (40 mL) was stirred for 1h at

room temperature and warmed to reflux overnight. After the evaporation of the solvent under reduced pressure, the residue was neutralized by 1 M NaOH solution. The resulting mixture was extracted with dichloromethane (3 x 40 mL), and the combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and concentrated yielding a light yellow solid (7.9 g). This crude product was purified by recrystalization from ethyl acetate to give a white solid (5.34 g, 19.1 mmol, 55 %). M.p. 166-167 °C.

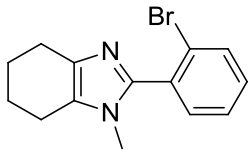
^{1}H-NMR (600 MHz, Methanol-d_4): δ = 7.67-7.64 (m, 1H), 7.47-7.38 (m, 2H), 7.37-7.32 (m, 1H), 3.21-3.13 (m, 2H), 2.27-2.22 (m, 2H), 1.89-1.82 (m, 2H), 1.59-1.52 (m, 2H), 1.45-1.35 (m, 2H) ppm. ^{13}C-NMR (151 MHz, Methanol-d_4): δ = 168.64, 135.47,134.34, 132.53, 131.52, 128.68, 122.37, 71.15, 31.85, 26.18 ppm. EI-MS (70 eV), *m/z* (%): 280 (38) [M^+], 278 (45) [M^+], 237 (100), 235 (98), 102 (28). IR (KBr): $\tilde{\nu}$ = 3024 (w), 2942 (w), 2822 (w), 1686 (s), 1583 (m), 1360 (m), 1300 (m), 1160 (vs), 923 (m), 902 (m), 817 (s), 762 (m) cm^{-1}. Anal. Calcd. for $C_{13}H_{15}BrN_2$: C 55.93, H 5.42, N 10.03; found: C 55.72, H 5.54, N 9.99.



2-(2-Bromophenyl)-4,5,6,7-tetrahydro-1H-benzimidazole

A stirred solution of oxalyl chloride (0.53 mL, 5.5 mmol, 1.1 equiv.) in dichloromethane (10 mL) under Nitrogen at -78 °C was treated with DMSO (0.79 mL, 11 mmol, 2.2 equiv.) in dichloromethane (5 mL), dropwise over 5 min. After 10 min, 2-(2-Bromophenyl)-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole (1.4 g, 5.0 mmol) in dichloromethane (10 mL) was added within 10 min, followed by triethylamine (3.66 mL, 25 mmol, 5.0 equiv.) dropwise over 10 min. The mixture was stirred with gradual warming overnight, and then the reaction was quenched with water. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a white solid which was washed by diethyl ether to give a white powder (926 mg, 3.34 mmol, 67 %). M.p. 205-206 °C.

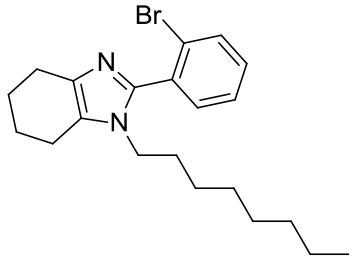
^{1}H-NMR (400 MHz, Methanol-d_4): δ = 7.68 (d, *J* = 8.0 Hz, 1H), 5.57 (d, *J* = 8.0 Hz, 1H), 7.43-7.38 (m, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 2.62 (br. s, 4H), 1.86 (br. s, 4H) ppm. ^{13}C-NMR (101 MHz, Methanol-d_4): δ = 144.43, 134.67, 134.08, 132.91, 131.33, 128.75, 122.83, 24.59, 23.66 ppm. EI-MS (70 eV), *m/z* (%):278 (79) [M^+], 276 (83), 250 (100), 248 (98), 207 (22), 181 (13), 102 (14). IR (KBr): $\tilde{\nu}$ = 2943 (m), 2905 (w), 2848 (w), 1608 (m), 1590 (w), 1437(s), 1390 (s), 1044 (m), 1025 (m), 866 (m), 759 (s), 722 (vs) cm^{-1}. Anal. Calcd. for $C_{13}H_{13}BrN_2$: C 56.34, H 4.73, N 10.11; found: C 56.07, H 4.64, N 10.02.



2-(2-Bromophenyl)-1-methyl-4,5,6,7-tetrahydro-1H-benzimidazole

To a solution of 2-(2-bromophenyl)-5,6-dimethyl-1H-benzimidazole (1.03 g, 3.7 mmol) in THF (30 mL), KHMDS (0.5 M in toluene, 7.8 mL, 3.9 mmol) was added under nitrogen at 0 °C. After 5 minutes, the ice bath was removed, and the formed brown solution was stirred for 1.5 h at room temperature. The reaction mixture was cooled to 0 °C, and iodomethane (0.24 mL, 3.9 mmol) was added dropwise to the solution. The resulting suspension was stirred for 2 h at room temperature. Saturated ammonium chloride solution (30 mL) was added into the resulted reaction mixture and the aqueous solution was extracted with ethyl acetate (3 x 30 mL). The conbined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of silica gel. After removing the solvent under reduced pressure, the residue was diluted with diethyl ether, and a orange solid precipitated. The rest was recrystallized from hexane and dichloromethane to give another crop of orange solid (Total amount: 911 mg, 3.13 mmol, 85 %). M.p. 122-123 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.49-7.44 (m, 1H), 7.38 (dt, *J* = 1.1, 8.0 Hz, 1H), 7.32-7.26 (m, 1H), 3.35 (s, 3H), 2.69-2.64 (m, 2H), 2.59-2.54 (m, 2H), 1.95-1.81 (m, 4H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 144.64, 135.97, 133.19, 132.89, 132.57, 130.42, 127.26, 126.51, 124.40, 30.72, 24.23, 23.40, 22.97, 20.89 ppm. EI-MS (70 eV), *m/z* (%): 292 (100) [M^+], 290 (100), 264 (72), 262 (72), 207 (23), 183 (30). IR (KBr): $\tilde{\nu}$ = 2934 (m), 2845 (w), 1469 (m), 1446 (m), 1433 (m), 1422 (m), 1389 (m), 1022 (s), 760 (vs) cm^{-1}. Anal. Calcd. for $C_{14}H_{15}BrN_2$: C 57.75, H 5.19, N 9.62; found: C 57.72, H 5.63, N 9.50.

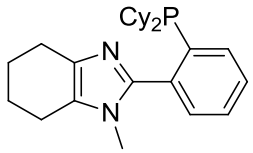


2-(2-Bromophenyl)-1-octyl-4,5,6,7-tetrahydro-1H-benzimidazole

Sodium hydride (60 %, suspension in mineral oil, 104 mg, 2.6 mmol) was added to the magnetically stirred 2-(2-bromophenyl)-5,6-dimethyl-1H-benzimidazole (360 mg, 1.3 mmol) in anhydrous THF (30 mL). 1-Bromooctane (507 mg, 2.6 mmol) was added dropwise to the mixture at room temperature. The reaction mixture was heated to 60 °C for 24 h, which was monitored by TLC (aluminium oxide neutral, 20 % ethyl acetate in hexane). After the reaction

was complete, the reaction mixture was partitioned between saturated aqueous NH_4Cl (30 mL) and ethyl acetate (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on aluminium oxide neutral (20 % ethyl acetate in hexane) to give a yellow oil (329 mg, 0.85 mmol, 65 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.63 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.43-7.32 (m, 2H), 7.30-7.24 (m, 1H), 3.65 (t, *J* = 8.0 Hz, 2H), 2.69-2.54 (m, 4H), 1.92-1.80 (m, 4H), 1.52-1.42 (m, 2H), 1.30-1.02 (m, 10H), 0.84 (t, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 144.15, 135.96, 133.57, 132.78, 132.56, 130.31, 127.07, 125.70, 124.61, 44.10, 31.61, 30.33, 28.89, 28.80, 26.38, 24.24, 23.36, 23.07, 22.50, 21.27, 14.00 ppm. EI-MS (70 eV), *m/z* (%): 390 (90) [M^+], 388 (100), 207 (82), 109 (35). IR (KBr): $\tilde{\nu}$ = 2928 (vs), 2854 (vs), 1467 (m), 1440 (m), 1402 (m), 1372 (m), 1024 (m), 761 (m), 729 (w) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{21}H_{29}BrN_2$ (M^+, ^{81}Br): 390.1494, *m/z* found: 390.1502; EI-HRMS *m/z* calcd. for $C_{21}H_{29}BrN_2$ (M^+, ^{79}Br): 388.1514, *m/z* found: 388.1525.

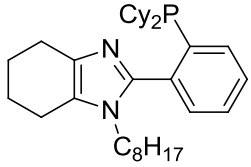


2-(2-(Dicyclohexylphosphino)phenyl)-1-methyl-4,5,6,7-tetrahydro-1H-benzimidazole (5.2-L11)

2-(2-Bromophenyl)-1-methyl-4,5,6,7-tetrahydro-1H-benzo[d]imidazole (612 mg, 2.1 mmol) was dissolved in freshly distilled THF (15 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in an ethanol/liquid nitrogen bath. *n*-Butyllithium (1.57 mL, 1.6 M, 2.52 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (586 g, 2.52 mmol) in THF (5 mL) was added dropwise by syringe. The reaction was stirred for 1 h at -78 °C and warmed to room temperature overnight. The reaction mixture was filter through a pad of celite and silica gel and washed with ethyl acetate. The reaction mixture was passed through a pad of celite and silica gel and washed with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on aluminium oxide neutral (30 % ethyl acetate in hexane), giving a white solid (582 mg, 1.42 mmol, 68 %). M.p. 133-134 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.56-7.50 (m, 1H), 7.45-7.33 (m, 3H), 3.23 (s, 3H), 2.66-2.51 (m, 4H), 1.90-1.58 (m, 16), 1.30-0.98 (m, 10H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ =

146.22, 146.19, 139.82, 139.62, 136.57, 136.43, 135.11, 132.13, 132.10, 131.78, 131.73, 128.47, 127.91, 125.08, 33.34, 33.27, 30.72, 30.65, 29.92, 29.81, 29.14, 29.08, 27.30, 27.22, 27.19, 27.14, 26.31, 24.22, 23.42, 23.01, 20.84 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -7.60 ppm. ESI-MS (70 eV), *m/z* (%): 409.3 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 2918 (vs), 2847 (s), 1441 (s), 1388 (m), 754 (m) cm^{-1}. Anal. Calcd. for $C_{26}H_{37}N_2P$: C 76.43, H 9.13, N 6.86; found: C 76.43, H 9.11, N 6.71.



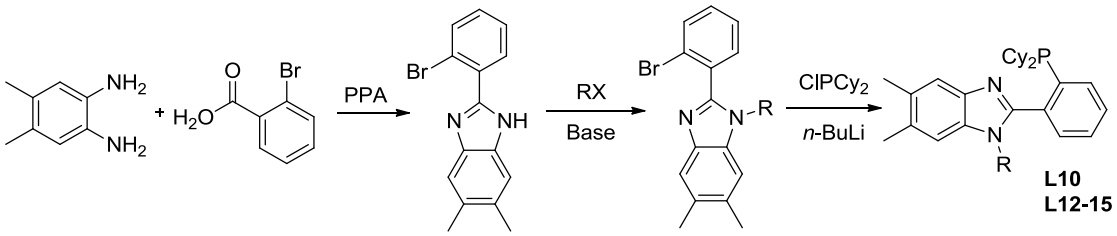
2-(2-(Dicyclohexylphosphino)phenyl)-1-octyl-4,5,6,7-tetrahydro-1H-benzimidazole (5.2-L12)

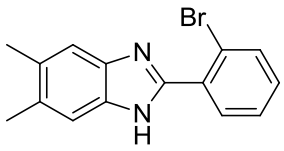
2-(2-Bromophenyl)-1-octyl-4,5,6,7-tetrahydro-1H-benzoimidazole (779 mg, 2.0 mmol) was dissolved in freshly distilled THF (15 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in an ethanol/liquid nitrogen bath. *n*-Butyllithium (1.38 mL, 1.6 M, 2.2 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (512 g, 2.2 mmol) in THF (5 mL) was added dropwise by syringe. The reaction was stirred for 1h at -78 °C and warmed to room temperature overnight. The reaction mixture was passed through a pad of celite and silica gel and washed with ethyl acetate. The reaction mixture was passed through a pad of celite and silica gel and washed with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on aluminium oxide neutral (10 % ethyl acetate in hexane), giving a light yellow oil (760 mg, 1.5 mmol, 75 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.56-7.50 (m, 1H), 7.45-7.33 (m, 3H), 3.60 (t, *J* = 8.0 Hz, 2H), 2.66-2.51 (m, 4H), 1.90-1.58 (m, 14), 1.45-0.98 (m, 22H), 0.84 (t, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 145.53, 136.47, 136.26, 135.01, 131.99, 131.98, 131.94, 128.29, 127.86, 124.53, 44.15, 44.08, 31.64, 30.09, 29.86, 29.71, 29.24, 28.87, 28.75, 27.30, 27.24, 27.20, 27.17, 26.50, 26.31, 24.21, 23.37, 23.13, 22.49, 21.23, 13.99 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -8.07 ppm;

ESI-MS (70 eV), *m/z* (%): 507.4 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 3053 (w), 2920 (vs), 2849 (s), 1652 (w), 1599 (w), 1445 (s), 1416 (m), 1273 (w), 1177 (m), 770 (m), 729 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{33}H_{51}N_2P$: 506.3790, *m/z* found: 506.3780.

Synthesis of 5.2-L0 and **L13-16**

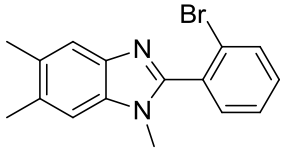




2-(2-Bromophenyl)-5,6-dimethyl-1H-benzimidazole:

2-bromobenzoic acid (10.1 g, 50 mmol) and 4,5-dimethylbenzene-1,2-diamine (7.6 g, 55 mmol) were dissolved in polyphosphoric acid (70 g) and heated to 150 °C for 6 h. The reaction mixture was poured on crushed ice and kept in a refrigerator overnight. The resulting violet solid precipitate was filtered and added to 0.5 M Na_2CO_3 solution (650 mL), stirred for 30 min and filtered. The yellow solid was dissolved in warm methanol (100 mL) and water (100 mL) was added dropwise to the previous solution in 1 h. A green-yellow solid (14.6 g, 48.5 mmol, 97 %) was obtained after filteration and drying under vacuum overnight. M.p. 191-192 °C.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.5 (br. s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.38 (s, 2H), 2.33 (s, 6H) ppm. ^{13}C-NMR (101 MHz, DMSO-d_6): δ = 149.45, 137.16, 133.58, 133.31, 132.43, 132.26, 132.17, 131.26, 130.93, 127.89, 127.72, 121.59, 115.32, 20.20, 19.91 ppm. EI-MS (70 eV), *m/z* (%): 302 (96) [M^+], 300 (100) [M^+], 287 (36), 285 (31), 207 (80). IR (KBr): $\tilde{\nu}$ = 3502 (m), 2641 (m), 1447 (vs), 1435 (vs), 1405 (s), 1355 (w), 1312 (m), 1040 (m), 1028 (s), 1000 (m), 968 (m), 874 (w), 856 (m), 756 (vs), 730 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{15}H_{13}BrN_2$: 300.0262, *m/z* found: 300.0274.

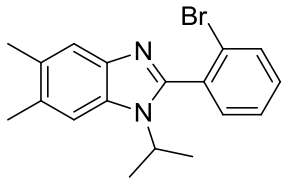


2-(2-Bromophenyl)-1,5,6-trimethyl-1H-benzimidazole

To a solution of 2-(2-bromophenyl)-5,6-dimethyl-1H-benzoimidazole (2.4 g, 8.0 mmol) in THF (30 mL), KHMDS (0.5 M in toluene, 16.8 mL, 8.4 mmol) was added under nitrogen at 0 °C. After 5 min, the ice bath was removed, and the formed brown solution was stirred for 1.5 h at room temperature. The reaction mixture was cooled to 0 °C, and iodomethane (0.52 mL, 8.4 mmol) was added dropwise to the solution. The resulting suspension was stirred for 2 h at room temperature. Saturated ammonium chloride solution (50 mL) was added into

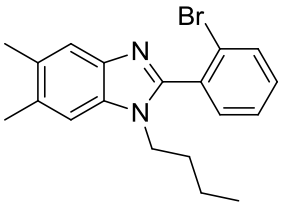
the resulting reaction mixture. The aqueous solution was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of silica gel. After removing the solvent under reduced pressure, a light yellow solid (2.4 g, 7.6 mmol, 95 %) was obtained, which was pure enough for the next step. M.p. 158-159 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.0 Hz, 1H), 7.61 (s, 1H), 7.56-7.51 (m, 1H), 7.45 (dt, *J* = 1.0, 8.0 Hz, 1H), 7.41-7.35 (m, 1H), 7.20 (s, 1H), 3.62 (s, 3H), 2.45 (s, 3H), 2.42 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 151.73, 141.36, 134.03, 132.69, 132.40, 132.38, 132.09, 131.20, 131.38, 127.38, 123.96, 120.07, 109.81, 30.74, 20.59, 20.25 ppm. EI-MS (70 eV), *m/z* (%): 316 (47) [M^+], 314 (41) [M^+], 281 (32), 235 (16), 207 (100). IR (KBr): $\tilde{\nu}$ = 2959 (m), 2929 (m), 2919 (m), 1641 (vs), 1617 (s), 1523 (vs), 1481 (s), 1409 (s), 1383 (vs), 1371 (s), 1332 (vs), 1292 (s), 1266 (m), 1208 (m), 1146 (m), 1126 (w), 1098 (s), 1062 (m), 1040 (m), 1026 (m), 1004 (m), 948 (w), 874 (w), 838 (m), 784 (w), 762 (s), 746 (s), 694 (m) cm^{-1}. Anal. Calcd. for $C_{16}H_{15}BrN_2$: C 60.97, H 4.80, N 8.89; found: C 60.79, H 4.78, N 8.60.



