Sustainable Methods for the Catalytic Regioselective Transformation of Aromatic Carboxylic Acids *via* C–COOH and C–H Bond Cleavage

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angefertigt im Arbeitskreis von

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To my parents

„Fantasie ist wichtiger als Wissen, denn Wissen ist begrenzt. Fantasie aber umfasst die ganze Welt und alles, was wir je wissen und verstehen können.“

Albert Einstein

Die vorliegende Arbeit wurde im Zeitraum von April 2014 bis August 2017 im Arbeitskreis von Prof. Dr. Lukas J. Gooßen am Fachbereich Chemie der Technischen Universität Kaiserslautern angefertigt.

Promotionskommission

Vorsitzender:	Prof. Dr. Stefan Kubik
Berichterstatter:	Prof. Dr. Lukas J. Gooßen
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Eidesstattliche Erklärung

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

Kaiserslautern, den _____ _____

Agostino A. Biafora

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Abbreviations

Ac	acetyl	Me	methyl group
acac	acetylacetone	Me_4Phen	3,4,7,8-tetramethyl-1,10-phenanthroline
Ad	adamantyl group	MeCN	acetonitrile
ASA	acetylsalicylic acids	$MesCO_2H$	2,4,6-Trimethylbenzoic acid
Asn	asparagine	m.p.	melting point
ATR	attenuated total reflection	MPAA	monoprotected amino acid
Boc	*tert*-butyloxycarbonyl group	MS	mass spectrometry
Bu	butyl group	µW	microwave
C_6H_6	benzene	NBD	norbornadiene
C_6Me_3	mesitylene	NCyP	*N*-cyclohexyl-2-pyrrolidone
C_6Me_6	hexamethylbenzene	n.d.	not detected
Cbz	benzyloxycarbonyl group	NHC	*N*-heterocyclic carbene
CMD	concerted metallation deprotonation	NMP	*N*-methyl-2-pyrrolidone
COD	1,5-cyclooctadiene	NMR	nuclear magnetic resonance
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl	*o*-	*ortho*-
Cy	cyclohexyl group	OAc	acetoxyl group
DABCO	1,4-diazabicyclo[2.2.2]octane	oct	octyl group
DavePhos	2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl	OLED	organic light emitting diodes
dba	dibenzylideneacetone	OMe	methoxyl group
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	OMs	methylsulfonyl group
DCC	dicyclohexylcarbodiimide	OTf	trifluoromethanesulfonyl group
DCE	1,2-dichloroethane	OTs	*p*-toluenesulfonyl group
DFT	density functional theory	Ox	oxidant
DG	directing group	*p*-	*para*-
DMA	dimethylacetamide	PC	propylene carbonate
DMF	dimethylformamide	*p*-cym	*para*-cymene
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone	Ph	phenyl group
DMSO	dimethylsulfoxide	Ph_2phen	4,7-diphenyl-1,10-phenanthroline
DSSC	dye-sensitized solar cell	Phe	phenylalanine
E	electrophilic coupling partner	PhMe	toluene
EDG	electron donating group	phen	1,10-phenanthroline
EI	electron impact ionization	piv	pivaloyl group
eq.	equivalents	ppm	parts per million
ESI	electron spray ionization	Pro	proline
Et	ethyl group	quin	quinoline

et al.	et alii	R	organic residue
EWG	electron withdrawing group	SA	salicylic acid
FG	functional group	S_EAr	electrophilic aromatic substitution
FT	Fourier transform	SPhos	2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
FWHM	full width at half maximum	synth-tactical	synthetic and tactical
GC	gas chromatography	^{t}AmOH	tert-amyl alcohol
gen.	generation	TBAOH	tert-butylammonium hydroxide
$GuanCO_3$	guanidine carbonate	^{t}BuCN	tert-butylnitrile
het	hetero	temp.	temperature
HFIP	hexafluoroisopropanol	TFA	trifluoroacetic acid
HOBt	1–hydroxybenzotriazole	TLC	thin-layer chromatography
HRMS	high resolution mass spectrometry	TM	transition metal
Ile	isoleucine	TMEDA	tetramethylethylenediamine
incorp.	incorporation	TOF	time-of-flight
^{i}Pr	isopropyl group	Tol	tolyl group
IR	infrared radiation	Val	valine
JohnPhos	(2-biphenyl)di-tert-butylphosphine	vs	versus
M	metal	XPhos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl
m-	*meta*-	XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Numbering of compounds