2-(2-Bromophenyl)-1-isopropyl-5,6-dimethyl-1H-benzimidazole

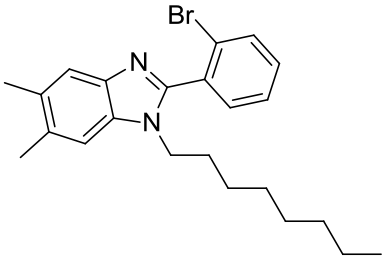
K_2CO_3 (2.8 g, 20.0 mmol) was added to magnetically stirred 2-(2-Bromophenyl)-5,6-dimethyl-1H-benzimidazole (3.0 g, 10.0 mmol) in acetonitrile (40 mL). The reaction mixture was heated to 80 °C for 0.5 h, then cooled to room temperature and isopropyl iodide (3.4 g, 20.0 mmol) was added dropwise in 10 min. The resulting reaction mixture was kept stirring overnight at 50 °C. The solvent was removed under reduced pressure and the residue was diluted by water (20 mL), extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (dichloromethane / ethyl acetate = 9:1) to give a mixture of unreacted starting material and product. After recrystallitation from dichloromethane and hexane, most of the unreacted starting material was removed. A light yellow foam (1.1 g, 3.2 mmol, 32 %) was obtained as a mixture of unreacted starting material and product (ratio was around: 1:2.4), which was used directly for the next step without further purification.



2-(2-Bromophenyl)-1-butyl-5,6-dimethyl-1H-benzimidazole

Sodium hydride (60 %, suspension in mineral oil, 240 mg, 6.0 mmol) was added to the magnetically stirred 2-(2-bromophenyl)-5,6-dimethyl-1H-benzimidazole (904 mg, 3.0 mmol) in anhydrous THF (15 mL). 1-Iodobutane (0.67 mL, 6.0 mmol) was added dropwise to the mixture, which was maintained below 5 °C for 0.5 h, and then stirred at room temperature. The reaction was monitored by TLC (30 % ethyl acetate in hexane). After the reaction was complete, the reaction mixture was partitioned between saturated aqueous NH_4Cl (30 mL) and ethyl acetate (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (20 % ethyl acetate in hexane) to give a yellow oil (920 mg, 2.6 mmol, 86 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.61 (s, 1H), 7.54-7.50 (m, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.37 (dt, *J* = 4.0, 8.0 Hz, 1H), 7.21 (s, 1H), 4.00 (t, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 2.41 (s, 3H), 1.68 (quint, *J* = 8.0 Hz, 2H), 1.17 (sext, *J* = 8.0 Hz, 2H), 0.78 (t, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 151.35, 141.59, 133.08, 132.74, 132.69, 132.31, 131.89, 131.08, 131.02, 127.26, 123.99, 120.18, 110.27, 44.18, 31.47, 20.63, 20.22, 19.78, 13.42 ppm. EI-MS (70 eV), *m/z* (%): 358 (92) [M^+], 356 (100) [M^+], 315 (30), 313 (28), 281 (27), 234 (53), 207 (77). IR (NaCl): $\tilde{\nu}$ = 3060(m), 3025 (m), 2932 (s), 2873 (s), 1629 (m), 1524 (m), 1454 (s), 1394 (s), 1177 (s), 1026 (s), 998 (m), 868 (m), 843 (m), 765 (m), 733 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{19}H_{21}BrN_2$: 356.0888, *m/z* found: 356.0886.

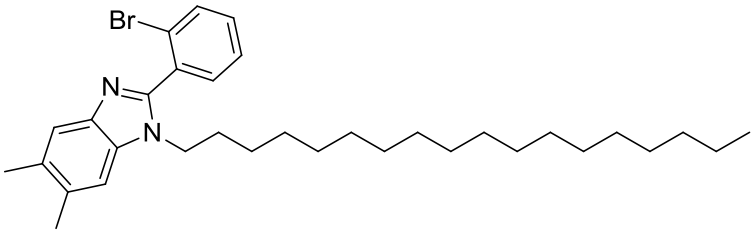


2-(2-Bromophenyl)-5,6-dimethyl-1-octyl-1H-benzimidazole

Sodium hydride (60 %, suspension in mineral oil, 336 mg, 14.0 mmol) was added to the magnetically stirred 2-(2-Bromophenyl)-5,6-dimethyl-1H-benzimidazole (2.1 g, 7.0 mmol) in anhydrous THF (30 mL). 1-Bromooctane (2.7 g, 14.0 mmol) was added dropwise to the

mixture, which was maintained below 5 °C for 0.5 h, and then stirred at room temperature. The reaction was monitored by TLC (30 % ethyl acetate in hexane). After the reaction was complete, the reaction mixture was partitioned between saturated aqueous NH_4Cl (30 mL) and ethyl acetate (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% ethyl acetate in hexane) to give a yellow oil (2.7 g, 6.5 mmol, 93 %).

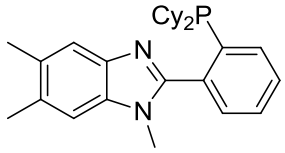
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.61 (s, 1H), 7.54-7.49 (m, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.21 (s, 1H), 3.99 (t, *J* = 8.0 Hz, 1H), 2.44 (s, 3H), 2.42 (s, 3H), 1.69 (t, *J* = 8.0 Hz, 1H), 1.28-1.10 (m, 10H), 0.85 (t, *J* = 8.0 Hz, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 151.35, 141.61, 133.08, 132.78, 132.73, 132.34, 131.91, 131.08, 131.05, 127.26, 124.01, 120.02, 110.28, 44.42, 31.64, 29.34, 28.94, 28.85, 26.55, 22.53, 20.64, 20.24, 14.02 ppm. EI-MS (70 eV), *m/z* (%): 414 (95) [M^+], 412 (100) [M^+], 315 (22), 313 (25), 234 (43), 207 (29). IR (NaCl): $\tilde{\nu}$ = 3058 (w), 3024 (w), 2926 (vs), 2855 (s), 1629 (w), 1523 (m), 1446 (vs), 1394 (m), 1322 (m), 1026 (s), 868 (m), 841 (m), 764 (s), 732 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{23}H_{29}BrN_2$: 412.1514, *m/z* found: 412.1519.



2-(2-Bromophenyl)-5,6-dimethyl-1-octadecyl-1H-benzimidazole

Sodium hydride (60 %, suspension in mineral oil, 336 mg, 14.0 mmol) was added to the magnetically stirred 2-(2-Bromophenyl)-5,6-dimethyl-1H-benzimidazole (2.1 g, 7.0 mmol) in anhydrous THF (30 mL). 1-Bromooctadecane (4.7 g, 14.0 mmol) was added dropwise to the mixture, which was maintained below 5 °C for 0.5 h, and then stirred at room temperature. The reaction was monitored by TLC (30 % ethyl acetate in hexane). After the reaction was complete, the reaction mixture was partitioned between saturated aqueous NH_4Cl (30 mL) and ethyl acetate (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (30 % ethyl acetate in hexane) to give a yellow solid (3.8 g, 6.9 mmol, 98 %). M. p. 47-48 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.61 (s, 1H), 7.54-7.49 (m, 1H), 7.48-7.42 (m, 1H), 7.41-7.35 (m, 1H), 7.21 (s, 1H), 3.99 (t, *J* = 8.0 Hz, 1H), 2.45 (s, 3H), 2.42 (s, 3H), 1.69 (t, *J* = 8.0 Hz, 1H), 1.35-1.10 (m, 30H), 0.89 (t, *J* = 8.0 Hz, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 151.33, 141.58, 133.06, 132.76, 132.71, 132.33, 131.89, 131.07, 131.03, 127.25, 124.01, 120.19, 110.27, 44.40, 31.88, 29.65, 29.62, 29.59, 29.53, 29.44, 29.32, 29.28, 28.88, 26.53, 22.65, 20.63, 20.23, 14.08 ppm. EI-MS (70 eV), *m/z* (%): 553.3, 555.3 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 2915 (vs), 2849 (vs), 1471 (s), 1444 (m), 1430 (m), 1400 (w), 1024 (m), 883 (w), 842 (m), 759 (m), 753 (m), 718 (m) cm^{-1}. Anal. Calcd. for $C_{33}H_{49}BrN_2$: C 71.59, H 5.06, N 8.92; found: C 71.48, H 8.87, N 5.04.

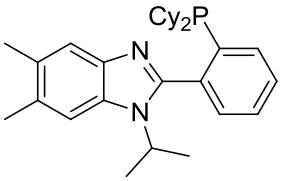


2-(2-(Dicyclohexylphosphino)phenyl)-1,5,6-trimethyl-1H-benzimidazole (5.2-L10)

2-(2-Bromophenyl)-1,5,6-trimethyl-1H-benzoimidazole (2.14 g, 6.8 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in ethanol/liquid nitrogen bath. *n*-Butyllithium (4.7 mL, 1.6 M, 7.5 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (1.65 mL, 7.5 mmol) in THF (10 mL) was added dropwise by syringe. The reaction was stirred for 1 h at -78 °C and warmed to room temperature overnight. The reaction mixture was passed through a pad of celite and silica gel and washed with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column column chromatography on silica gel (20 % ethyl acetate in hexane) to give a light yellow solid. After the solvent was removed, hexane (10 mL) was added to the residue and evaporated again under reduced pressure precipitating a white solid, which was collected by filtration. The filtrate was concentrated, and recrystallized from acetonitrile giving another white solid. (Total amount: 2.6 g, 6.0 mmol, 88 %). M.p. 166-167 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65-7.60 (m, 1H), 7.57 (s, 1H), 7.55-7.40 (m, 3H), 7.15 (s, 1H), 3.52 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 1.90-1.60 (m, 12H), 1.29-1.00 (m, 10H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 153.80, 153.75, 141.29, 139.06, 138.75, 136.79, 136.56, 133.73, 132.33, 132.30, 131.23, 131.12, 131.06, 130.39, 128.64, 128.60, 119.65, 109.75, 33.23, 30.80, 30.72, 29.96, 29.80, 29.03, 27.21, 27.14, 27.10, 27.06, 26.25, 20.47, 20.18 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -7.89 ppm. ESI-MS (70 eV), *m/z* (%): 433.3 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 3049 (w), 2914 (vs),

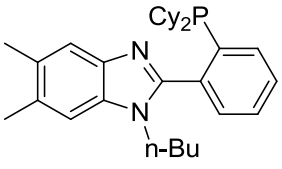
2847 (s), 1486 (m), 1445 (vs), 1423 (s), 1389 (s), 1324 (m), 1262 (w), 996 (m), 860 (s), 773 (vs), 742 (m), 724 (m), 717 (m) cm^{-1}. Anal. Calcd. for $C_{28}H_{37}N_2P$: C 77.74, H 8.62, N 6.48; found: C 77.56, H 8.65, N 6.41.



2-(2-(Dicyclohexylphosphino)phenyl)-1-isopropyl-5,6-dimethyl-1H-benzimidazole (5.2-L13)

2-(2-Bromophenyl)-1-isopropyl-5,6-dimethyl-1H-benzimidazole (1.0 g, 2.0 mmol) was dissolved in freshly distilled THF (20 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in an ethanol/liquid nitrogen bath. *n*-Butyllithium (3.4 mL, 1.6 M, 5.4 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (1.3 g, 5.4 mmol) in THF (10 mL) was added dropwise by syringe. The reaction was stirred for 1h at -78 °C and warmed to room temperature overnight. The reaction mixture was passed through a pad of celite and silica gel, then washed with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (15 % ethyl acetate in hexane) giving a light yellow solid (360 mg, 0.78 mmol, 38 %). M.p. 91-92 ^{o}C.

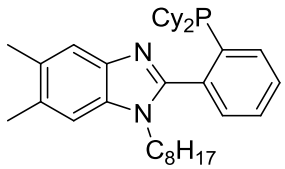
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.53-7.45 (m, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.39-7.33 (m, 2H), 4.20 (quint, *J* = 8.0 Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 2.16 (br. s, 1H), 1.85-0.97 (m, 27 H) ppm. ^{13}C-NMR (151 MHz, $CDCl_3$): δ = 153.01, 142.39, 139.92, 139.70, 137.27, 137.13, 132.44, 132.41, 131.06, 130.71, 130.67, 130.10, 128.58, 128.39, 120.13, 112.19, 48.45, 35.55, 35.45, 32.17, 32.09, 30.31, 30.23, 29.94, 29.91, 29.82, 28.60, 27.64, 27.55, 27.05, 26.98, 26.92, 26.84, 26.47, 26.22, 21.59, 21.48, 20.70, 20.15 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -9.78 ppm. ESI-MS (70 eV), *m/z* (%): 461.3 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 2921 (vs), 2848 (vs), 1446 (vs), 1428 (m), 1369 (s), 1310 (s), 1180 (m), 997 (m), 849 (m), 770 (s), 741 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{30}H_{41}N_2P$: 460.3007, *m/z* found: 460.2984.



1-Butyl-2-(2-(dicyclohexylphosphino)phenyl)-5,6-dimethyl-1H-benzimidazole (5.2-L14)

2-(2-Bromophenyl)-1-butyl-5,6-dimethyl-1H-benzimidazole (704 mg, 2.0 mmol) was dissolved in freshly distilled THF (20 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in ethanol/liquid nitrogen bath. *n*-Butyllithium (1.35 mL, 1.6 M, 2.2 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (0.48 mL, 2.2 mmol) in THF (10 mL) was added dropwise by syringe. The reaction was stirred for 1 h at -78 °C and warmed to room temperature overnight. The reaction mixture was filtered through a pad of celite and silica gel, then washed with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (15 % ethyl acetate in hexane) giving a light yellow solid (720 mg, 1.52 mmol, 77 %). M.p. 52-53 ^{o}C.

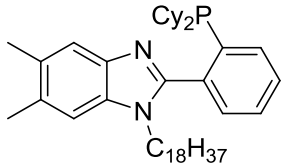
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65-7.59 (m, 1H), 7.57 (s, 1H), 7.53-7.40 (m, 3H), 7.18 (s, 1H), 3.94 (t, *J* = 8.0 Hz, 1H), 2.43 (s, 3H), 2.40 (s, 3H), 1.98-0.88 (m, 26H), 0.74 (t, *J* = 8.0 Hz, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 153.25, 153.21, 141.45, 139.17, 138.86, 136.49, 136.26, 132.85, 132.19, 132.16, 131.32, 131.25, 131.03, 130.20, 128.50, 128.43, 119.72, 110.19, 44.13, 44.06, 31.26, 29.86, 29.71, 29.14, 27.16, 27.09, 26.24, 20.52, 20.16, 19.80, 13.34 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -8.29 ppm. ESI-MS (70 eV), *m/z* (%): 475.3 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 2921 (vs), 2851 (m), 1447 (s), 1431 (m), 1396 (m), 775 (m), 728 (vs) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{31}H_{43}N_2P$: 474.3164, *m/z* found: 474.3117.



2-(2-(Dicyclohexylphosphino)phenyl)-5,6-dimethyl-1-octyl-1H-benzimidazole (5.2-L15)

2-(2-Bromophenyl)-5,6-dimethyl-1-octyl-1H-benzimidazole (2.5 g, 6.1 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in an ethanol/liquid nitrogen bath. *n*-Butyllithium (4.2 mL, 1.6 M, 6.7 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (1.48 mL, 6.7 mmol) in THF (10 mL) was added dropwise by syringe. The reaction was stirred for 1 h at -78 °C and warmed to room temperature overnight. The reaction mixture was passed through a pad of celite and silica gel, then washed with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (15% ethyl acetate in hexane) giving a light yellow oil (2.8 g, 5.3 mmol, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.0 Hz, 1H), 7.56 (s, 1H), 7.53-7.40 (m, 3H), 7.17 (s, 1H), 3.92, 2.43 (s, 3H), 2.40 (s, 3H), 1.80-1.60 (m, 12H), 1.30-0.94 (m, 20H), 0.85 (t, *J* = 8.0 Hz, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 153.31, 153.27, 141.53, 139.30, 138.98, 136.49, 136.27, 132.91, 132.26, 132.22, 131.40, 131.33, 131.09, 130.25, 128.55, 128.48, 119.77, 110.24, 44.39, 44.32, 31.66, 29.91, 29.78, 29.14, 28.90, 28.79, 27.21, 27.15, 26.61, 26.29, 22.51, 20.57, 20.22, 14.01 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -8.33 ppm. ESI-MS (70 eV), *m/z* (%): 531.4 $[M+H]^+$. IR (KBr): $\tilde{\nu}$ = 2922 (vs), 2851 (s), 1519 (w), 1447 (s). 1390 (m), 1321 (w), 1157 (s), 997 (w), 774 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{35}H_{51}N_2P$: 530.3790, *m/z* found: 530.3791.

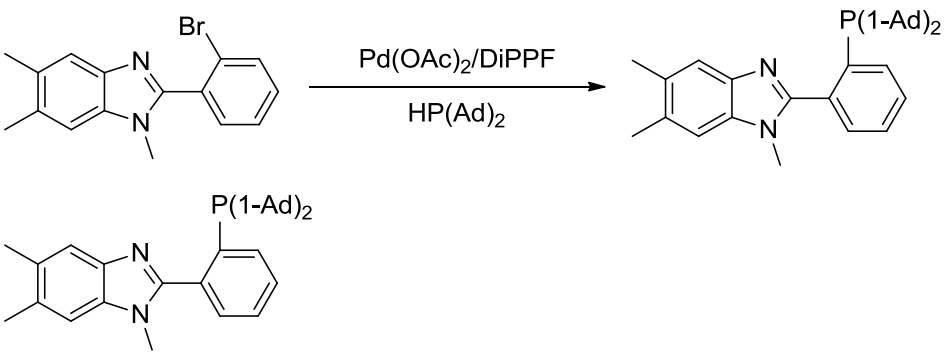


2-(2-(Dicyclohexylphosphino)phenyl)-5,6-dimethyl-1-octadecyl-1H-benzimidazole (5.2-L16)

2-(2-Bromophenyl)-5,6-dimethyl-1-octyl-1H-benzimidazole (2.93 g, 5.3 mmol) was dissolved in freshly distilled THF (30 mL) at room temperature under a nitrogen atmosphere. The solution was cooled to -78 °C in an ethanol/liquid nitrogen bath. *n*-Butyllithium (4.0 mL, 1.6 M, 6.36 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78 °C, chlorodicyclohexylphosphine (1.53 g, 6.36 mmol) in THF (10 mL) was added dropwise by syringe. The reaction was stirred for 1h at -78 °C and warmed to room temperature overnight. The reaction mixture was filtered through a pad of celite and Silica gel, then washed with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (15 % ethyl acetate in hexane), giving a light yellow oil (3.3 g, 4.92 mmol, 93 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.53-7.40 (m, 3H), 7.17 (s, 1H), 3.92 (br. s, 2H), 1.80-1.50 (m, 12H), 1.40-0.94 (m, 40H), 0.89 (t, *J* = 8.0 Hz, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 153.23, 141.48, 139.21, 138.99, 136.44, 136.29, 132.86, 132.23, 132.21, 131.38, 131.34, 131.10, 130.26, 128.55, 128.49, 119.74, 110.23, 44.37, 44.31, 31.87, 29.87, 29.77, 29.64, 29.62, 29.59, 29.58, 29.51, 29.46, 29.30, 29.24, 29.21, 29.11, 28.82, 27.19, 26.58, 26.29, 22.63, 20.57, 20.20, 14.06 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = -8.33 ppm. ESI-MS (70 eV), *m/z* (%): 671.5 $[M+H]^+$. IR (NaCl): $\tilde{\nu}$ = 2920 (vs), 2850 (vs), 1464 (m), 1450 (s), 1427 (m), 1173 (vs), 784 (m), 723 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{45}H_{71}N_2P$: 670.5355, *m/z* found: 670.5322.

Synthesis of 5.2-L17



1-(Di-1-adamantylphosphino)-2-(2-(dicyclohexylphosphino)phenyl)-5,6-dimethyl-1H-benzimidazole (5.2-L17)

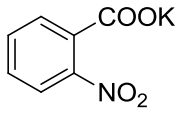
$Pd(OAc)_2$ (6.41 mg, 0.028 mmol, 4 mol%) was placed in a vial and dissolved in freshly distilled toluene (2.0 mL). This solution was then transferred to a vial containing DiPPF (1,1'-bis(diisopropylphosphino)ferrocene, 14.6 mg, 0.035 mmol, 5 mol %) and the mixture was stirred for 10 min. A separate glass vial was first charged with NaO*t*Bu (103 mg, 1.05 mmol, 1.5 equiv.), and then a solution of $(1\text{-adamantyl})_2PH$ (212 mg, 0.7 mmol) in toluene (2.0 mL) was added. 2-(2-Bromophenyl)-1,5,6-trimethyl-1H-benzimidazole (232 g, 0.74 mmol, 1.05 equiv.) and the above $Pd(OAc)_2$/DiPPF solution were then added and the vial was sealed with a cap containing a PTFE septum. The mixture was stirred for 20 h at 110 °C, at which point the reaction was deemed complete on the basis of ^{31}P NMR data obtained from a withdrawn aliquot. The reaction mixture was then allowed to cool and passed through a plug of silica, and the plug was then washed with CH_2Cl_2 (40 mL) and ethyl acetate (50 mL). The combined eluent was collected and the solvent was removed *in vacuo*. The resulting pale-orange solid was purified by column chromatography on aluminium oxide neutral yielded the product as a white powder (120 mg, 0.224 mmol, 32 %). M.p. 286-287 °C.

^1H-NMR (400 MHz, CDCl3): δ = 7.93 (d, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.53-7.40 (m, 3H), 7.16 (s, 1H), 3.57 (s, 3H), 2.45 (s, 3H), 2.42 (s, 3H), 2.04-1.57 (m, 30H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 154.37, 141.44, 140.31, 139.88, 136.48, 136.38, 136.35, 136.19, 133.73, 131.52, 131.44, 131.09, 130.32, 128.49, 127.75, 119.72, 109.74, 42.52, 41.00, 36.83, 31.44, 31.39, 28.79, 20.54, 20.25 (unresolved complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, CDCl3): δ = 25.92 ppm. ESI-MS (70 eV), m/z (%): 537.3 $[M+H]^+$;

IR (KBr): = 2897 (vs), 2849 (s), 1480 (m), 1443 (vs), 1428 (s), 1387 (m), 1321 (m), 845 (m), 781 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{36}H_{45}N_2P$: 536.3320, *m/z* found: 536.3313.

8.8.2 General Procedure for the Synthesis of Potassium Carboxylate salts

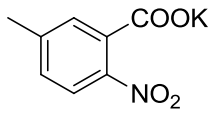
A 250 mL, two-necked, round-bottomed flask was charged with the carboxylic acid (20.0 mmol) and ethanol (20.0 mL). To this, a solution of potassium *tert*-butoxide (2.24 g, 20.0 mmol) in ethanol (20.0 mL) was added dropwise over 2 h. After complete addition, the reaction mixture was stirred for another 1 h at room temperature. A gradual formation of a white precipitate was observed. The resulting solid was collected by filtration washed sequentially with ethanol (2 x 10.0 mL) and cold (0 °C) diethyl ether (10.0 mL), and dried in vacuum to provide the corresponding potassium salts of the carboxylic acids.



Potassium 2-nitrobenzoate (5.2-1a) [CAS No. 15163-59-4]

Compound **5.2-1a** was prepared following the general procedure starting from 2-nitrobenzoic acid (16.7 g, 100 mmol) and potassium *tert*-butoxide (11.2 g, 100 mmol). After filtration, the carboxylate salt was isolated as a white powder (18 g, 88 %). M.p. 241-242 °C.

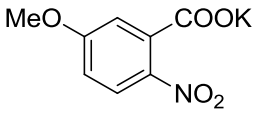
^{1}H NMR (400 MHz, D_2O): δ = 8.00 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.52-7.45 (m, 2H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 174.69, 144.62, 135.86, 134.79, 129.14, 127.53, 124.09 ppm. IR (KBr): $\tilde{\nu}$ = 1611 (vs), 1597 (vs), 1521 (vs), 1379 (m), 1350 (vs), 862 (m), 829 (m), 795 (m), 747 (s), 700 (vs) cm^{-1}. Anal. Calcd. for $C_7H_4KNO_4$: C, 40.97; H, 1.96; N, 6.83. Found: C, 41.07; H, 2.17; N, 6.85.



Potassium 5-methyl-2-nitrobenzoate (5.2-1b) [CAS No. 59639-92-8]

Compound **5.2-1b** was prepared following the general procedure starting from 5-methyl-2-nitrobenzoic acid (3.62 g, 20 mmol) and potassium *tert*-butoxide (2.24 g, 20 mmol). After filtration, the carboxylate salt was isolated as a white powder (4.27 g, 97 %). M.p. 232-233 °C (decomposed).

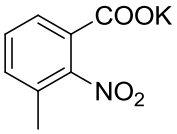
^{1}H NMR (600 MHz, D_2O): δ = 7.92 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.25 (s, 1H), 2.37 (s, 3H) ppm. ^{13}C NMR (151 MHz, D_2O): δ = 175.26, 147.11, 142.01, 136.20, 129.50, 127.75, 124.30, 20.81 ppm. IR (KBr): $\tilde{\nu}$ = 1600 (s), 1573 (vs), 1516 (vs), 1345 (vs), 850 (m) cm^{-1}. Anal. Calcd. for $C_8H_6KNO_4$: C, 43.83; H, 2.76; N, 6.39. Found: C, 43.82; H, 2.85; N, 6.40.



Potassium 5-methoxy-2-nitrobenzoate (5.2-1c) [CAS No.: 1071850-00-4]

Compound **5.2-1c** was prepared following the general procedure starting from 5-methoxy-2-nitrobenzoic acid (1.38 g, 7 mmol) and potassium *tert*-butoxide (0.78 g, 7 mmol). After filtration, the carboxylate salt was isolated as a light yellow powder (1.5 g, 91 %). M.p. 215-216 °C.

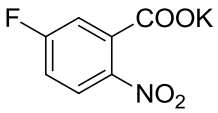
^{1}H NMR (600 MHz, D_2O): δ = 8.17 (d, *J* = 9.2 Hz, 1H), 7.07 (d, *J* = 9.2 Hz, 1H), 7.00 (s, 1H), 3.96 (s, 3H) ppm. ^{13}C NMR (151 MHz, D_2O): δ = 174.7, 164.4, 139.0, 137.0, 127.1, 114.0, 112.0, 56.3 ppm. IR (KBr): $\tilde{\nu}$ = 1595 (vs), 1583 (vs), 1508 (vs), 1381 (m), 1333 (vs), 1243 (vs), 1063 (s), 1021 (m), 856 (m) cm^{-1}. Anal. Calcd. for $C_8H_6KNO_5$: C 40.85, H 2.57, N 5.95. Found: C 40.69, H 2,87, N 5.79.



Potassium 3-methyl-2-nitrobenzoate (5.2-1d) [CAS No. 80841-44-7]

Compound **5.2-1b** was prepared following the general procedure starting from 3-methyl-2-nitrobenzoic acid (3.7 g, 20 mmol) and potassium *tert*-butoxide (2.24 g, 20 mmol). After filtration, the carboxylate salt was isolated as a white powder (4.0 g, 91 %). M.p. 266-267 °C (decomposed).

^{1}H NMR (600 MHz, D_2O): δ = 7.49-7.39 (m, 2H), 7.35 (dd, *J* = 7.5, 0.7 Hz, 1H), 2.26 (s, 3H) ppm. ^{13}C NMR (151 MHz, D_2O): δ = 172.85, 148.76, 132.87, 132.77, 131.18, 130.69, 126.47, 16.81 ppm. IR (KBr): $\tilde{\nu}$ = 2930 (w), 1612 (vs), 1599 (vs), 1572 (vs), 1520 (vs), 1370 (vs), 922 (m), 858 (m), 791 (s), 768 (s), 699 (m) cm^{-1}. Anal. Calcd. for $C_8H_6KNO_4$: C, 43.83; H, 2.76; N, 6.39. Found: C, 43.90; H, 2.83; N, 6.52.

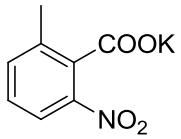


Potassium 5-fluoro-2-nitrobenzoate (5.2-1e) [CAS No. 92449-40-6]

Compound **5.2-1e** was prepared following the general procedure starting from 5-fluoro-2-nitrobenzoic acid (3.74 g, 20 mmol) and potassium *tert*-butoxide (2.24 g, 20 mmol). After filtration, the carboxylate salt was isolated as a white powder (3.98 g, 89 %). M.p. 229 °C (Decomposed).

^{1}H NMR (600 MHz, D_2O): δ = 8.15 (dd, *J* = 9.1, 4.7 Hz, 1H), 7.3-7.1 (m, 2H) ppm. ^{13}C NMR (151 MHz, D_2O): δ = 173.35, 165.70 (d, $J_{C\text{-}F}$ = 256.7 Hz), 140.52, 139.13 (d, $J_{C\text{-}F}$ = 7.6 Hz),

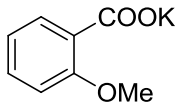
127.59 (d, $J_{C\text{-}F}$ = 12.1 Hz), 116.05 (d, $J_{C\text{-}F}$ = 24.2 Hz), 114.50 (d, $J_{C\text{-}F}$ = 25.7 Hz) ppm. IR (KBr): $\tilde{\nu}$ = 1643 (m), 1610 (m), 1579 (m), 1514 (vs), 1367 (vs), 1222 (m), 826 (s), 789 (s), 747(m) cm^{-1}. Anal. Calcd. for $C_7H_3FKNO_4$: C, 37.67; H, 1.35; N, 6.28. Found: C, 37.73; H, 1.57; N, 6.35.



Potassium 6-methyl-2-nitrobenzoate (5.2-1g) [CAS No. 1227469-81-9]

Compound **5.2-1g** was prepared following the general procedure starting from 6-methyl-2-nitrobenzoic acid (1.15 g, 6.2 mmol) and potassium *tert*-butoxide (0.7 g, 6.2 mmol). After filtration, the carboxylate salt was isolated as a white powder (0.86 g, 63 %). M.p. 223-224 °C (decomposed).

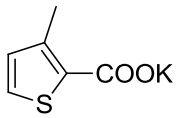
^{1}H NMR (600 MHz, D_2O): δ = 7.96 (d, *J* = 8.5 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 2.33 (s, 3H) ppm. ^{13}C NMR (151 MHz, D_2O): δ = 174.88, 143.65, 136.92, 135.83, 135.48, 128.0, 121.7, 18.5 ppm. IR (KBr): $\tilde{\nu}$ = 2918 (w), 2850 (w), 1592 (vs), 1526 (vs), 1611 (vs), 1458 (m), 1433 (m), 1373 (s), 1346 (vs), 1295 (m), 862 (m), 829 (m), 740 (s) cm^{-1}. Anal. Calcd. for $C_8H_6KNO_4$: C, 43.83; H, 2.76; N, 6.39. Found: C, 43.76; H, 2.84; N, 6.48.



Potassium 2-methoxybenzoate (5.2-1h) [CAS No. 16463-34-6]

Compound **5.2-1h** was prepared following the general procedure starting from 2-methoxybenzoic acid (3.1 g, 20 mmol) and potassium *tert*-butoxide (2.24 g, 20 mmol). After filtration, the carboxylate salt was isolated as a white powder (2.1 g, 55 %). M.p. 272-273 °C (decomposed).

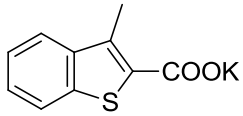
^{1}H NMR (400 MHz, D_2O): δ = 7.37 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.34-7.23 (m, 1H), 7.03-6.84 (m, 2H), 3.73 (s, 3H) ppm. ^{13}C NMR (101 MHz, D_2O): δ = 176.17, 155.78, 130.55, 128.50, 128.38, 120.59, 112.03, 55.57 ppm. IR (KBr): $\tilde{\nu}$ = 2918 (w), 2850 (w), 1602 (m), 1586 (m), 1566 (vs), 1389 (m), 1237 (m), 841 (m), 753 (m), 742 (m) cm^{-1}. Anal. Calcd. for $C_8H_7KO_3$: C, 50.51; H, 3.71. Found: C, 49.80; H, 4.02.



Potassium 3-methylthiophene-2-carboxylate (5.2-1i) [CAS No. 1227469-82-0]

Compound **5.2-1i** was prepared following the general procedure starting from 3-methylthiophene-2-carboxylic acid (2.93 g, 20 mmol) and potassium *tert*-butoxide (2.24 g, 20 mmol). After filtration, the carboxylate salt was isolated as a white powder (2.8 g, 78 %). M.p. > 300 °C (decomposed).

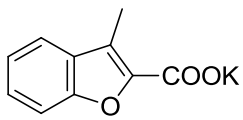
^{1}H NMR (400 MHz, CD_3OD): δ = 7.22 (d, *J* = 5.1 Hz, 1 H), 6.82 (d, *J* = 5.1 Hz, 1 H), 2.49 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ = 171.57, 141.50, 137.91, 132.36, 127.16, 15.88 ppm. IR (KBr): $\tilde{\nu}$ = 2918 (m), 2850 (w), 1563 (vs), 1539 (vs), 1418 (s), 1367 (m), 1349 (vs), 803 (m), 792 (s), 705 (m) cm^{-1}. Anal. Calcd. for $C_6H_5KO_2S$: C, 39.98; H, 2.80; S, 17.79. Found: C, 39.72; H, 2.92; S, 17.61.



Potassium 3-methylbenzothiophene-2-carboxylate (5.2-1j) [CAS No. 1312551-98-6]

Compound **5.2-1j** was prepared following the general procedure starting from 3-methylbenzothiophene-2-carboxylic acid (1.35 g, 7 mmol) and potassium *tert*-butoxide (0.79 g, 7 mmol). After filtration, the carboxylate salt was isolated as a white powder (1.3 g, 81 %). M.p. > 300 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 7.78-7.72 (m, 2 H), 7.25-7.40 (m, 2 H), 2.71 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ = 171.63, 142.71, 140.91, 138.50, 135.17, 126.59, 124.92, 123.96, 123.35, 13.06 ppm. IR (KBr): $\tilde{\nu}$ = 2918 (m), 2850 (w), 1575 (vs), 1560 (vs), 1375 (vs), 753 (m), 728 (m) cm^{-1}. Anal. Calcd. for $C_{10}H_7KNO_4$: C 52.15, H 3.06, S 13.92. Found: C 50.06, H 3.42, S 13.40.

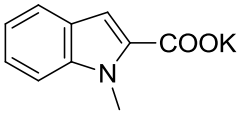


Potassium 3-methylbenzofuran-2-carboxylate (5.2-1k) [CAS No. 835912-81-7]

Compound **5.2-1k** was prepared following the general procedure starting from 3-methylbenzofuran-2-carboxylic acid (1.06 g, 6 mmol) and potassium *tert*-butoxide (0.67 g, 6 mmol). After filtration, the carboxylate salt was isolated as a white powder (1.15 g, 90 %). M.p. > 300 °C (decomposed).

^{1}H NMR (400 MHz, CD_3OD): δ = 7.55-7.62 (m, 1 H), 7.47 (d, *J* = 8.3 Hz, 1 H), 7.34 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.18-7.26 (m, 1 H), 2.56 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ =

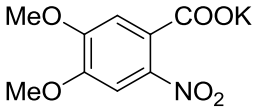
168.50, 154.94, 148.57, 131.55, 127.04, 123.62, 121.58, 120.52, 112.49, 9.66 ppm. IR (KBr): $\tilde{\nu}$ = 2919 (w), 1613 (s), 1571 (vs), 1390 (vs), 1374 (vs), 1321 (vs), 845 (m), 747 (m), 735 (m) cm^{-1}. Anal. Calcd. for $C_{10}H_7KO_3$: C 56.06, H 3.29; Found: C 55.46, H 3.69.



Potassium 1-methyl-1H-indole-2-carboxylate (5.2-1l) [CAS No. 1354455-59-6]

Compound **5.2-1l** was prepared following the general procedure starting from 1-methyl-1H-indole-2-carboxylic acid (0.88 g, 5 mmol) and potassium *tert*-butoxide (0.56 g, 5 mmol). After filtration, the carboxylate salt was isolated as a white powder (1.01 g, 95 %). M.p. > 300 °C (decomposed).