The present work mainly consists of original published manuscripts. Therein, all compounds were numbered independently. For the sake of clarity, the numbers assigned within the publications remain unchanged. However, in the corresponding subchapters all compounds were numbered individually. Compounds were newly numbered if they are not mentioned in the publications but are mentioned in the present text. In order to avoid the same terminal designation, especially in the experimental section, the numbering is composed of the corresponding chapter level followed by a second consecutive number. For instance, the number assigned to the third compound in the subchapter 3.1.2 is **3.1.2-3**. In the case of strongly generalized schemes that are supposed to shed light on reaction concepts, the numbering is fully omitted. All intermediates present in catalytic cycles were numbered with roman numerals.

Publications

Most results of the present work were published in scientific journals:

1. J. Tang, A. Biafora, L. J. Gooßen *Angew. Chem.* **2015**, *127*, 13324–13327; *Angew. Chem. Int. Ed.* **2015**, *54*, 13130–13133: *Catalytic Decarboxylative Cross-Coupling of Aryl Chlorides and Benzoates without Activating ortho Substituents*.
2. L. Huang, A. Biafora, G. Zhang, V. Bragoni, L. J. Gooßen *Angew. Chem.* **2016**, *128*, 7047–7051; *Angew. Chem. Int. Ed.* **2016**, *55*, 6933–6937: *Regioselective C–H Hydroarylation of Internal Alkynes with Arenecarboxylates: Carboxylates as Deciduous Directing Group.*
3. A. Biafora, T. Krause, D. Hackenberger, F. Belitz, L. J. Gooßen *Angew. Chem.* **2016**, *128*, 14972–14975; *Angew. Chem. Int. Ed.* **2016**, *55*, 14752–14755: *ortho-C–H Arylation of Benzoic Acids with Aryl Bromides and Chlorides Catalyzed by Ruthenium.*
4. A. Biafora, B. A. Khan, J. Bahri, J. M. Hewer, L. J. Gooßen *Org. Lett.* **2017**, *19*, 1232–1235: *Doubly Regioselective C–H Hydroarylation of Unsymmetrical Internal Alkynes Using Carboxylates as Deciduous Directing Groups.*
5. A. Biafora, L. J. Gooßen *Synlett* **2017**, DOI: 10.1055/s-0036-1588450: *New Reaction Mode in Carboxylate-Directed C–H Functionalizations: Carboxylates as Deciduous Directing Groups.*
6. A. Biafora, P. Weber, L. J. Gooßen *Org. Process Res. Dev.* **2017**, manuscript in preparation: *What Makes the Activity of Pd(dba) Unpredictable?*.
7. S. Trita, A. Biafora, M. Pichette-Drapeau, P. Weber, L. J. Gooßen, **2017**, manuscript in preparation: *Ruthenium-Catalyzed ortho C–H Allylation of Benzoic Acids*.

Patent

Results arisen from projects in collaboration with Umicore AG & Co. KG have been submitted for patenting:

1. A. Biafora, L. J. Gooßen **2014**, patent pending: *One-Pot Synthesis of 1st and 2nd Generation Buchwald pre-catalysts.*

Poster presentations

Most results of the present work were presented by me at international conferences:

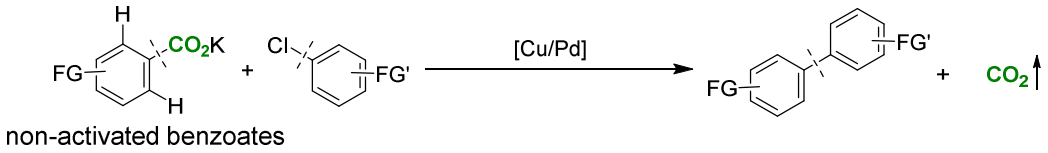
1. A. Biafora, P. Weber, L. J. Gooßen, 18th IUPAC International Symposium on Organometallic Chemistry, Barcelona **2015**: *Spectroscopic and Catalytic Investigations of Different Pd(0)dibenzylideneacetone Species.*
2. J. Tang, A. Biafora, L. J. Gooßen, 18th IUPAC International Symposium on Organometallic Chemistry, Barcelona **2015**: *Catalytic Decarboxylative Cross-Coupling of Aryl Chlorides and Benzoates without Activating ortho Substituents.*
3. A. Biafora, L. Huang, G. Zhang, V. Bragoni, L. J. Gooßen, 15th Belgian Organic Synthesis Symposium, Antwerp **2016**: *Regioselective C–H Hydroarylation of Internal Alkynes with Arenecarboxylates: Carboxylates as Deciduous Directing Groups.*