^{1}H NMR (400 MHz, CD_3OD): δ = 7.55 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.20 (td, *J* = 7.6, 1.1 Hz, 1H), 6.95-7.08 (m, 2 H) 4.05 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CD_3OD): δ = 170.75, 140.27, 137.94, 128.08, 124.00, 122.51, 120.64, 111.00, 107.15, 31.97 ppm. IR (KBr): $\tilde{\nu}$ = 2934 (w), 1556 (vs), 1521 (vs), 1458 (s), 1391 (vs), 1325 (s), 1308 (m), 842 (m), 788 (s), 753 (s), 733 (vs) cm^{-1}. Anal. Calcd. for $C_{10}H_8KNO_2$: C 56.32, H 3.78, N 6.57; Found: C 55.57, H 4.21, N 6.36.

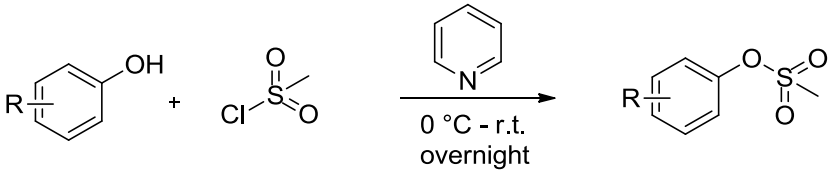


Potassium 4,5-dimethoxy-2-nitrobenzoate (5.2-1m)

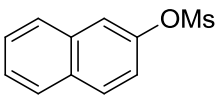
Compound **5.2-1m** was prepared following the general procedure starting from 4,5-dimethoxy-2-nitrobenzoic acid (4.64 g, 20.0 mmol) and potassium *tert*-butoxide (2.24 g, 20.0 mmol). After filtration, the carboxylate salt was isolated as a yellow powder quantatively. M.p. 285-286 °C (decomposed).

^{1}H NMR (600 MHz, D_2O): δ = 7.63 (s, 1H), 6.95 (s, 1H), 3.91 (s, 1H), 3.86 (s, 1H) ppm. ^{13}C NMR (151 MHz, D_2O): δ = 174.75, 153.76, 147.57, 136.90, 131.48, 109.08, 107.29, 56.44, 56.25 ppm. IR (KBr): $\tilde{\nu}$ = 2934 (w), 1596 (s), 1582 (m), 1514 (s), 1401 (m), 1322 (m), 1256 (vs), 1219 (s), 1054 (s), 874 (m), 764 (s) cm^{-1}. Anal. Calcd. for $C_9H_8KNO_6$: C 40.75, H 3.04, N 5.28; Found: C 40.78, H 3.11, N 5.33.

8.8.3 General Procedure for the Synthesis of Aryl Mesylates



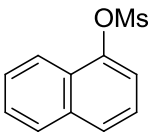
An oven dried round bottom flask equipped with a stirring bar was charged with the corresponding phenol and freshly distilled dichloromethane along with pyridine (5.0 equiv.). The reaction mixture was cooled to 0 °C in an ice bath under nitrogen. Methanesulfonyl chloride (1.5 equiv.) dissolved in dichloromethane was added dropwise with stirring. The reaction was allowed to proceed with stirring in the ice water bath for 1 hours, then the reaction was allowed to warm slowly to room temperature overnight. The reaction was monitored by TLC. The reaction was quenched by addition of water and the organic phase was separated. The aqueous phase was further extracted with dichloromethane and the combined organic layers were washed successively with 15 % HCl solution and brine, and dried over $MgSO_4$. Following filtration, the solvent was removed under reduced pressure and purified by recrystallization from dichloromethane and hexane or column chromatography on silica gel.



2-Naphthyl methanesulfonate (5.2-2a) [CAS No. 10290-91-2]

Compound **5.2-2a** was synthesized according to the general procedure from 2-naphthol (7.21 g, 50 mmol), methansulfonylchloride (5.4 mL, 8.0 mmol) and pyridine (20 mL, 250 mmol). After recrystallization from dichloromethane and hexane, **5.2-2a** (11 g, 49.5 mmol, 99 %) was obtained as a white solid. M.p. 104-105 °C.

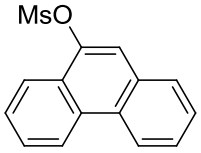
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.94-7.84 (m, 3H), 7.78 (d, *J* = 2.3 Hz, 1H), 7.60-7.50 (m, 2H), 7.45-7.40 (m, 1H), 3.20 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 146.78, 133.52, 131.99, 130.24, 127.83, 127.80, 127.11, 126.54, 120.75, 119.37, 37.35 ppm. EI-MS (70 eV), *m/z* (%): 222 (45) [M^+], 144 (26), 143 (54), 115 (100), 89 (11). IR (KBr): $\tilde{\nu}$ = 3035 (w), 3020 (w), 1630 (w), 1592 (m), 1578 (m), 1507 (m), 1362 (vs), 1328 (s), 1174 (vs), 752 (vs) cm^{-1}. Anal. Calcd. for $C_{11}H_{10}O_3S$: C 59.44, H 4.53, S 14.43; found: C 59.44, H 4.61, S 14.59.



1-Naphthyl methanesulfonate (5.2-2b) [CAS No. 38262-42-9]

Compound **5.2-2b** was synthesized according to the general procedure from 1-naphthol (7.21 g, 15 mmol), methansulfonylchloride (2.6 mL, 22.5 mmol) and pyridine (6.1 mL, 75 mmol). After purification by column chromatography on silica gel, **5.2-2b** (2.87 g, 12.9 mmol, 86 %) was obtained as a yellow oil.

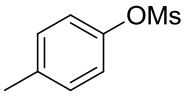
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.19-8.14 (m, 1H), 7.92-7.88 (m, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.64-7.53 (m, 3H), 7.48 (t, *J* = 8.0 Hz, 1H), 3.21 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 145.16, 134.75, 127.91, 127.27, 127.13, 126.88, 125.26, 121.23, 118.27, 37.77 ppm. EI-MS (70 eV), *m/z* (%): 222 (48) [M^+], 144 (18), 143 (94), 115 (100), 89 (14). IR (KBr): $\tilde{\nu}$ = 3060 (s), 3034 (s), 2939 (s), 1633 (m), 1599 (s), 1574 (m), 1506 (m), 1463 (m), 1388 (m), 1366 (vs), 1180 (s), 969 (s), 889 (s), 809 (s), 772 (s)753 (s), 697 (m) cm^{-1}. Anal. Calcd. for $C_{11}H_{10}O_3S$: C 59.44, H 4.53, S 14.43; found: C 59.09, H 4.46, S 14.50.



Phenanthren-9-yl methanesulfonate (5.2-2c) [CAS No. 913536-87-5]

Compound **5.2-2c** was synthesized according to the general procedure from 1-naphthol (971 mg, 5 mmol), methansulfonylchloride (0.59 mL, 7.5 mmol) and pyridine (2.0 mL, 25 mmol). After purification by column chromatography on silica gel, **5.2-2c** (780 mg, 2.86 mmol, 57 %) was obtained as a white solid. M.p. 116-117 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.75-8.65 (m, 2H), 8.26-8.21 (m, 1H), 7.93-7.89 (m, 1H), 7.84 (s, 1H), 7.79-7.62 (m, 4H), 3.26 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 143.71, 131.80, 130.96, 129.20, 128.86, 127.77, 127.41, 127.38, 127.25, 126.21, 123.00, 122.66, 122.16, 118.07, 37.93 ppm. EI-MS (70 eV), *m/z* (%): 272 (29) [M^+], 207 (26), 193 (40), 165 (100). IR (KBr): $\tilde{\nu}$ = 3039 (w), 3019 (w), 2914 (w), 1629 (w), 1602 (m), 1498 (w), 1347 (s), 1332 (s), 1176 (vs), 1168 (s), 1301 (m), 1176 (vs), 1168 (s), 1051 (m), 1026 (m), 972 (m), 821 (m), 763 (m), 753 (m), 736 (m), 728 (m) cm^{-1}. Anal. Calcd. for $C_{15}H_{12}O_3S$: C 66.16, H 4.44, S 11.77; found: C 66.23, H 4.59, S 11.56.

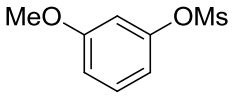


***p*-Tolyl methanesulfonate (5.2-2d)** [CAS No. 17177-63-8]

Compound **5.2-2d** was synthesized according to the general procedure from 1-naphthol (5.46 g, 50 mmol), methansulfonylchloride (4.64 mL, 60 mmol) and pyridine (20.2 mL, 250 mmol). After purification by column chromatography on silica gel, **5.2-2d** (8.5 g, 45.6 mmol, 91 %) was obtained as a white solid. M.p. 44-45 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23-7.16 (m, 4H), 3.12 (s, 3H), 2.37 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 147.07, 137.32, 130.43, 121.65, 37.07, 20.82 ppm. EI-MS (70 eV), *m/z* (%): 187 (18), 186 (82) [M^+], 108 (51), 107 (100), 79 (40), 78 (11), 77 (45). IR (KBr): $\tilde{\nu}$ = 3030 (w), 2942 (w), 1595 (w), 1503 (m), 1353 (vs), 1332 (m), 1170 (s), 1142 (vs),

981 (m), 967 (m), 863 (vs), 839 (s), 821 (s), 801 (m), 767 (m), 678 (m) cm^{-1}. Anal. Calcd. for $C_8H_{10}O_3S$: C 51.60, H 5.41, S 17.22; found: C 51.64, H 5.32, S 17.29.



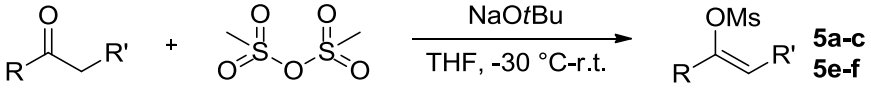
3-Methoxyphenyl methanesulfonate (5.2-2e) [CAS No. 92017-95-3]

Compound **5.2-2d** was synthesized according to the general procedure from 1-naphthol (1.92 g, 15 mmol), methansulfonylchloride (1.78 mL, 22.5 mmol) and pyridine (6.1 mL, 75 mmol). After purification by column chromatography on silica gel, **5.2-2d** (2.57 g, 12.7 mmol, 85 %) was obtained as a yellow oil.

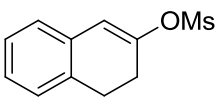
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 8.0 Hz, 1H), 6.89-6.82 (m, 3H), 3.80 (s, 3H), 3.13 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 160.65, 150.02, 130.23, 113.72, 113.06, 107.95, 55.45, 37.16 ppm. EI-MS (70 eV), *m/z* (%): 202 (52) [M^+], 124 (100), 95 (52). IR (KBr): $\tilde{\nu}$ = 3079 (w), 3025 (s), 2943 (s), 2741 (m), 1608 (vs), 1589 (s), 1487 (m), 1367 (vs), 1180 (m), 1122 (s), 943 (s), 817 (s), 686 (s) cm^{-1}. Anal. Calcd. for $C_8H_{10}O_4S$: C 47.51, H 4.98, S 15.86; found: C 47.37, H 5.33, S 16.12.

8.8.4 Synthesis of Vinyl Mesylates

8.4.2.1 General Procedure for the Synthesis of 5.2-5a-c, 5e-f.



These starting materials were prepared according to literature procedures.[6] In a round-bottomed flask under magnetic stirring and nitrogen atmosphere were added the corresponding ketones in THF. The reaction mixture was cooled to -20 °C. Sodium *tert*-butoxide (1.1 equiv.) was added in one portion. The solution was stirred at -5 °C for 1 h and then at room temperature for 30 min. The solution was cooled to -15 °C. Mesyl anhydride (1.1-1.3 equiv.) was added in one portion. The resulting solution was stirred at -15 to -5 °C for 1.5 h and quenched with aq $NaHCO_3$. The aqueous phase was further extracted with ethyl acetate and the combined organic phase was washed with water, brine, dried on Na_2SO_4, concentrated and purified by colomn chromatography on silica gel.

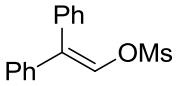


3,4-Dihydronaphthalen-2-yl methanesulfonate (5.2-5a)

Compound **5.2-5a** was synthesized according to the general procedure from *beta*-tetralone (1.43 g, 9.8 mmol), sodium *tert*-butoxide (1.06 g, 10.8 mmol) and mesyl anhydride (1.88 g,

10.8 mmol). After purification by column chromatography on silica gel, **5.2-5a** (1.2 g, 5.35 mmol, 55 %) was obtained as a white solid. M.p. 34-35 °C.

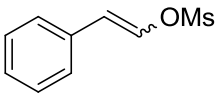
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.21-7.12 (m, 3H), 7.09-7.04 (m, 1H), 6.45 (s, 1H), 3.18 (s, 3H), 3.03 (t, *J* = 8.0 Hz, 1H), 2.67 (t, *J* = 8.0 Hz, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 149.57, 133.00, 132.03, 127.67, 127.38, 126.75, 116.65, 37.75, 28.46, 26.75 ppm. EI-MS (70 eV), *m/z* (%): 224 (30) [M^+], 145 (35), 117 (100), 115 (53), 91 (15). IR (KBr): $\tilde{\nu}$ = 3024 (w), 3004 (w), 2929 (w), 2840 (w), 1657 (m), 1484 (m), 1452 (m), 1436 (m), 1353 (vs), 1332 (s), 1177 (vs), 1075 (vs), 975 (s), 867 (m), 810 (vs), 761 (m), 739 (m), 710 (m) cm^{-1}. Anal. Calcd. for $C_{11}H_{12}O_3S$: C 58.91, H 5.39, S 14.30; found: C 58.94, H 5.59, S 14.28.



2,2-Diphenylvinyl methanesulfonate (5.2-5b)

Compound **5.2-5b** was synthesized according to the general procedure from 2,2-diphenylacetaldehyde (2.35 g, 12 mmol), sodium *tert*-butoxide (1.29 g, 13.2 mmol) and mesyl anhydride (2.72 g, 15.6 mmol). After purification by column chromatography on silica gel, **5.2-5b** (2.5 g, 9.11 mmol, 76 %) was obtained as a white solid. M.p. 89-90 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43-7.32 (m, 8H), 7.30-7.26 (m, 2H), 7.05 (s, 1H), 2.98 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 137.51, 135.16, 132.49, 131.57, 129.80, 128.54, 128.34, 128.30, 128.27, 128.21, 37.68 ppm. EI-MS (70 eV), *m/z* (%): 274 (19) [M^+], 195 (97), 167 (100), 165 (54), 115 (19). IR (NaCl): $\tilde{\nu}$ = 3103 (w), 3013 (w), 1634 (w), 1496 (w), 1445 (w), 1366 (m), 1350 (s), 1185 (s), 1169 (s), 1063 (vs), 968 (s), 953 (m), 816 (s), 761 (m), 696 (vs) cm^{-1}. Anal. Calcd. for $C_{15}H_{14}O_3S$: C 65.67, H 5.14, S 11.69; found: C 65.95, H 5.18, S 11.39.

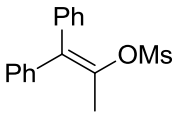


β-Styryl methanesulfonate (5.2-5c)

Compound **5.2-5c** was synthesized according to the general procedure from phenylacetaldehyde (90 % purity, 2.0 g, 15 mmol), sodium *tert*-butoxide (1.62 g, 16.5 mmol) and mesyl anhydride (2.72 g, 15.6 mmol). After purification by column chromatography on silica gel, **5.2-5c** (*E/Z* = 2.3:1, 1.1 g, 5.55 mmol, 37 %) was obtained as a light yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60-7.56 (m, 2H), 7.42-7.28 (m, 15H), 7.22 (d, *J* = 12.0 Hz, 2.5H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 12.0 Hz, 2.3H), 5.92 (d, *J* = 8.0 Hz, 1H), 3.13 (s, 6.9 H), 3.09 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 135.92, 133.84, 132.37, 132.24, 129.12, 128.79, 128.55, 128.27, 128.16, 126.40, 120.48, 116.00, 37.70, 37.31 ppm;

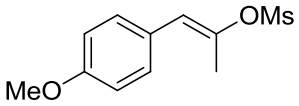
EI-MS (70 eV), *m/z* (%): 198 (28) [M^+], 119 (31), 91 (100). IR (NaCl): $\tilde{\nu}$ = 3081 (m), 3029 (m), 2939 (m), 1653 (s), 1495 (m), 1449 (m), 1368 (vs), 1181 (vs), 1052 (s), 968 (s), 798 (s), 753 (m), 694 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_9H_{10}O_3S$: 198.0351, *m/z* found: 198.0344.



1,1-Diphenylprop-1-en-2-yl methanesulfonate (5.2-5e)

Compound **5.2-5e** was synthesized according to the general procedure from 1,1-diphenylacetone (3.15 g, 15 mmol), sodium *tert*-butoxide (1.77 g, 18 mmol) and mesyl anhydride (2.87 g, 16.5 mmol). After purification by column chromatography on silica gel, **5.2-5e** (1.6 g, 5.55 mmol, 37 %) was obtained as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39-7.20 (m, 10H), 2.45 (s, 3H), 2.23 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 143.39, 138.93, 138.45, 133.03, 129.89, 129.83, 128.32, 128.22, 127.74, 127.60, 38.35, 20.07 ppm. EI-MS (70 eV), *m/z* (%): 288 (4) [M^+], 207 (39), 167 (100), 152 (18), 78 (28). IR (NaCl): $\tilde{\nu}$ = 3056 (m), 3027 (m), 2938 (m), 1651 (m), 1600 (m), 1494 (m), 1444 (m), 1361 (vs), 1189 (s); 1138 (s), 968 (m), 940 (m), 893 (m), 798 (m), 766 (m), 701 (m) cm^{-1}. Anal. Calcd. for $C_{16}H_{16}O_3S$: C 66.64, H 5.59, S 11.12; found: C 66.27, H 5.97, S 11.10.

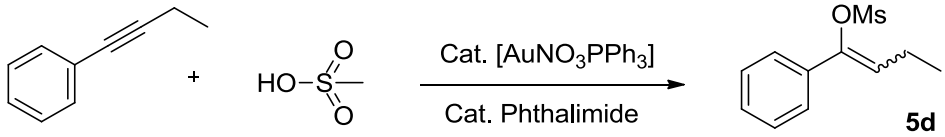


(*E*)-1-(4-Methoxyphenyl)prop-1-en-2-yl methanesulfonate (5.2-5f)

Compound **5.2-5f** was synthesized according to the general procedure from 4-methoxyphenylacetone (985 mg, 6 mmol), sodium *tert*-butoxide (706 mg, 7.2 mmol) and mesyl anhydride (1.15 g, 6.6 mmol). After purification by column chromatography on silica gel, **5.2-5f** (400 mg, 1.65 mmol, 28 %) was obtained as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.45-7.40 (m, 2H), 6.90-6.86 (m, 2H), 5.99 (s, 1H), 3.81 (s, 3H), 2.83 (s, 3H), 2.25 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 159.03, 144.18, 130.05, 125.77, 118.14, 113.98, 55.19, 38.4, 21.35 ppm. EI-MS (70 eV), *m/z* (%): 242 (6) [M^+], 200 (16), 163 (100), 91 (15), 77 (14). IR (NaCl): $\tilde{\nu}$ = 3033 (m), 2939 (m), 2840 (m), 1678 (m), 1608 (s), 1511 (s), 1357 (vs), 1253 (s), 1179 (m), 1034 (m), 905 (m), 829 (m), 789 (m), 697 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{11}H_{14}O_4S$: 242.0613, *m/z* found: 242.0603.

8.8.4.2 Synthesis of 5.2-5d

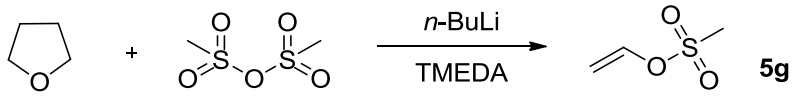


1-Phenylbut-1-en-1-yl methanesulfonate (5.2-5d)

This starting material was prepared according to literature procedures.[7] To a 50 mL vial containing alkyne (1.3 g, 10 mmol, 2.0 equiv.), phthalimide (29.4 mg, 0.2 mmol, 4 mol %), PPh_3AuNO_3 (52.1 mg, 0.1 mmol, 2 mol %), and dichlorethane (20 mL) was added methanesulfonic acid (0.32 mL, 5 mmol, 1.0 equiv.) under nitrogen. The mixture was then sealed and stirred at 100 °C for 4 h. It was quenched with saturated solution of $NaHCO_3$ and then extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography giving a light yellow oil (*E/Z* = 1:3.2, 900 mg, 3.98 mmol, 80 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53-7.32 (m, 6.4 H), 5.86-5.77 (m, 1.3 H), 2.97 (s, 1H), 2.85 (s, 3H), 2.42 (quint, *J* = 8.0 Hz, 0.64 H), 2.23 (quint, *J* = 8.0 Hz, 2 H), 1.12 (t, *J* = 8.0 Hz, 2 H), 1.08 (t, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 145.26, 145.16, 134.68, 132.86, 129.14, 128.74, 128.60, 128.53, 128.42, 125.58, 125.35, 124.80, 39.32, 38.53, 20.86, 20.38, 14.07, 13.38 ppm. EI-MS (70 eV), *m/z* (%): 226 (7) [M^+], 130 (44), 105 (100), 77 (50). IR (NaCl): $\tilde{\nu}$ = 3032 (w), 2970 (m), 2938 (w), 2876 (w), 1664 (m), 1492 (w), 1364 (vs), 1175 (vs), 1044 (m), 961 (m), 819 (m), 700 (m) cm^{-1}. Anal. Calcd. for $C_{22}H_{14}O_3S$: C 58.38, H 6.24, S 14.17; found: C 58.37, H 6.11, S 14.24.

8.8.4.3 Synthesis of 5.2-5g



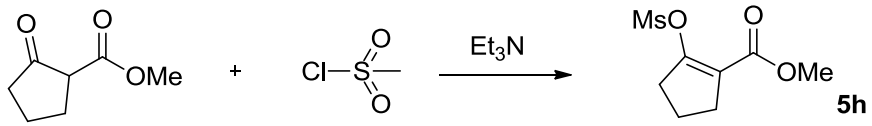
Vinyl methanesulfonate (5.2-5g) [CAS No. 63918-53-6]

This starting material was prepared according to literature procedures.[8] A solution of *n*-butyllithium in hexane (2.5 M in hexane, 15.6 mL, 39 mmol, 1.3 equiv.) was added to a mixture of THF (30 mL) and TMEDA (11.9 mL, 78 mmol, 2.6 equiv.) and the resulting yellow solution was stirred for 3 h at 35 °C in a 250 mL Schlenk flask. Then the reaction mixture was cooled to -78 °C. A solution of mesyl anhydride (5.23 g, 30 mmol) in THF (10 mL) was added dropwise with a syringe over a period of 30 min. Then the reaction mixture was stirred for 30 min at -78 °C and slowly warmed to room temperature overnight. The reaction solution was poured into 80 mL of diethyl ether and 80 mL of ice, saturated

$NaHCO_3$ solution was added under vigorous stirring. The aqueous phase was extracted with diethyl ether (3 x 50 mL) and the combined organic phase was washed with 2 N HCl solution (2 x 50 mL) and brine (2 x 30 mL) and dried over sodium sulfate. After concentration *in vacuo* the crude product was purified by column chromatography on silica gel (30 % diethyl ether in pentane), which was monitored by TLC with the indicator of $KMnO_4$ solution. This afforded the product as colorless oil (1.9 g, 15.6 mmol, 52 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.71 (dd, *J* = 6.0, 13.6 Hz, 1 H), 5.09 (dd, *J* = 2.5, 13.7 Hz, 1 H), 4.84 (dd, *J* = 2.7, 5.9 Hz, 2 H), 3.08 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 141.44, 102.64, 37.40 ppm. IR (NaCl): $\tilde{\nu}$ = 3093 (w), 3034 (m), 2943 (m), 1642 (s), 1366 (vs), 1184 (vs), 1106 (s), 958 (vs), 807 (s), 741 (m), 689 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_3H_6O_3S$: 122.0038, *m/z* found: 122.0039.

8.8.4.4 Synthesis of 5.2-5h



Methyl 2-((methylsulfonyl)oxy)cyclopent-1-enecarboxylate (5.2-5h) [CAS No. 132079-95-9]

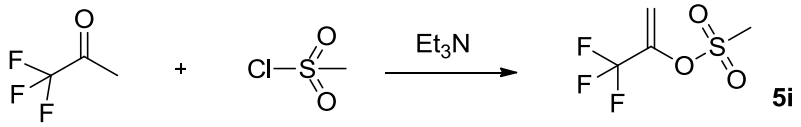
This starting material was prepared according to the literature.[9] To a mixture of 2-acetylcyclohexanone (1.28 mL, 10 mmol) in DME (100 mL) at 0 °C were added triethylamine (7.2 mL, 49 mmol, 4.9 equiv.) and then mesyl chloride (2.05 mL, 26 mmol, 2.6 equiv.). The reaction mixture was then allowed to warm to room temperature within 12 h, diluted with Et_2O (100 mL), and washed with water (120 mL). The aqueous layer was back-extracted with Et_2O (3 x 50 mL), and the organic layers were combined, washed with water (2 x 50 mL) and brine (2 x 50 mL), dried over Na_2SO_4, and filtered through a pad of silica gel. Concentration under reduced pressure afforded a brown oil, which was distilled under reduced pressure to give a colorless oil (1.51 g, 6.7 mmol, 67 %).

Caution: β-Mesyloxy enones decompose on standing neat at room temperature for several hours, but can be stored in dichloromethane or chloroform in fridge for several days. The mesylates were generally used in coupling reactions without further purification immediately after formation.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 3H), 3.23 (s, 3H), 2.82-2.75 (m, 2H), 2.66-2.59 (m, 2H), 1.96 (quint, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 163.34, 156.53, 119.67, 51.43, 39.14, 33.65, 29.00, 19.04 ppm. IR (NaCl): $\tilde{\nu}$ = 3023 (w), 2954 (w), 2860 (w),

1713 (vs), 1656 (m), 1438 (m), 1355 (vs), 1160 (vs), 1130 (s), 811 (vs) cm^{-1}. Anal. Calcd. for $C_8H_{12}O_5S$: C 43.63, H 5.49, S 14.56; found: C 43.06, H 5.37, S 14.73.

8.8.4.5 Synthesis of 5.2-5i



5i

3,3,3-trifluoroprop-1-en-2-yl methanesulfonate (**5.2-5i**) [CAS No. 25230-01-7]

This starting material was prepared according literature procedures.[10] To a solution of 1,1,1-trifluoroacetone (2.77 mL, 30 mmol) and mesyl chloride (2.37 ml, 30 mmol) in diethyl ether, was added dry triethylamine (4.39 mL, 30 mmol) at -10 °C under nitrogen. The reaction mixture was stirred under -10 °C for 2 h and then quenched by addition of saturated $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with diethyl ether and the combined organic layers were washed with 1 N HCl solution and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the light yellow crude product (93 % purity determined by GC) was further purified by Kugelrohr distillation (105 °C under 84 mbar) to give a colorless oil (4.2 g, 22.1 mmol, 74 %).

^{19}F-NMR (376 MHz, $CDCl_3$): δ = - 72.04 (s, $-CF_3$) ppm. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.77-5.69 (m, 2H), 3.20 (s, 3H) ppm. ^{13}C-NMR (51 MHz, $CDCl_3$): δ = 140.83 (q, J_{C-F} = 38.2 Hz), 118.71 (q, J_{C-F} = 272.7 Hz), 109.26 (q, J_{C-F} = 3.5 Hz), 38.40 ppm. IR (NaCl): $\tilde{\nu}$ = 3149 (w), 3034 (m), 2948 (m), 1673 (s), 1378 (vs), 1342 (s), 1191 (vs), 1148 (s), 1125 (s), 957 (s), 810 (s), 674 (m), 522 (s) cm^{-1}. Anal. Calcd. for $C_4H_5F_3O_3S$: C 25.27.63, H 2.65, S 16.86; found: C 25.40, H 2.84, S 17.25.

8.8.5 General Procedures for the Decarboxylative Coupling of Mesylates

Method A: The decarboxylative coupling of carboxylate salts with aryl mesylates under microwave conditions

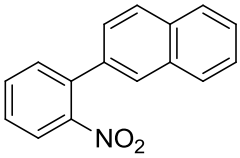
An oven-dried, nitrogen-flushed 10 mL microwave vessel was charged with the potassium carboxylate (0.50 mmol), bis(dibenzylideneacetone)palladium(0) (14.4 mg, 0.025 mmol, 5.0 mol %), copper(I) oxide (1.81 mg, 0.0125 mmol, 2.5 mol %), 3,4,7,8-tetramethyl-1,10-phenanthroline (5.91 mg, 0.025 mmol, 5.0 mol %), and aryl mesylate (0.75 mmol, 1.5 equiv.). A degassed solution of **L15** in NMP (0.06 M, 1 mL, 0.06 mol, 12 mol %) and mesitylene (3 mL) was added via syringe. The resulting solution was then stirred for 5 min at 50 ºC followed by microwave irradiation at 180 ºC for 30 min at a maximum power of 100 W and cooled afterwards with air jet cooling. The maximal pressure noted was 2 bar. The isolated

yield was determined by combining two identical 0.5 mmol-scale reactions. The mixture was then diluted with aqueous HCl (1 N, 20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient) yielding the corresponding biaryl.

Method B: The decarboxylative coupling of carboxylate salts with alkenyl mesylates under thermal conditions

An oven-dried, nitrogen-flushed 10 mL microwave vessel was charged with the potassium carboxylate (0.50 mmol), palladium acetate (5.73 mg, 0.025 mmol, 5.0 mol %), **L8** (28.4 mg, 0.06 mmol, 5.0 mol %), copper(I) oxide (1.81 mg, 0.0125 mmol, 2.5 mol %), 2,2'-bipyridine (3.94 mg, 0.025 mmol, 5.0 mol %), and alkenyl mesylate (0.75 mmol, 1.5 equiv.). A degassed mixture of NMP (1 mL) and mesitylene (3 mL) was added via syringe. The resulting solution was then stirred at 170 °C for 1 h. The isolated yield was determined by combining two identical 0.5 mmol-scale reactions. After the reaction was complete, the mixture was cooled to room temperature, diluted with aqueous HCl (1 N, 20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient) yielding the corresponding aryl olefin.

8.8.5 Synthesis of Biaryls from Aryl Mesylates

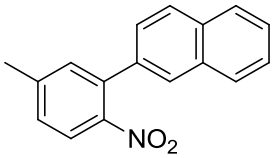


2-(2-Nitrophenyl)naphthalene (5.2-3aa) [CAS-No. 94064-83-2]

Compound **5.2-3aa** was prepared following method A from potassium 2-nitrobenzoate (103 mg, 0.5 mmol) and 2-naphthyl mesylate (167 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3aa** was obtained as a yellow solid (214 mg, 86 %). M.p. 104-105 °C.

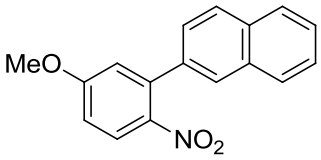
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00-7.86 (m, 4H), 7.84 (s, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.60-7.50 (m, 4H), 7.43 (d, *J* = 8.0 Hz, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 149.29, 136.39, 134.93, 133.23, 132.80, 132.37, 132.26, 128.30, 128.21, 128.15, 127.74, 126.94, 126.53, 125.73, 124.19 ppm. EI-MS (70 eV), *m/z* (%): 249 (80) [M^+], 248 (86), 232 (100), 204 (83), 193 (38), 165 (35). IR (KBr): $\tilde{\nu}$ = 3047 (w), 1608 (w), 1596 (w), 1518 (vs), 1351

(vs), 862 (m), 818 (m), 758 (m), 707 (m) cm^{-1}. Anal. Calcd. for $C_{16}H_{11}NO_2$: C 77.10, H 4.45, N 5.62; found: C 77.16, H 4.53, N 5.63.



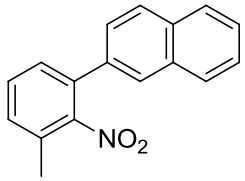
2-(5-Methyl-2-nitrophenyl)naphthalene (5.2-3ba) [CAS-No. 1218992-99-4]

Compound **5.2-3ba** was prepared following method A from potassium 5-methyl-2-nitrobenzoate (110 mg, 0.5 mmol) and 2-naphthyl mesylate (167 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3ba** was obtained as a white solid (232 mg, 88 %). M.p. 111-112 ^oC. ^1H-NMR (400 MHz, $CDCl_3$): δ = 7.92-7.84 (m, 4H), 7.82 (s, 1H), 7.58-7.50 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 2.49 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 146.90, 143.53, 136.61, 135.41, 133.24, 132.90, 132.73, 128.71, 128.13, 128.10, 127.73, 126.77, 126.43, 126.42, 125.86, 124.50, 21.38 ppm. EI-MS (70 eV), *m/z* (%):264 (16), 263 (89) [M^+], 262 (65), 246 (100), 234 (40), 218 (68), 203 (33), 133 (37). IR (KBr): $\tilde{\nu}$ = 3057 (w), 2921 (w), 2850 (w), 1607 (w), 1599 (w), 1582 (w), 1512 (vs), 1347 (vs), 831 (m), 817 (m), 758 (m), 751 (m) cm^{-1}. Anal. Calcd. for $C_{17}H_{13}NO_2$: C 77.55, H 4.98, N 5.32; found: C 77.47, H 5.09, N 5.22.



2-(5-Methoxy-2-nitrophenyl)naphthalene (5.2-3ca) [CAS-No.1218993-02-2]

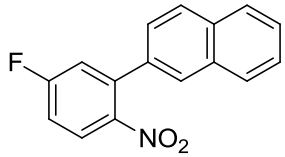
Compound **5.2-3ca** was prepared following method A from potassium 5-methoxy-2-nitrobenzoate (118 mg, 0.5 mmol) and 2-naphthyl mesylate (167 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3ca** was obtained as a yellow solid (236 mg, 85 %). M. p. 63-64 °C. ^1H-NMR (400 MHz, $CDCl_3$): δ = 8.08-8.04 (m, 1H), 7.93-7.85 (m, 3H), 7.81 (s, 1H), 7.57-7.51 (m, 2H), 7.40 (dd, *J* = 4.0, 12.0 Hz, 1H), 7.00-6.95 (m, 2H), 3.92 (s, 1H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 162.51, 141.97, 139.53, 135.82, 133.19, 132.76, 128.10, 128.04, 127.76, 127.13, 126.59, 126.47, 125.83, 117.28, 113.14, 55.93 ppm; EI-MS (70 eV), *m/z* (%): 280 (14), 279 (76) [M^+], 278 (33), 262 (100), 234 (32), 219 (33), 208 (41), 202 (13), 190 (31), 152 (14), 106 (15); IR (KBr): $\tilde{\nu}$ = 3056 (w), 3016 (w), 2920 (w), 2850 (w), 1609 (m), 1599 (m), 1571 (m), 1509 (vs), 1337 (s), 1293 (s), 1232 (m), 1097 (m), 1020 (m), 862 (m), 749 (s) cm^{-1}; EI-HRMS *m/z* calcd. for $C_{17}H_{13}NO_3$: 279,0895, *m/z* found: 279.0901.



2-(3-Methyl-2-nitrophenyl)naphthalene (5.2-3da) [CAS-No. 1218993-01-1]

Compound **5.2-3da** was prepared following method A from potassium 3-methyl-2-nitrobenzoate (110 mg, 0.5 mmol) and 2-naphthyl mesylate (167 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3da** was obtained as a white solid (222 mg, 84 %). M. p. 89-90 °C.

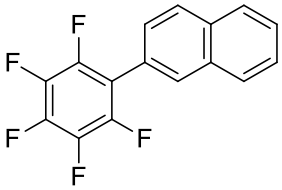
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.92-7.84 (m, 4H), 7.56-7.52 (m, 2H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.39 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 2.43 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 150.99, 134.31, 134.10, 133.14, 132.90, 130.28, 130.02, 129.80, 128.92, 128.51, 128.26, 127.69, 127. 32, 126. 59, 126.54, 125.66, 17.50 ppm. EI-MS (70 eV), *m/z* (%): 264 (14), 263 (78) [M^+], 247 (100), 234 (36), 219 (47), 203 (28). IR (KBr): $\tilde{\nu}$ = 3058 (w), 2929 (w), 1578 (w), 1596 (w), 1520 (vs), 1479 (m), 1458 (m), 1370 (s), 784 (s), 751 (s), 708 (m) cm^{-1}. Anal. Calcd. for $C_{17}H_{13}NO_2$: C 77.55, H 4.98, N 5.32; found: C 77.57, H 5.00, N 5.30.