Table of contents

1. Abstract

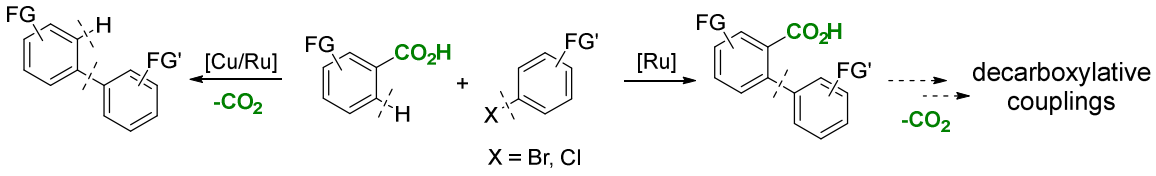
In the present work the concept of decarboxylative couplings and the strategy to use carboxylates as directing groups for C–H functionalizations have been decisively improved in three ways. These concepts emphasize the multifaceted nature of aromatic carboxylic acids as expedient starting materials in homogeneous catalysis to construct highly desirable molecular scaffolds in a straightforward fashion.

In the first project, the restriction of decarboxylative biaryl synthesis to exclusively couple aryl halides with *ortho*-substituted benzoic acids has been overcome by a holistic optimization of a Cu/Pd bimetallic catalyst system (**Scheme 1**). Long ago postulated, this is now the proof that decarboxylative cross-couplings are not intrinsically limited to different decarboxylation propensities of benzoic acids or hampered by excess halides, accessing for the first time the entire spectrum of aromatic carboxylic acids as starting materials for the decarboxylative biaryl synthesis.



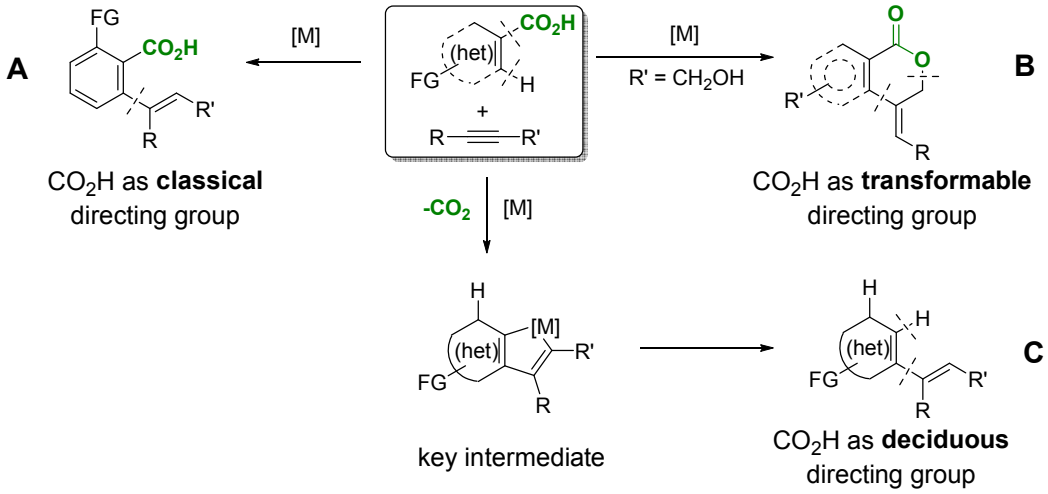
Scheme 1: Decarboxylative cross-coupling of non-*ortho*-substituted benzoates with aryl chlorides.

The second project uses the carboxyl moiety as directing group for the *ortho*-arylation with aryl bromides and -chlorides catalyzed by comparatively inexpensive ruthenium. The carboxylic acid group remains untouched after the *ortho*-functionalization giving the possibility to a wealth of further diversifications *via* decarboxylative *ipso*-substitutions. Within the same project, a Cu/Ru bimetallic catalyst system was found to be able to switch the decarboxylative biaryl coupling from the *ipso*- to the *ortho*-position, complementing the Cu/Pd system developed in the first project (**Scheme 2**).