2-(5-Fluoro-2-nitrophenyl)naphthalene (5.2-3ea)

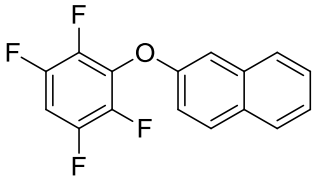
Compound **5.2-3fa** was prepared following method A from potassium 5-fluoro-2-nitrobenzoate (230 mg, 1.0 mmol) and 2-naphthyl mesylate (115 mg, 0.5 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3ea** was obtained as a bright yellow solid (214 mg, 80 %). M. p. 85-86 °C.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -104.50 (m, 1F) ppm. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.87 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.79-7.75 (m, 3H), 7.69 (s, 1H), 7.44-7.40 (m, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.13-7.02 (m, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 163.92 (d, $J_{C\text{-}F}$ = 256.6 Hz), 145.23 (d, $J_{C\text{-}F}$ = 3.0 Hz), 139,66 (d, $J_{C\text{-}F}$ = 9.1 Hz), 134.04, 133.03 (d, $J_{C\text{-}F}$ = 19.1 Hz), 128.44, 128.17, 127.75, 127.08, 126.98, 126.88, 126.80, 126.68, 125.28, 119.11 (d, $J_{C\text{-}F}$ = 24.1 Hz), 115.11 (d, $J_{C\text{-}F}$ = 23.1 Hz) ppm. EI-MS (70 eV), *m/z* (%): 268 (15), 267 (100) [M^+], 266 (55), 238 (46), 223 (73), 221 (48), 211 (22), 210 (20). IR (KBr): $\tilde{\nu}$ = 3055 (w), 1619 (m), 1598 (m), 1580 (m), 1521 (s), 1340 (s), 1284 (m), 748 (m) cm^{-1}. Anal. Calcd. for $C_{16}H_{10}FNO_2$: C 71.91, H 3.77, N 5.24; found: C 71.98, H 3.96, N 5.19.



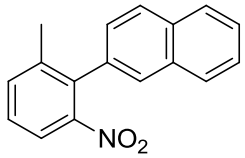
2-(Perfluorophenyl)naphthalene (5.2-3fa) [CAS-No. 52331-48-3]

Compound **5.2-3fa** was prepared following method A from potassium pentafluorobenzoate (250 mg, 1.0 mmol) and 2-naphthyl mesylate (115 mg, 0.5 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). GC yield: 4%. EI-MS (70 eV), *m/z* (%): 295 (17), 294 (100) [M^+], 275 (23), 255 (3), 244 (5), 147 (5), 127 (1).



2-(2,3,5,6-Tetrafluorophenoxy)naphthalene (5.2-3fa′)

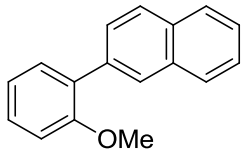
Compound **5.2-3fa** was prepared following method A from potassium 5-fluoro-2-nitrobenzoate (250 mg, 1.0 mmol) and 2-naphthyl mesylate (115 mg, 0.5 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3ea** was obtained as a white solid (126 mg, 43 %). M. p. 93-94 °C. ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -138.49 (m, 2F), -153.85 (m, 2F) ppm. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.87 (t, *J* = 8.0 Hz, 2H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.53-7.42 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.21 (s, 1H), 7.08-6.98 (m, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 154.99, 146.51 (ddt, J_{C-F} = 4.0, 12.1, 249.5 Hz), 141.61 (dm, J_{C-F} = 251.5 Hz), 134.24 (tt, J_{C-F} = 4.0, 13.1 Hz), 133.91, 130.32, 130.18, 127.79, 127.11, 126.91, 125.02, 117.16, 110.18, 102.05 (t, J_{C-F} = 22.2 Hz) ppm. EI-MS (70 eV), *m/z* (%): 293 (17), 292 (100) [M^+], 272 (11), 265 (24), 149 (2), 127 (25), 115 (14). IR (KBr): $\tilde{\nu}$ = 3093 (w), 1644 (w), 1628 (m), 1599 (m), 1512 (vs), 1499 (m), 1485 (vs), 1460 (m), 1245 (m), 1208 (m), 1179 (m), 1162 (s), 1063 (m), 1053 (m), 940 (vs), 844 (s), 817 (m) cm^{-1}. Anal. Calcd. for $C_{16}H_8OF_4$: C 65.76, H 2.76; found: C 65.87, H 3.06.



2-(2-Methyl-6-nitrophenyl)naphthalene (5.2-3ga)

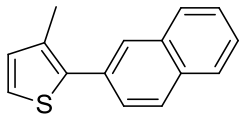
Compound **5.2-3ga** was prepared following method A from potassium 6-methyl-2-nitrobenzoate (220 mg, 1.0 mmol) and 2-naphthyl mesylate (115 mg, 0.5 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3ga** was obtained as light yellow oil (132 mg, 50 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.0 Hz, 1H), 7.94-7.92 (m, 1H), 7.87-7.84 (m, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 7.60-7.52 (m, 3H), 7.46-7.38 (m, 2H), 2.19 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 150.44, 139.35, 135.22, 133.76, 133.57, 133.15, 132.64, 128.15, 127.97, 127.85, 127.74, 127.04, 126.60, 126.33, 126.31, 121.04, 20.62 ppm. EI-MS (70 eV), *m/z* (%): 264 (16), 263 (100) [M^+], 262 (66), 246 (43), 234 (29), 218 (54), 203 (22). IR (NaCl): $\tilde{\nu}$ = 3055 (s), 2977 (w), 2927 (w), 2868 (w), 1599 (m), 1519 (vs), 1455 (m), 1359 (vs), 1285 (m), 821 (m), 801 (m), 748 (m), 712 (m) cm^{-1}. Anal. Calcd. for $C_{17}H_{13}NO_2$: C 77.55, H 4.98, N 5.32; found: C 77.21, H 5.03, N 5.31.



2-(2-Methoxyphenyl)naphthalene (5.2-3ha) [CAS-No. 93321-12-1

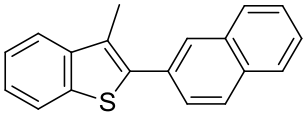
Compound **5.2-3ha** was prepared following method A from potassium potassium 2-methoxybenzoate (95 mg, 0.5 mmol) and 2-naphthyl mesylate (167 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). GC yield: 17 %. EI-MS (70 eV), *m/z* (%): 235 (19), 234 (100) [M^+], 220 (48), 219 (17), 203 (3), 192 (25), 128 (6).



3-Methyl-2-(2-naphthyl)thiophene (5.2-3ia)

Compound **5.2-3ia** was prepared following method A from potassium potassium 3-methylthiophene-2-carboxylate (91 mg, 0.5 mmol) and 2-naphthyl mesylate (167 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3ia** was obtained as a colorless oil (100 mg, 45 %).

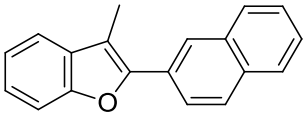
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1H), 8.00-7.90 (m, 3H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.62-7.54 (m, 2H), 7.34 d, *J* = 8.0 Hz, 1H (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 2.50 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 137.81, 133.44, 133.30, 132.29, 132.19, 131.15, 128.01, 127.96, 127.63, 127.20, 126.33, 126.00, 123.64, 15.00 ppm. EI-MS (70 eV), *m/z* (%): 225 (20), 224 (100) [M^+], 223 (61), 191 (11), 127 (4). IR (NaCl): $\tilde{\nu}$ = 3056 (m), 2922 (m), 2863 (w), 1599 (s), 1500 (s), 1451 (m), 891 (w), 856 (s), 815 (vs), 746 (s), 710 (s) cm-^{1}. Anal. Calcd. for $C_{15}H_{12}S$: C 80.31, H 5.39, S 14.29; found: C 80.34, H 5.63, S 13.65. EI-HRMS *m/z* calcd. for $C_{15}H_{12}S$: 224.0660, *m/z* found: 224.0666.



3-Methyl-2-(2-naphthyl)benzothiophene (5.2-3ja)

Compound **5.2-3ja** was prepared following method A from potassium potassium 3-methylbenzothiophene-2-carboxylate (115 mg, 0.5 mmol) and 2-naphthyl mesylate (167 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3ja** was obtained as a white solid (200 mg, 73 %) M.p. 96-97 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1H), 7.97-7.88 (m, 4H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.73 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.60-7.53 (m, 2H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 2.57 (s, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 141.27, 139.04, 138.04, 133.24, 132.64, 132.17, 128.76, 128.13, 128.11, 127.76, 127.71, 127.52, 126.49, 126.38, 124.32, 124.17, 122.13, 12.75 ppm. EI-MS (70 eV), *m/z* (%): 275 (22), 274 (100) [M^+], 259 (6) 240 (6), 147 (7), 127 (3). IR (KBr): $\tilde{\nu}$ = 3049 (w), 2922 (w), 2852 (w), 1598 (m), 1501 (m), 1459 (w), 1434 (m), 1218 (m), 823 (vs), 744(vs), 725 (vs) cm^{-1}. Anal. Calcd. for $C_{19}H_{14}S$: C 83.17, H 5.14, S 11.69; found: C 82.87, H 5.24, S 11.39.

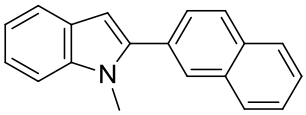


3-Methyl-2-(2-naphthyl)benzofuran (5.2-3ka)

Compound **5.2-3ka** was prepared following method A from potassium 3-methylbenzofuran-2-carboxylate (107 mg, 0.5 mmol) and 2-naphthyl mesylate (167 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3ka** was obtained as a white solid (130 mg, 50 %). M.p. 92-93 °C.

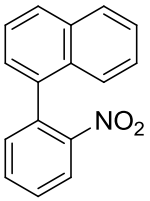
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1H), 8.02-7.86 (m, 4H), 7.63-7.51 (m, 4H), 7.39-7.28 (m, 2H), 2.60 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 153.89, 150.71, 133.32,

132.72, 131.23, 128.82, 128.32, 128.24, 127.71, 126.47, 126.36, 125.84, 124.41, 124.32, 122.39, 119.30, 111.74, 110.93, 9.64 ppm. EI-MS (70 eV), *m/z* (%): 259 (22),258 (100) [M^+], 229 (6), 131 (5), 127 (3). IR (KBr): $\tilde{\nu}$ = 3053 (w), 2919 (w), 2856 (w), 1594 (m), 1500 (m), 1340 (m), 1101 (s), 860 (s), 822 (s), 748 (m), 736 (vs) cm^{-1}. Anal. Calcd. for $C_{19}H_{14}O$: C 88.34, H 5.46; found: C 88.26, H 5.69.



1-Methyl-2-(2-naphthyl)-1H-indole (5.2-3la) [CAS-No. 244141-64-8]

Compound **5.2-3la** was prepared following method A from potassium 1-methyl-1H-indole-2-carboxylate (107 mg, 0.5 mmol) and 2-naphthyl mesylate (167 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3la** was obtained as a white solid (160 mg, 62 %). M.p. 152-153 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1H), 7.99-7.92 (m, 3H), 7.74-7.66 (m, 2H), 7.61-7.54 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.72 (s, 1H), 3.85 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 141.52, 138.49, 133.21, 132.69, 130.20, 128.26, 128.10, 128.07, 128.01, 127.74, 127.17, 126.51, 126.36, 121.75, 120.49, 119.90, 109.62, 102.10, 31.32 ppm. EI-MS (70 eV), *m/z* (%): 258 (44), 257 (100) [M^+], 255 (21), 242 (12), 128 (16), 127 (10). IR (KBr): $\tilde{\nu}$ = 3551 (w), 2940 (w), 1600 (m), 1503 (w), 1463 (m), 1341 (m), 865 (m), 823(m), 791 (s), 751 (s), 733 (s) cm^{-1}. Anal. Calcd. for $C_{19}H_{15}N$: C 88.68, H 5.88, N 5.44; found: C 88.28, H 6.19, N 5.33.

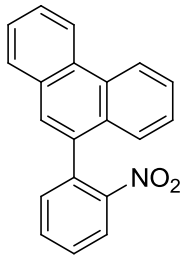


1-(2-Nitrophenyl)naphthalene (5.2-3ab) [CAS-No. 5415-59-8]

Compound **5.2-3ab** was prepared following method A from potassium 2-nitrobenzoate (144 mg, 0.7 mmol) and 1-naphthyl mesylate (233 mg, 1.05 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.7 mmol-scale reactions, compound **5.2-3ab** was obtained as a yellow solid (90 mg, 27 %). M.p. 92-93 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.11 (dd, *J* = 4.0, 12.0 Hz, 1H), 7.95 (d, *J* = 20.0 Hz, 2H), 7.75-7.36 (m, 8H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 149.71, 135.45, 135.15, 133.38, 133.0, 132.47, 131.40, 128.58, 128.49, 128.39, 126.50, 125.99, 125.98, 125.15, 124.77, 124.13 ppm. EI-MS (70 eV), *m/z* (%): 250 (25), 249 (100) [M^+], 232 (89), 219 (14), 204 (76), 203 (53). IR (KBr): $\tilde{\nu}$ = 3053 (w), 2916 (w), 2846 (w), 1611 (w), 1591 (w), 1575 (m), 1520

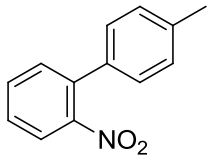
(vs), 1337 (vs), 778 (s), 750 (m) cm^{-1}. Anal. Calcd. for $C_{16}H_{11}NO_2$: C 77.10, H 4.45, N 5.62; found: C 76.93, H 4.65, N 5.51.



9-(2-Nitrophenyl)phenanthrene (5.2-3ac) [CAS-No. 911217-05-5]

Compound **5.2-3ac** was prepared following method A from potassium 2-nitrobenzoate (103 mg, 0.5 mmol) and 9-phenanthyl mesylate (211 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3ac** was obtained as a yellow solid (78 mg, 26 %). M.p. 138-139 ^oC.

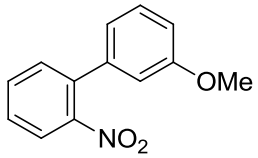
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.79 (d, *J* = 8.0 Hz, 1H), 8.75 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.75-7.60 (m, 6H), 7.57-7.49 (m, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 149.87, 135.35, 134.49, 133.11, 132.76, 131.15, 130.67, 130.32, 130.27, 128.74, 128.72, 127.06, 126.92, 126.87, 126.74, 125.71, 124.29, 123.06, 122.61 ppm; EI-MS (70 eV), *m/z* (%): 299 (14) [M^+], 282 (19), 267 (100), 240 (14), 207 (75), 133 (20). IR (KBr): $\tilde{\nu}$ = 3063 (w), 2916 (w), 2851 (w), 1607 (w), 1515 (vs), 1347 (vs), 745 (m), 726 (m), 714 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{20}H_{13}NO_2$: 299.0946, *m/z* found: 299.0955.



4'-Methyl-2-nitro-1,1'-biphenyl (5.2-3ad) [CAS-No. 70680-21-6]

Compound **5.2-3ad** was prepared following method A from potassium 2-nitrobenzoate (103 mg, 0.5 mmol) and *p*-tolyl mesylate (186 mg, 1.0 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3ad** was obtained as a yellow oil (60 mg, 28 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.52-7.45 (m, 2H), 7.31-7.24 (m, 4H), 2.44 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 149.34, 138.09, 136.18, 134.33, 132.12, 131.86, 129.38, 127.84, 127.69, 123.92, 21.16 ppm. EI-MS (70 eV), *m/z* (%): 212 (21), 198 (14), 196 (100), 185 (86), 184 (44), 170 (46), 168 (97), 156 (60), 129 (47), 115 (54), 77 (21). IR (NaCl): $\tilde{\nu}$ = 3062 (w), 3028 (m), 2923 (m), 2886 (m), 1614 (m), 1525 (vs), 1476 (m), 1356 (s), 853 (m), 819 (m), 782 (m), 750 (m) cm^{-1}. Anal. Calcd. for $C_{13}H_{11}NO_2$: C 72.23, H 5.20, N 6.57; found: C 73.06, H 5.39, N 6.54.

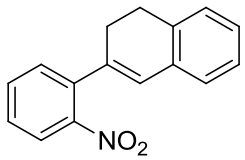


3'-Methoxy-2-nitro-1,1'-biphenyl (5.2-3ae) [CAS-No. 92017-95-3]

Compound **5.2-3ae** was prepared following method A from potassium 2-nitrobenzoate (103 mg, 0.5 mmol) and 3-methoxyphenyl mesylate (202 mg, 1.0 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-3ae** was obtained as a yellow solid (80 mg, 35 %). M.p. 69-70 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.62 (dt, dd, *J* = 4.0, 8.0 Hz, 1H), 7.52-7.44 (m, 2H), 7.35 (t, *J* = 4.0, 8.0 Hz, 1H), 6.98-6.87 (m, 3H), 3.83 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 159.62, 149.26, 138.61, 136.02, 132.15, 131.75, 129.66, 128.16, 123.88, 120.19, 113.64, 113.57, 55.19 ppm. EI-MS (70 eV), *m/z* (%): 229 (55) [M^+], 212 (12), 201 (100), 198 (15), 186 (29), 170 (49), 168 (27), 158 (58), 152 (19). IR (KBr): $\tilde{\nu}$ = 3008 (w), 2961 (w), 2937 (w), 2833 (w), 1597 (s), 1571 (m), 1522 (vs), 1426 (s), 1351 (s), 1321 (s), 1322 (s), 1221 (vs), 788 (s), 749 (s), 694 (m) cm^{-1}. Anal. Calcd. for $C_{13}H_{11}NO_3$: C 68.11, H 4.84, N 6.11; found: C 68.04, H 4.94, N 5.93.

8.8.6 Synthesis of Aryl Olefins from Alkenyl Mesylates

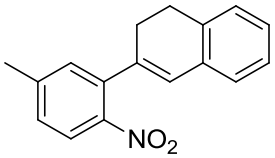


3-(2-Nitrophenyl)-1,2-dihydronaphthalene (5.2-6aa)

Compound **5.2-6aa** was prepared following method B from potassium 2-nitrobenzoate (103 mg, 0.5 mmol) and 3,4-dihydronaphthalen-2-yl methanesulfonate (174 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-6aa** was obtained as a yellow solid (108 mg, 86 %). M.p. 92-93 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98-7.93 (m, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.25-7.16 (m, 3H), 7.15-7.09 (m, 1H), 3.01 (t, *J* = 8.0 Hz, 2H), 2.56 (dt, *J* = 4.0, 8.0 Hz, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 148.24, 138.08, 137.59, 134.86, 133.84, 132.93, 130.79, 128.04, 127.56, 127.38, 126.78, 126.61, 126.57, 124.43, 28.22, 27.91 ppm. EI-MS (70 eV), *m/z* (%): 251 (1) [M^+], 250 (4), 235 (19), 234 (100), 217 (43), 216 (85), 204 (32), 203 (29), 179 (11), 178 (11), 132 (16), 128 (14), 91 (26). IR (KBr): $\tilde{\nu}$ = 3012 (w), 2931

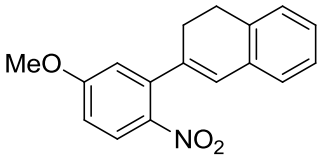
(w), 2829 (w), 1609 (w), 1568 (w), 1515 (vs), 1484 (m), 1337 (vs), 864 (m), 763 (s), 744 (m) cm^{-1}. Anal. Calcd. for $C_{16}H_{13}NO_2$: C 76.48, H 5.21, N 5.57; found: C 76.39, H 5.39, N 5.51.



3-(5-Methyl-2-nitrophenyl)-1,2-dihydronaphthalene (5.2-6ba)

Compound **5.2-6ba** was prepared following method B from potassium 5-methyl-2-nitrobenzoate (132 mg, 0.6 mmol) and 3,4-dihydronaphthalen-2-yl methanesulfonate (208 mg, 0.9 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.6 mmol-scale reactions, compound **5.2-6ba** was obtained as a yellow solid (260 mg, 82 %). M. p. 151-152 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.0 Hz, 1H), 7.26-7.09 (m, 6H), 6.50 (s, 1H), 3.01 (t, *J* = 8.0 Hz, 2H), 2.53 (t, *J* = 8.0 Hz, 2H), 2.46 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 145.91, 144.24, 138.32, 138.28, 134.90, 133.95, 131.41, 128.62, 127.44, 127.38, 126.53, 126.27, 124.74, 119.93, 28.28, 28.06, 21.38 ppm. EI-MS (70 eV), *m/z* (%): 265 (14) [M^+], 248 (99), 230 (100), 202 (52), 146 (23). IR (KBr): $\tilde{\nu}$ = 3066 (w), 3025 (w), 2945 (w), 2839 (w), 1604 (m), 1579 (m), 1509 (vs), 1482 (m), 1340 (vs), 885 (m), 837 (s), 751 (s) cm^{-1}. Anal. Calcd. for $C_{17}H_{15}NO_2$: C 76.96, H 5.70, N 5.28; found: C 76.73, H 5.71, N 5.25.

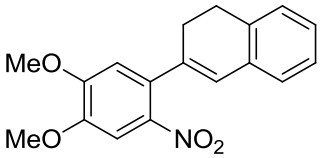


3-(5-Methoxy-2-nitrophenyl)-1,2-dihydronaphthalene (5.2-6ca)

Compound **5.2-6ca** was prepared following method B from potassium 5-methoxy-2-nitrobenzoate (141 mg, 0.6 mmol) and 3,4-dihydronaphthalen-2-yl methanesulfonate (208 mg, 0.9 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.6 mmol-scale reactions, compound **5.2-6ca** was obtained as a yellow oil (284 mg, 84 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.0 Hz, 1H), 7.23 (m, 3H), 7.15-7.10 (m, 1H), 6.91 (dd, *J* = 4.0, 8.0 Hz, 1H), 6.87 (d, *J* = 4.0 Hz, 1H), 6.50 (s, 1H), 3.92 (s, 3H), 3.04 (t, *J* = 8.0 Hz, 2H), 2.54 (t, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 163.10, 141.12, 140.94, 138.87, 134.87, 133.82, 127.42, 127.35, 127.32, 126.48, 126.45, 125.88, 115.74, 112.88, 55.86, 28.23, 28.09 ppm. EI-MS (70 eV), *m/z* (%): 281 (15) [M^+], 264 (37), 249 (100), 232 (42), 204 (50). IR (NaCl): $\tilde{\nu}$ = 3015 (w), 2918 (s), 2849 (w), 1607 (m), 1573 (s), 1508 (vs), 1480 (m), 1330 (s), 1295 (s), 1226 (s), 1086 (s), 1027 (m), 749 (vs) cm^{-1}. Anal. Calcd. for

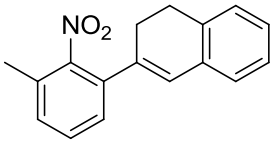
$C_{17}H_{15}NO_3$: C 72.58, H 5.37, N 4.98; found: C 72.01, H 5.41, N 4.98. EI-HRMS *m/z* calcd. for $C_{17}H_{15}NO_3$: 281.1052, *m/z* found: 281.1054.



3-(4,5-Dimethoxy-2-nitrophenyl)-1,2-dihydronaphthalene (5.2-6ma)

Compound **5.2-6ma** was prepared following method B from potassium 4,5-dimethoxy-2-nitrobenzoate (159 mg, 0.6 mmol) and 3,4-dihydronaphthalen-2-yl methanesulfonate (208 mg, 0.9 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.6 mmol-scale reactions, compound **5.2-6ma** was obtained as a yellow solid (310 mg, 83 %). M.p. 123-124 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 1H), 7.21-7.09 (m, 4H), 6.79 (s, 1H), 6.47 (s, 1H), 3.99 (s, 3H), 3.98 (s, 3H), 3.03, 2.52 (t, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 152.92, 147.96, 140.09, 139.16, 134.89, 133.94, 133.34, 127.41, 127.38, 126.50, 126.38, 125.77, 112.47, 107.90, 56.44, 56.36, 28.41, 28.37 ppm. EI-MS (70 eV), *m/z* (%): 311 (5) [M^+], 294 (17), 279 (100), 262 (33), 234 (31), 219 (20), 190 (16). IR (KBr): $\tilde{\nu}$ = 2927 (w), 2827 (w), 1614 (w), 1572 (m), 1515 (s), 1498 (s), 1316 (s), 1283 (s), 1263 (s), 1219 (vs), 1081 (s), 1019 (m), 855 (m), 788 (m), 750 (m) cm^{-1}. Anal. Calcd. for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found: C 69.64, H 5.79, N 4.51.

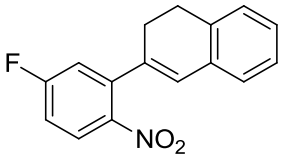


3-(3-Methyl-2-nitrophenyl)-1,2-dihydronaphthalene (5.2-6da)

Compound **5.2-6da** was prepared following method B from potassium 3-methyl-2-nitrobenzoate (136 mg, 0.6 mmol) and 3,4-dihydronaphthalen-2-yl methanesulfonate (208 mg, 0.9 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.6 mmol-scale reactions, compound **5.2-6da** was obtained as a yellow solid (272 mg, 85 %). M. p. 100-101 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 8.0 Hz, 1H), 7.19-7.04 (m, 5H), 7.03-6.97 (m, 1H), 6.46 (s, 1H), 2.84 (t, *J* = 8.0 Hz, 2H), 2.50 (t, *J* = 8.0 Hz, 2H), 2.29 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 149.98, 135.65, 135.43, 134.72, 133.66, 130.05, 129.97, 129.85, 127.74, 127.64, 127.30, 126.85, 126.80, 126.60, 28.02, 27.56, 17.60 ppm. EI-MS (70 eV), *m/z* (%): 265 (35) [M^+], 248 (69), 230 (100), 220 (58), 202 (67), 146 (53). IR (KBr): $\tilde{\nu}$ = 2918 (m),

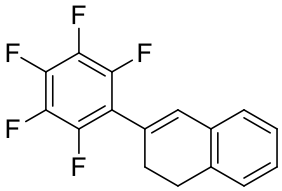
2850 (m), 1606 (w), 1520 (vs), 1476 (m), 1372 (s), 781 (s), 757 (vs) cm^{-1}. Anal. Calcd. for $C_{17}H_{15}NO_2$: C 76.96, H 5.70, N 5.28; found: C 76.44, H 6.01, N 4.98.



3-(5-Fluoro-2-nitrophenyl)-1,2-dihydronaphthalene (5.2-6ea)

Compound **5.2-6ea** was prepared following method B from potassium 5-fluoro-2-nitrobenzoate (159 mg, 0.6 mmol) and 3,4-dihydronaphthalen-2-yl methanesulfonate (208 mg, 0.9 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.6 mmol-scale reactions, compound **5.2-6ea** was obtained as a yellow solid (258 mg, 80 %). M. p. 78-79 ^oC.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = - 104.01 (m, 1F) ppm. ^1H-NMR (400 MHz, $CDCl_3$): δ = 8.06-8.00 (m, 1H), 7.25-7.09 (m, 6H), 6.54 (s, 1H), 3.01 (t, *J* = 8.0 Hz, 2H), 2.54 (t, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 164.44 (d, $J_{C\text{-}F}$ = 256.6 Hz), 144.29, 141.37 (d, $J_{C\text{-}F}$ = 9.1 Hz), 136.77, 134.87, 133.47, 127.86, 127.44, 127.33 (d, $J_{C\text{-}F}$ = 10.1 Hz), 127.30, 126.79, 126.64, 117.67 (d, $J_{C\text{-}F}$ = 24.1 Hz), 114.92 (d, $J_{C\text{-}F}$ = 22.1 Hz), 28.11, 27.73 ppm. EI-MS (70 eV), *m/z* (%): 269 (14) [M^+], 252 (71), 235 (97), 234 (100), 220 (47), 91 (18). IR (KBr): $\tilde{\nu}$ = 3073 (w), 3018 (w), 2966 (w), 2887 (w), 2834 (w), 1615 (w), 1577 (m), 1519 (vs), 1473 (m), 1350 (s), 881 (m), 763 (m), 751 (s) cm^{-1}. Anal. Calcd. for $C_{16}H_{12}FNO_2$: C 71.37, H 4.49, N 5.20; found: C 71.30, H 4.66, N 5.16.

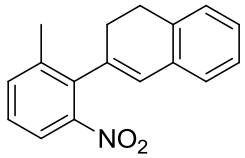


3-(Perfluorophenyl)-1,2-dihydronaphthalene (5.2-6fa)

Compound **5.2-6fa** was prepared following method B from potassium 2,3,4,5,6-pentafluorobenzoate (175 mg, 0.7 mmol) and 3,4-dihydronaphthalen-2-yl methanesulfonate (243 mg, 1.05 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.7 mmol-scale reactions, compound **5.2-6fa** was obtained as a white solid (92 mg, 22 %). M. p. 119-120 ^oC.

^{19}F-NMR (376 MHz, $CDCl_3$): δ = -141.18 (dd, J_F = 7.5, 15.1 Hz, 2F), -156.85 (t, J_F = 15.1 Hz, 1F), -162.57 (dt, J_F = 7.5, 15.1 Hz, 2F) ppm. ^1H-NMR (200 MHz, $CDCl_3$): δ = 7.27-7.10 (m, 4H), 6.72 (s, 1H), 2.99 (t, *J* = 8.0 Hz, 2H), 2.64 (t, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 144.24 (dm, $J_{C\text{-}F}$ = 251.6 Hz), 139.98 (dm, $J_{C\text{-}F}$ = 253.1 Hz), 137.77 (dm, $J_{C\text{-}F}$ =

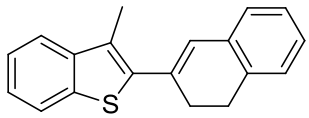
252.6 Hz), 135.01, 133.11, 132.24 (dt, J_{C-F} = 1.0, 2.5 Hz), 128.28, 127.50, 127.03, 126.75, 125.29 (m), 116.83 (dt, J_{C-F} = 4.0, 17.6 Hz), 27.88, 27.53 (t, J_{C-F} = 2.5 Hz) ppm. EI-MS (70 eV), *m/z* (%): 296 (100) [M^+], 274 (18), 115 (82). IR (KBr): $\tilde{\nu}$ = 3021 (w), 2954 (w), 2835 (w), 1650 (w), 1516 (m), 1483 (vs), 1456 (m), 981 (vs), 751 (m) cm^{-1}. Anal. Calcd. for $C_{16}H_8F_5$: C 64.87, H 3.06; found: C 65.09, H 3.27.



3-(2-Methyl-6-nitrophenyl)-1,2-dihydronaphthalene (5.2-6ga)

Compound **5.2-6ga** was prepared following method B from potassium 6-methyl-2-nitrobenzoate (110 mg, 0.5 mmol) and 3,4-dihydronaphthalen-2-yl methanesulfonate (168 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-6ga** was obtained as a yellow oil (111 mg, 42 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.21-7.17 (m, 3H), 7.07-7.02 (m, 1H), 6.27 (s, 1H), 3.23-2.95 (m, 2H), 2.75-2.56 (m, 2H), 2.41 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 149.68, 138.43, 136.74, 136.09, 134.72, 134.08, 133.58, 127.38, 126.49, 126.36, 126.12, 121.27, 28.00, 27.76, 19.92 ppm. EI-MS (70 eV), *m/z* (%): 265 (8) [M^+], 248 (68), 230 (100), 202 (37), 115 (17). IR (NaCl): $\tilde{\nu}$ = 3064 (w), 3019 (w), 2937 (m), 2892 (w), 2833 (w), 1606 (w), 1530 (vs), 1355 (s), 802 (s), 757 (s) cm^{-1}. Anal. Calcd. for $C_{17}H_{15}NO_2$: C 76.96, H 5.70, N 5.28; found: C 76.73, H 5.83, N 5.19.

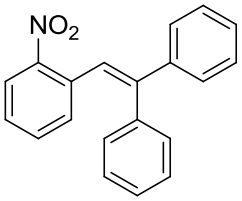


2-(3,4-Dihydronaphthalen-2-yl)-3-methylbenzothiophene (5.2-6ja)

Compound **5.2-6ja** was prepared following method B from potassium 3-methylbenzothiophene-2-carboxylate (161 mg, 0.7 mmol) and 3,4-dihydronaphthalen-2-yl methanesulfonate (243 mg, 1.05 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.7 mmol-scale reactions, compound **5.2-6ja** was obtained as a light yellow solid (210 mg, 54 %). M. p. 77-78 °C.

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.74 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.50-7.32 (m, 2H), 7.29-7.17 (m, 4H), 6.82 (s, 1H), 3.04 (t, *J* = 8.0 Hz, 2H), 2.84 (t, *J* = 8.0 Hz, 2H), 2.57 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 141.31, 139.64, 138.17, 134.60, 134.05, 133.49, 128.61, 127.39, 127.34, 126.67, 126.64, 124.24, 124.05, 122.05,

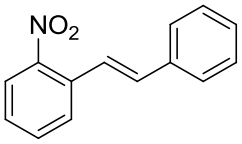
121.81, 28.96, 28.17, 13.44 ppm. EI-MS (70 eV), *m/z* (%): 276 (100) [M^+], 261 (20), 161 (11). IR (KBr): $\tilde{\nu}$ = 3053 (w), 3015 (w), 2935 (w), 2888 (w), 2832 (w), 1599 (w), 1484 (m), 1450 (m), 1433 (m), 749 (vs), 726 (s) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{19}H_{16}S$: 276.0973, *m/z* found: 276.1006.



(2-(2-Nitrophenyl)ethene-1,1-diyl)dibenzene (5.2-6ab)

Compound **5.2-6ab** was prepared following method B from potassium 2-nitrobenzoate (103 mg, 0.5 mmol) and 2,2-diphenylvinyl methanesulfonate (206 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-6ab** was obtained as a yellow solid (250 mg, 83 %). M.p. 133-134 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00-7.95 (m, 1H), 7.40-7.34 (m, 5H), 7.30-7.21 (m, 6H), 7.15-7.11 (m, 2H), 7.06-7.01 (m, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 148.90, 145.47, 142.21, 139.21, 133.74, 132.66, 132.31, 130.70, 128.26, 128.23, 128.16, 128.14, 127.65, 127.35, 124.26, 123.73 ppm. EI-MS (70 eV), *m/z* (%): 301 (1) [M^+], 285 (10), 284 (37), 256 (37), 119 (100), 105 (39), 92 (85). IR (KBr): $\tilde{\nu}$ = 3058 (w), 3021 (w), 1620 (w), 1602 (m), 1568 (w), 1512 (vs), 1443 (m), 1341 (s), 696 (s) cm^{-1}. Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.72, H 5.02, N 4.65; found: C 79.46, H 4.93, N 4.66.

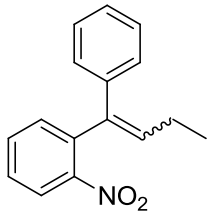


1-Nitro-2-styrylbenzene (5.2-6ac) [CAS-No. 4714-25-4]

Compound **5.2-6ac** was prepared following method B from potassium 2-nitrobenzoate (103 mg, 0.5 mmol) and styryl methanesulfonate (E/Z = 2.3/1) (149 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-6ac** was obtained as a mixture of E- and Z-isomers. (194 mg, 86 %, E/Z = 2.8/1, the ratio was determined according to the GC yields). After recrystallization from hexane, the pure E-isomer product was obtained as a yellow solid. M.p.66-67 °C.

(E)-1-Nitro-2-styrylbenzene [CAS-No. 4264-29-3]:

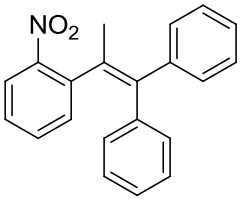
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.65-7.54 (m, 4H), 7.43-7.31 (m, 4H), 7.10 (d, *J* = 16.0 Hz, 1H), 6.79 (d, *J* = 12.0 Hz, 1H), 6.66 (d, *J* = 12.0 Hz, 1H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 147.84, 136.35, 133.70, 132.96, 132.82, 128.68, 128.47, 128.00, 127.81, 126.96, 124.80, 123.32 ppm. EI-MS (70 eV), *m/z* (%): 225 (1) [M^+], 208 (39), 180 (30), 152 (24), 119 (95), 92 (100), 77 (35) ppm. IR (KBr): $\tilde{\nu}$ = 3053 (w), 3027 (w), 1631 (w), 1603 (m), 1568 (m), 1510 (s), 1495 (m), 1342 (vs), 957 (s), 753 (vs), 739 (s), 698 (s), 690 (s) cm^{-1}.Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65, H 4.92, N 6.22; found: C 74.83, H 5.05, N 6.07.