Scheme 2: Carboxylate directed *ortho*-arylation with aryl bromides and -chlorides.

In a third project, a redox neutral C–C bond formation revealed the full synthetic potential of the carboxyl group. The CO_2H moiety acts as a classical directing group for the C–H hydroarylation of internal alkynes to form highly desirable 2-vinyl benzoic acids (**Scheme 3A**). With propargylic alcohols the hydroarylation is followed by an *in situ* esterification, showing that after easing the C–H cleavage, the directing group can be transformed into another functional group, thus, acting as a transformable directing group (**Scheme 3B)**. Most importantly, a new fascinating reaction mode is activated by embedding the decarboxylation within the C–H functionalization event. This mode of action is capable to solve regioselectivity issues that inherently occur when dealing with carboxylates as directing groups. A so-called deciduous directing group is cast off simultaneously within the C–H functionalization event, resulting in an inherently monoselective pathway (**Scheme 3C**).



Scheme 3: Multipurpose directing ability of a carboxylic acid group.

These methods were developed with the permanent goal of ensuring high sustainability. They do require neither pre-functionalized starting materials nor additional oxidants and provide access to a number of chemically relevant molecules from abundant, inexpensive and toxicologically innocuous educts.

2. Structure of the thesis

The present thesis is written in a cumulative form. The regioselective catalytic transformation of aromatic carboxylic acids covers the main part of this work. Based on the doctoral regulation of a cumulative dissertation, this work contains 5 original and published manuscripts. Sources cited in the present work as well as the citations within the depicted original publications are part of the corresponding projects. A detailed statement of contributions of each author is listed in front of the depicted publications.

The introduction emphasizes the importance and characteristics of aromatic carboxylic acids as well as their application in regioselective transformations, ranging from classical to modern synthetic approaches. Herein, the tremendous progress experienced in this field over the past decade exemplifies the multifaceted nature of aromatic carboxylic acids as a privileged starting material for a plethora of catalytic diversifications constituting an advantageous alternative to preformed carbon nucleophiles. Moreover, a new reaction concept in carboxylate-directed C–H functionalizations - carboxylates as *deciduous* directing groups - is presented as a key technology for the catalytic regioselective construction of complex molecules from readily available precursors.

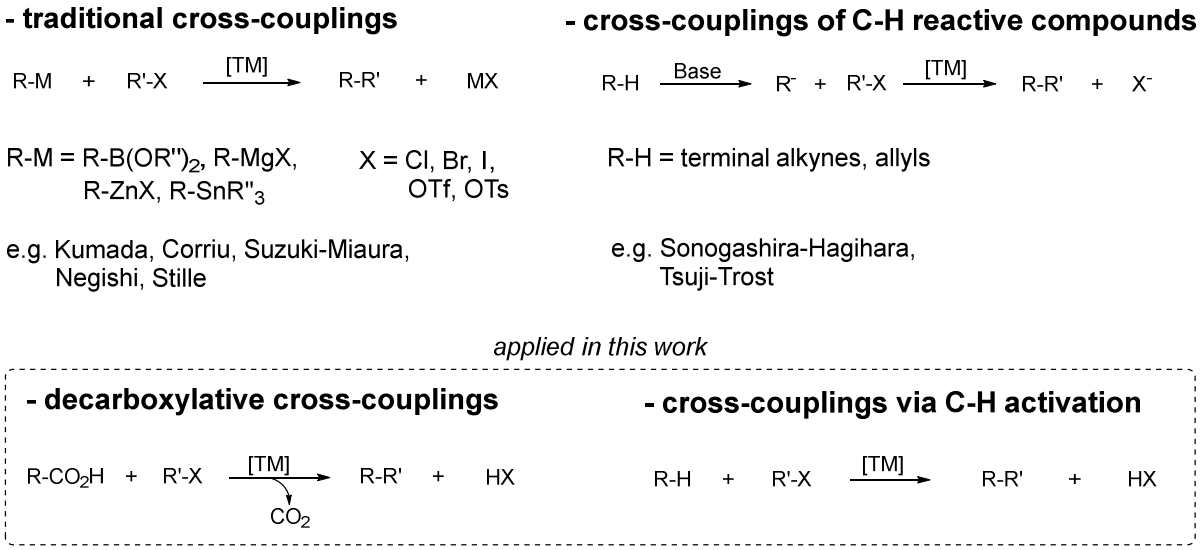
Subsequently, the section “research objectives” is supposed to pinpoint the remaining central challenges in catalytic transformations of benzoic acids as well as the conceptual strategies that have been applied to face them. The “result and discussion” chapter consists of each elaborated project. They are briefly introduced and contain a depicted reprint of each respective original and published work.