1-Nitro-2-(1-phenylbut-1-en-1-yl)benzene (5.2-6ad)

Compound **5.2-6ad** was prepared following method B from potassium 2-nitrobenzoate (206 mg, 1.0 mmol) and 1-phenylbut-1-en-1-yl methanesulfonate (*E/Z* = 1/3.2) (113 mg, 0.5 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-6ad** was obtained as a light yellow oil. (100 mg, 40 %, *E/Z* = 1/2, the ratio was determined according to the ^{1}H NMR).

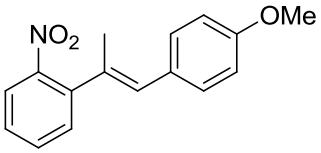
^{1}H-NMR (400 MHz, $CDCl_3$) (a mixture of *E*- and *Z*-isomers, ratio = 1/2): δ = 8.25 (d, *J* = 8.0 Hz, 1H), 8.03 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.78-7.69 (m, 1H), 7.68-7.62 (m, 1H), 7.59-7.48 (m, 2.5H), 7.43-7.37 (m, 1H), 7.36-7.30 (m, 1.5H), 7.31-7.18 (m, 8H), 6.18 (vinyl H of *Z*-isomer) (t, *J* = 8.0 Hz, 1H), 5.77 (vinyl H of *E*-isomer) (t, *J* = 8.0 Hz, 0.5H), 2.29 (quintet, *J* = 8.0 Hz, 1H), 1.95 (quintet, *J* = 8.0 Hz, 2H), 1.06 (t, *J* = 8.0 Hz, 1.5H), 1.00 (t, *J* = 8.0 Hz, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 140.29, 138.63, 136.96, 135.18, 134.86, 134.56, 132.83, 132.76, 132.25, 132.02, 129.62, 129.29, 128.28, 128.25, 127.93, 127.75, 127.31, 127.19, 126.44, 124.47, 123.93, 123.49, 23.34, 22.88, 14.08, 13.88 ppm. EI-MS (70 eV), *m/z* (%): 253 (11) [M^+], 236 (38), 221 (80), 207 (47), 206 (100), 195 (63), 178 (43), 167 (70), 105 (79). IR (NaCl): $\tilde{\nu}$ = 3060 (w), 3025 (w), 2968 (m), 2933 (w), 2874 (w), 1607 (m), 1526 (vs), 1495 (m), 1352 (vs), 763 (s), 701 (s) cm^{-1}. Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87, H 5.97, N 5.53; found: C 76.09, H 5.67, N 5.76.



(2-(2-Nitrophenyl)prop-1-ene-1,1-diyl)dibenzene (5.2-6ae)

Compound **5.2-6ae** was prepared following method B from potassium 2-nitrobenzoate (103 mg, 0.5 mmol) and 1,1-diphenylprop-1-en-2-yl methanesulfonate (223 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-6ae** was obtained as a light yellow solid (200 mg, 63 %). M. p. 91-92 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.84-7.76 (m, 1H), 7.50-7.22 (m, 10H), 7.05-6.85 (m, 5H), 2.14 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 148.86, 141.86, 141.74, 139.88, 139.78, 132.65, 132.16, 132.08, 129.57, 128.14, 127.59, 127.35, 126.92, 126.37, 124.36, 22.61 ppm. EI-MS (70 eV), *m/z* (%): 315 (2) [M^+], 283 (100), 165 (77), 133 (86), 104 (35). IR (KBr): $\tilde{\nu}$ = 3064 (w), 3023 (w), 2923 (w), 2853 (w), 1604 (w), 1568 (w), 1521 (vs), 1491 (m), 1441 (m), 1346 (s), 761 (s), 748 (s), 698 (vs) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{21}H_{17}NO_2$: 315.1259, *m/z* found: 315.1298.

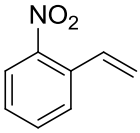


(*E*)-1-(1-(4-Methoxyphenyl)prop-1-en-2-yl)-2-nitrobenzene (5.2-6af)

Compound **5.2-6af** was prepared following method B from potassium 2-nitrobenzoate (103 mg, 0.5 mmol) and (E)-1-(4-methoxyphenyl)prop-1-en-2-yl methanesulfonate (187 mg, 0.75 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-6af** was obtained as a light yellow solid (197 mg, 73 %). M. p. 66-67 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.25 (dd, *J* = 4.0, 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.63 (d, *J* = 8.0 Hz, 2H), 6.49 (s, 1H),3.71 (s, 3H), 2.19 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 156.16, 148.43, 138.30, 133.63, 133.14, 131.43, 129.49, 129.22, 127.90, 127.39, 124.66, 113.49, 55.05, 25.92 ppm. EI-MS (70 eV), *m/z* (%): 269 (22) [M^+], 237 (59), 178 (33), 165 (26), 133 (100), 104 (73), 78 (21). IR (KBr): $\tilde{\nu}$ = 3010 (w), 2962 (w), 2905 (w), 2836 (w), 1605 (s), 1572 (m), 1523 (s), 1509 (vs), 1342 (vs), 1295 (m), 1248 (vs), 1178 (s), 1030 (s), 856 (m),

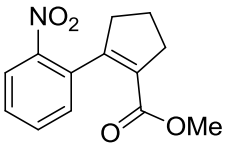
826 (m), 759 (m), 737 (m), 702 (m) cm^{-1}. Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36, H 5.61, N 5.20; found: C 71.15, H 5.81, N 5.08.



1-Nitro-2-vinylbenzene (5.2-6ag) [CAS No. 579-71-5]

Compound **5.2-6ag** was prepared following method B from potassium 2-nitrobenzoate (103 mg, 0.5 mmol) and vinyl methanesulfonate (183 mg, 1.5 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.5 mmol-scale reactions, compound **5.2-6ag** was obtained as a light yellow oil (81 mg, 54 %).

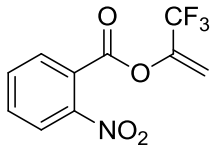
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.0 Hz, 1H), 7.68-7.54 (m, 2H), 7.47-7.37 (m, 1H), 7.26-7.11 (m, 2H), 5.76 (dd, *J* = 0.9, 16 Hz, 1H), 5.50 (dd, *J* = 0.9, 12 Hz, 1H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 147.90, 133.35, 133.07, 132.47, 128.48, 128.32, 124.39, 118.93 ppm. EI-MS (70 eV), *m/z* (%): 150 (2) [M^+ +1], 120 (79), 104 (29), 91 (84), 65 (100), 51 (60). IR (NaCl): $\tilde{\nu}$ = 3085 (w), 3028 (s), 2921 (m), 2871 (w), 1943, 1857, 1802, 1736, 1604 (m), 1497 (s), 1466 (s), 1378 (m), 1080 (m), 1030 (m), 728 (s), 694 (m) cm^{-1}.



Methyl 2-(2-nitrophenyl)cyclopent-1-enecarboxylate (5.2-6ah)

Compound **5.2-6ah** was prepared following method B from potassium 2-nitrobenzoate (220 mg, 1.05 mmol) and methyl 2-((methylsulfonyl)oxy)cyclopent-1-enecarboxylate (159 mg, 0.7 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.7 mmol-scale reactions, compound **5.2-6ah** was obtained as a light yellow oil. (90 mg, 26 %).

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.60 (dt, *J* = 2.0, 8.0 Hz, 1H), 7.45 (dt, *J* = 2.0, 8.0 Hz, 1H), 7.22 (dd, *J* = 2.0, 8.0 Hz, 1H), 3.50 (s, 3H), 2.92-2.74 (m, 4H), 2.10 (quintet, *J* = 8.0 Hz, 2H) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.04, 152.22, 147.47, 134.36, 132.90, 130.11, 129.17, 128.09, 124.16, 51.14, 40.63, 33.58, 22.42 ppm. EI-MS (70 eV), *m/z* (%): 247 (3) [M^+], 216 (11), 201 (41), 188 (39), 146 (89), 145 (100), 132 (63), 115 (77), 104 (18), 91 (21), 77 (26). IR (NaCl): $\tilde{\nu}$ = 3067 (w), 2952 (s), 2858 (m), 1714 (vs), 1651 (m), 1525 (vs), 1435 (s), 1352 (vs), 1258 (s), 1193 (m), 1126 (m), 1049 (m), 853 (m), 787 (m), 769 (m), 747 (m), 700 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{13}H_{13}NO_4$: 247.0845, *m/z* found: 247.0844.

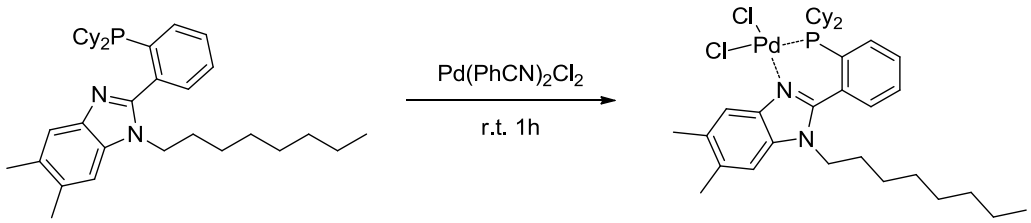


3,3,3-Trifluoroprop-1-en-2-yl 2-nitrobenzoate (5.2-6ai')

Compound **5.2-6ai'** was prepared following method B from potassium 2-nitrobenzoate (144 mg, 0.7 mmol) and 3,3,3-trifluoroprop-1-en-2-yl methanesulfonate (399 mg, 2.1 mmol) in a mixture of NMP (1 mL) and mesitylene (3 mL). After combining two identical 0.7 mmol-scale reactions, compound **5.2-6ai'** was obtained as a light yellow oil. (76 mg, 21 %).

^{19}F-NMR (376 MHz, $CDCl_3$): δ = - 71.97 (s, -CF_3) ppm. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 8.09-8.00 (m, 1H), 7.81-6.67 (m, 3H), 5.90-5.76 (m, 2H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 162.34, 147.65, 144.51 (q, J_{C-F} = 38.2 Hz), 133.47, 132.61, 129.85, 126.15, 124.34, 119.00 (q, J_{C-F} = 272.7 Hz), 109.42 (q, J_{C-F} = 3.0 Hz) ppm. EI-MS (70 eV), *m/z* (%): 167 (2), 150 (100), 104 (9), 76 (29). IR (NaCl): $\tilde{\nu}$ = 3142 (w), 3083 (w), 3034 (w), 1774 (vs), 1677 (m), 1541 (vs), 1352 (s) ,1281 (m), 1247 (m), 1197 (s), 1141 (vs), 1057 (m), 931 (m), 853 (m), 788 (m), 725 (m), 602 (m) cm^{-1}. EI-HRMS *m/z* calcd. for $C_{10}H_6F_3NO_4$: 261.0249, *m/z* found: 261.0234.

8.8.7 Synthesis of $PdCl_2$-L15 Complex

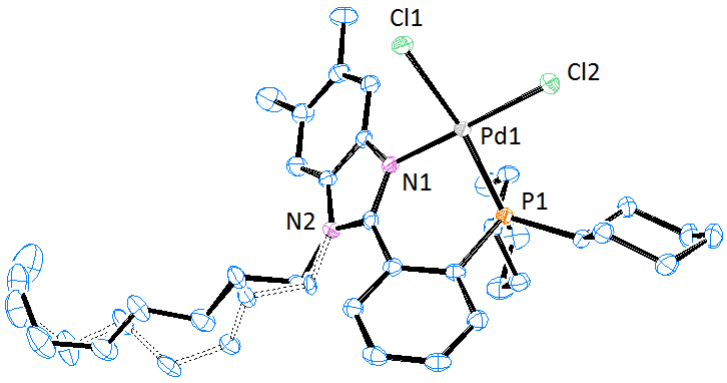


To a solution of **L15** (372 mg, 0.7 mmol) in 8 mL of dichloromethane, the solution of $Pd(PhCN)_2Cl_2$ (268 mg, 0.7 mmol) in 10 mL of dichloromethane was added dropwise under nitrogen. This mixture was kept stirring for 1h under nitrogen. After the complition of the reaction checked by TLC, the solution was filtered. The filtrate was concentrated under reduced pressure. Diethylether (10 mL) was added to the residue and dried again. The precipitated solid was filtered and washed with diethyl ether and hexane to give a yellow powder (445 mg, 0.63 mmol, 90 %). M.p. 233.2 °C (decomposed).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.65 (s, 1H), 7.77-7.59 (m, 4H), 7.13 (s, 1H), 4.13 (t, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 2.37 (s, 3H), 1.88-0.83 (m, 30H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 145.76, 145.68, 138.46, 135.35, 134.30, 134.18, 132.09, 131.99, 131.66, 130.90, 130.88, 130.70, 130.63, 130.32, 130.25, 129.07, 126.72, 126.35, 122.63, 110.20, 46.14, 31.57, 30.87, 29.72, 28.89, 28.76, 27.04, 26.92, 26.82, 26.55, 25.47, 22.50, 20.62, 20.33, 13.98 (unresolved

complex C-P splittings were observed) ppm. ^{31}P-NMR (162 MHz, $CDCl_3$): δ = 34.4 ppm. ESI-MS (70 eV), *m/z* (%): 743.2 $[M+Cl]^-$. IR (KBr): $\tilde{\nu}$ = 2926 (vs), 2853 (s), 1480 (m), 1464 (m), 1448 (s), 1424 (m), 1373 (m), 1204 (m), 1000 (m), 851 (m), 777 (m) cm^{-1}. Anal. Calcd. for $C_{35}H_{51}Cl_2N_2PPd$: C, 59.37, H 7.26, N 3.96; found: C 59.40, H 7.34, N 4.05.

8.8.8 Crystal Structure of $PdCl_2$-L15 Complex



Hydrogen atoms haven been omitted for clarity. Selected bond distance [Å] and angles [°]: Pd(1)-N(1) 2.0415 (16), Pd(1)-P(1) 2.2393 (5), Pd(1)-Cl(1) 2.3796 (5), Pd(1)-Cl(2) 2.2897 (5), C(13)-P(1) 1.839(2), N(1)-Pd(1)-P(1) 82.97(5), N(1)-Pd(1)-Cl(1) 90.49(5), N(1)-Pd(1)-Cl(2) 173.07(5), P(1)-Pd(1)-Cl(1) 170.060(18), P(1)-Pd(1)-Cl(2) 96.225(18), Cl(2)-Pd(1)-Cl(1) 91.158(18), C(13)-P(1)-Pd(1) 102.46(6), C(8)-C(13)-P(1) 119.02(15), C(7)-N(1)-Pd(1) 127.75(13), N(1)-C(7)-C(8) 124.24(17), C(13)-C(8)-C(7), 119.21(17).

Crystal data and structure refinement

Identification code	12029ocu	
Empirical formula	$C_{36}H_{52}C_{l5}N_2PPd$	
Formula weight	827.42	
Temperature	150(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.3547(3) Å	α= 79.796(3)°.
	b = 13.1988(5) Å	β= 70.872(3)°.
	c = 15.3560(5) Å	γ = 74.047(3)°.
Volume	1897.68(11) $Å^3$	
Z	2	
Density (calculated)	1.448 Mg/m^3	

Absorption coefficient	7.788 mm^{-1}
F(000)	856
Crystal size	0.41 x 0.20 x 0.18 mm^3
Theta range for data collection	3.06 to 62.65°.
Index ranges	-11<=h<=8, -15<=k<=15, -17<=l<=16
Reflections collected	12824
Independent reflections	6039 [R(int) = 0.0182]
Completeness to theta = 62.65°	99.3 %
Absorption correction	Analytical
Max. and min. transmission	0.3346 and 0.1425
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	6039 / 6 / 505
Goodness-of-fit on F^2	1.053
Final R indices [I>2sigma(I)]	R1 = 0.0238, wR2 = 0.0620
R indices (all data)	R1 = 0.0245, wR2 = 0.0624
Extinction coefficient	0.00295(11)
Largest diff. peak and hole	0.539 and -0.799 e.$Å^{-3}$

8.9 References

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CURRICULUM VITAE

Personal Information

Name	Bingrui Song
Nationality	Chinese
Address	Wackenmühlstraße 16, App.240 67655, Kaiserslautern, Germany
E-mail	bsong@chemie.uni-kl.de

Education

10/2009 – 03/2013	PhD studies in Organic Chemistry, Department of Chemistry, TECHNICAL UNIVERSITY KAISERSLAUTERN. Advisor: Prof. Dr. Lukas J. Gooßen. Thesis: *Palladium-catalyzed C–C bond formations via activation of carboxylic acids and their derivatives.*
08/2006 – 07/2009	M.Sc. studies in Organic Chemistry, Department of Chemistry, SHANGHAI UNIVERSITY. Grade: GPA 3.7 (4.0 highest – 0.0 lowest mark). Advisor: Prof. Dr. Bin Xu. Thesis: *Regioselective Carbon-Halogen Bond Formation via Palladium Catalysis*.
08/2001 – 07/2004	B.Sc. in Chemistry Science, Department of Chemistry, SHANGHAI UNIVERSITY. The degree was achieved one year ahead of time. Grade: GPA: 3.2. Advisor: Prof. Jianmin Zhang Thesis: *The synthesis of imines and quinoline derivatives under microwave conditions*.
07/2001	Graduation from Weihui No.1 Senior High School, Henan Province

Awards and Honors

BAYER Fellowship (**2010-2011**)
STIBET Scholarship (DAAD) of TU Kaiserslautern (**2010**)
Outstanding Thesis (Master) Award of Shanghai (**2010**)
"Kwang-Hua" Scholarship (**2008**)
1st scholarship of Shanghai University (**2003**)
"Three Goods" student of Shanghai University (**2003**)
2nd National Scholarship (**2002**)
1st scholarship of Shanghai University (**2002**)
"Three Goods" student of Shanghai University (**2002**)