In the experimental section, all analytical and preparative instruments as well as the standard parallel reaction set-up are specified. All procedures for the synthesis of the used starting material as well as all isolated compounds are given. This part consists mainly of the supporting information of each published work.

References and a brief CV are given in the end of this document.

3. Introduction

The development of sustainable methods for the concise construction of complex organic compounds from simple molecules is a major objective in modern synthetic chemistry.[1–4] Based on the founding works of Ullmann[5] and Goldberg[6] in the early 20th century, the synthesis of new C–C or C–heteroatom bonds mostly rely on transition metal-catalyzed cross-couplings of preformed organometallic reagents, such as organoboronates, Grignard reagents or organotin compounds, with carbon electrophiles (**Scheme 4**, left top).[7–11] Back then, these discoveries were at the forefront of the advancement of research and their significance was certified with the Nobel Prize in Chemistry in 2010 for "*for palladium-catalyzed cross couplings in organic synthesis*" awarded to Negishi, Suzuki and Heck.[12] Although highly effective, these reactions have innate disadvantages such as laborious preparation of sensitive organometallic reagents and the production of copious amounts of waste, which are reputed to be ecologically as well as toxicologically alarming. Due to the increasing level of environmental awareness over the past decades, the need for sustainable approaches to replace these traditional coupling reactions gained increased attention.[13–19]



Scheme 4: Approaches for C–C or C–heteroatom bond formations.

A major improvement regarding waste and toxicity reduction is witnessed by Sonogashira-Hagihara or Tsuji-Trost type reactions (**Scheme 4**, right top).[20–22] Carbon nucleophiles are generated from innately reactive compounds, such as C–H acidic compounds or allylic scaffolds bearing leaving groups, avoiding pre-synthesis of organometallic reagents and

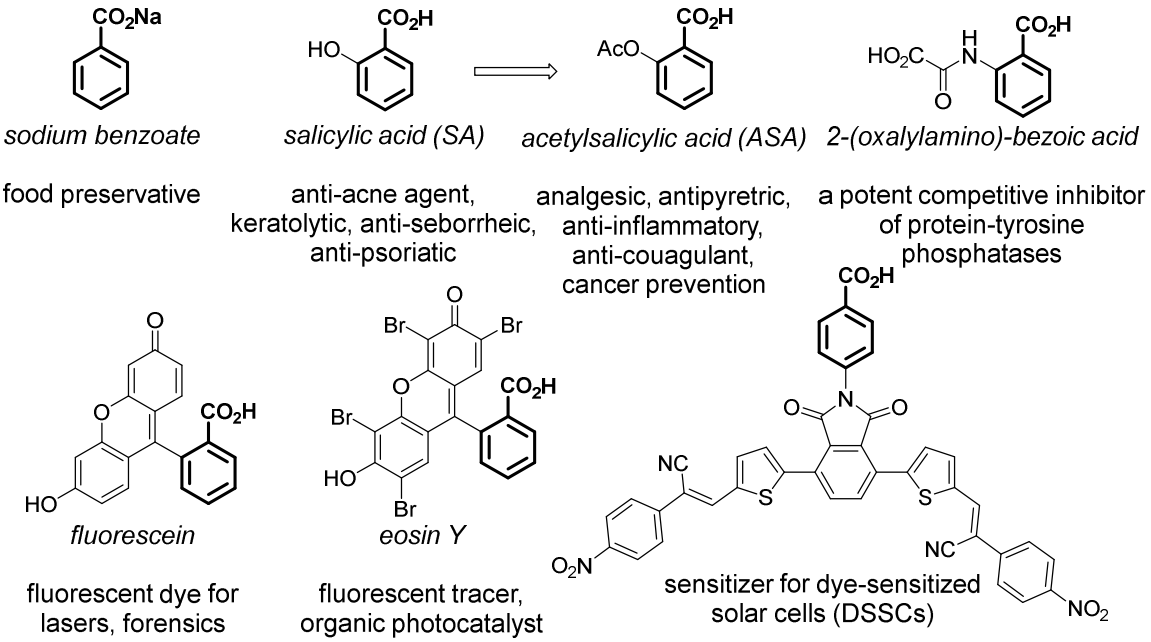
accruing metal salts as waste. These systems have been applied in numerous, highly valuable transformations. However, these reactions are limited to the intrinsic reactivity of either coupling partner and are therefore limited in scope and functional group tolerance. In the meantime, two major strategies have been established that diminish the major drawbacks of traditional cross-coupling reactions to a certain extend (**Scheme 4**, bottom). Firstly, the decarboxylative cross-coupling as one of the alternative strategies is particularly worth mentioning. Carboxylic acids or carboxylate salts are readily available in great structural diversity, are toxicologically harmless and can be easily handled under ambient conditions. Therefore, no laborious preparation compared to classical carbon nucleophiles are required, which additionally guarantees a certain quality of the starting material. Moreover, innocuous CO_2 is released in the course of the reaction instead of stoichiometric amounts of often toxic metal salts. Decarboxylative couplings of aromatic carboxylates allow the *ipso*-substitution with various carbon residues such as aryl, vinyl, allyl or heteroaryl groups, with alkoxy, amino, halo and other functionalities.[23–30] The second strategy, which avoids preformed organometallic coupling partners, is C–H activation (**Scheme 4**, right bottom). C–H bonds, which are chemically inert under traditional cross-coupling conditions, are used as anchor points for the generation of carbon nucleophiles and the bond formation occurs with relatively high atom economy.[31–44] The C–H bond cleavage is triggered either by its intrinsic reactivity (e.g. acidic C–H bonds), or is aided by strong coordinating moieties that bring the metal into their proximity. The nature of the directing group is decisive to keep the high atom economy for which C–H activation reactions are designed. However, in most cases particularly efficient directing groups need to be pre-installed and removed *a posteriori*, thus deteriorating the atom efficiency. In this context, aromatic carboxylic acids are ideal substrates as the relatively small carboxylate group has shown the ability to trigger *ortho*-C–H functionalizations and can be removed with particular ease, maintaining high levels of atom efficiency.[45–50]

The following work consists in the development of reactions which apply the strategies of decarboxylative cross-couplings and carboxylate-directed C–H functionalizations. Moreover, it includes examples in which both approaches are merged into one to overcome selectivity issues, which is a major limitation in C–H activation reactions. It gives an overview of the full synthetic potential of aromatic carboxylic acids in modern catalytic cross-coupling chemistry to achieve inexpensive, waste-minimized, and regioselective formation of new, chemically relevant scaffolds.

3.1. Aromatic carboxylic acids

3.1.1. Occurrence, application and characteristics of aromatic carboxylic acids

Implementing aromatic carboxylic acids as versatile building blocks in organic synthesis is highly desirable because these acids are among the most privileged naturally occurring structural motives.[51–54] The so-called benzoic acid is the simplest example of aromatic carboxylic acids. It contains a carboxyl group directly bound to a benzene ring and is a colorless crystalline solid (m.p.: 122 °C) with faint, pleasant odor.[55] It naturally occurs in numerous berries, such as cranberries, bilberries and cowberries, is also a component in honey and it is formed in yogurt and curdled milk as a result of microbial decomposition of hippuric acid.[56–61] Benzoic acid was first described by Nostradamus in 1556 and obtained by sublimation from gum benzoin, a resin from several trees of the genus *Styrax*. Despite that, the right elemental composition was first reported almost 300 years later by Wöhler and Liebig in 1832.[62] With a pK_a-value of 4.20, benzoic acid is slightly more acidic than acetic acid (pK_a = 4.76), but less acidic than formic acid (pK_a = 3.77). Thus it is present in its deprotonated form under physiological conditions.[63] The acidity of a benzoic acid derivative can vary substantially depending on the electronic properties of a substituent. The Hammett equation is a powerful tool to predict the acidity of benzoic acids carrying *para*- and *meta* substituents.[64–67]

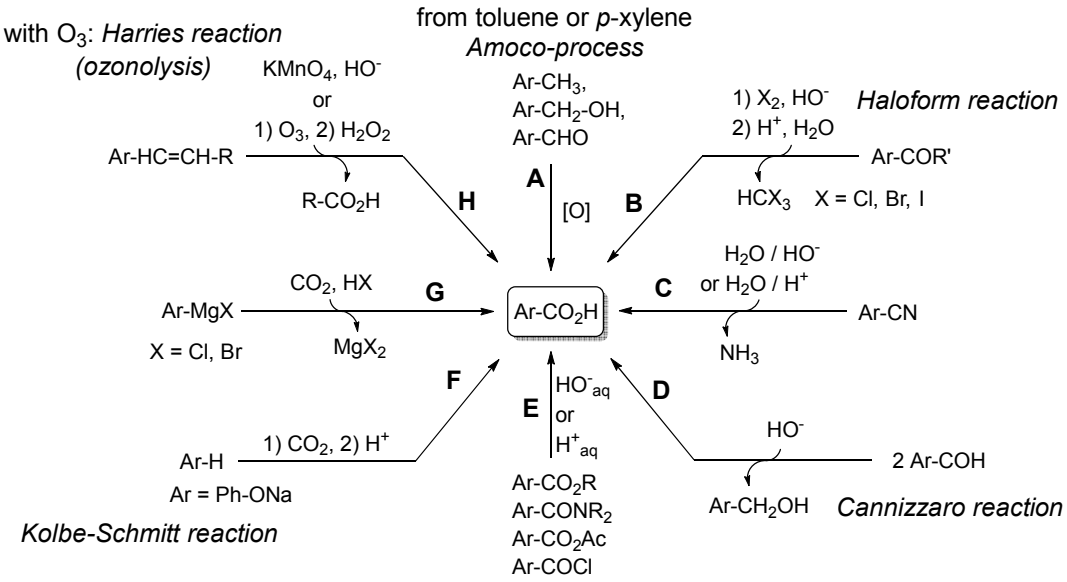


Scheme 5: Selected examples for benzoic acid-based pharmacophores and functional materials.

The pharmacological activity of carboxylic acid-based compounds is usually enhanced as a result of electrostatic interactions caused by the inherent polarity of the carboxyl group. This aspect is often critical for sufficient binding on a specific target.[68] In fact, benzoic acid itself already has antifungal properties and is therefore often used as a food preservative in beverages as a sodium salt (**Scheme 5**).[57,69–71] In general, aromatic carboxylic acids are particularly popular among chemists as they show great versatility serving as potential biocide as well as drug candidates, functional materials, food additives and recently as organic photocatalysts (**Scheme 5**).[68–91] Derivatives of benzoic acids are known to be biologically active and were used in ancient times for medicinal purposes.[92–94] Even in the era of Hippocrates (400 B.C.), people were advised to chew on the bark of white willow (*Salix alba*) to treat fever and inflammations. The extract of the willow bark contains a cocktail of compounds, some of which are still used today to cure low back pains and osteoarthritis.[95–97] One of these components is salicylic acid, which was first discovered by Piria in 1838 as an oxidation product of salicin.[98] One year later Löwig and Weidmann, extracted salicylic acid directly from meadowsweet.[99] Albeit its antipyretic and anti-inflammatory effect, salicylic acid as active ingredient became soon unpopular in pharmaceutical chemistry because of the numerous documented adverse reactions by oral intake ranging from strong gastric irritation to hearing loss.[100–103] Despite this medical impairments, it is still a commonly used additive in creams and solutions to treat acne.[71,102] In mid to late 19th century, acetylsalicylic acid (better known as Aspirin©) became an increasingly famous, less irritating surrogate of salicylic acid. Initially commercialized by Bayer, it is now one of the most consumed pharmaceuticals worldwide.[104,105] compared to their pharmaceutical application, the utilization of aromatic carboxylic acids in functional materials is less common. Nevertheless, due to the electron withdrawing effect of the carboxyl group and extended delocalized π-system, aromatic carboxylic acid derivatives are merging as electron acceptors in sensitizers for organic light emitting diodes (OLEDs) and dye-sensitized solar cells (DSSCs).[89,90,106–109] Moreover, the carboxyl moiety shows particular convenience in serving as anchor point for the straightforward fixation of the dye to a TiO_2 semiconducting surface.[110–113] Beyond that, the so-called xanthane dyes, such as eosin Y, rhodamine, fluoresceine and rose bengal, which contain a benzoic acid moiety, are commonly used as fluorescent target agents or laser dyes as well as organic photocatalysts.[91,114–119] The latter is recently emerging as a powerful application to substitute expensive transition metal catalysts for cross-coupling chemistry.[120]

3.1.2. Synthesis of aromatic carboxylic acids

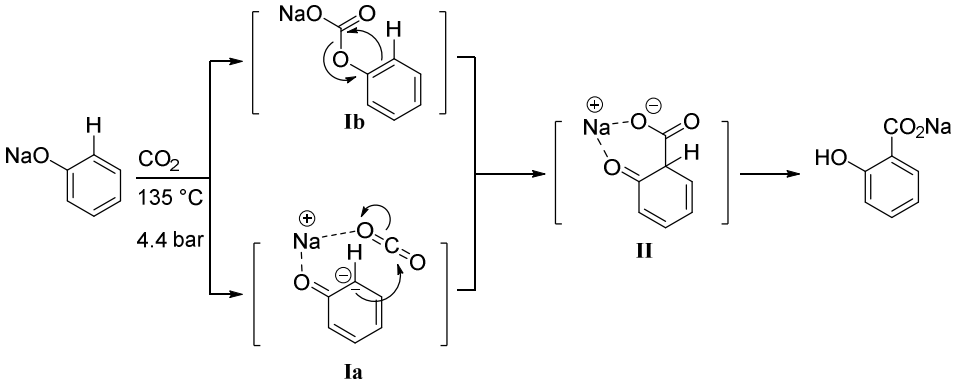
The wide spectrum of applications for aromatic carboxylic acids inspired chemists to provide straightforward approaches for the synthesis of benzoic acid and its derivatives. Traditionally, (hetero-)aromatic carboxylic acids are synthesized *via* oxidation of the corresponding alcohols or aldehydes. However, the necessary strong oxidants, such as potassium permanganate, potassium dichromate or Jones reagent (a solution of CrO_3 in H_2SO_4) are ecologically questionable.[121–125] An alternative approach utilized within the industry is to convert toluene or *p*-xylene into benzoic acid or *p*-phthalic acid, respectively, by the oxidation of the benzylic position with molecular oxygen in the presence of cobalt, manganese or vanadium catalysts (Amoco process, **Scheme 6A**).[121–123,126–130]



Scheme 6: Traditional and industrial syntheses for aromatic carboxylic acids.

α-Acidic carbonyl compounds, e.g. ketones, react with halides under basic conditions to the corresponding carboxylic acids and chloro-, bromo-, or iodoform, depending on the used halide (haloform reaction, **Scheme 6B**).[131–133] Under both acidic or basic conditions, nitriles as well as esters, amides, anhydrides and acid chlorides, can be hydrolyzed to provide carboxylic acids from various starting materials (**Scheme 6C** and **E**).[121,122] The Cannizzaro reaction offers the possibility to convert two equivalents of aldehydes into one equivalent of the corresponding acid and alcohol, respectively (**Scheme 6D**).[134–136] However, due to strong basic conditions, scope and functional group tolerance are very limited. Aromatic carboxylic acids can also be prepared by the direct implementation of CO_2 into a carbon nucleophile. Grignard reagents offer the opportunity to formally transform a C–X bond into a C–CO_2H

bond (**Scheme 6G**).[121,122,137] However, multiple steps and stoichiometric metal waste are major drawbacks of this approach. A more elegant carboxylation reaction was discovered by Hermann Kolbe in 1860 and later on improved by Rudolf Schmitt, commonly known as Kolbe-Schmitt reaction (**Scheme 6F**).[138–141] Sodium phenolate is treated with CO_2 (4.4 bar) at 135 °C and after hydrolysis exclusively yields the *ortho*-hydroxy benzoic acid; also known as salicylic acid.[142] By increasing the temperature to 185 °C in combination with NaH as base, the reaction requires only 1 atm of CO_2.[143] To date, the exact mechanism remains unclear, however, the high regioselectivity for the *ortho*-substitution is presumed to be a result of an *in situ* formed complex between the sodium phenolate and carbon dioxide (**Scheme 7**, **Ia**) or of an intermediary formed carbonate (**Scheme 7**, **Ib**).[105,142] It is worth mentioning, that the corresponding potassium phenolates react to the *para*-hydroxy benzoic acids, which is expected for a S_EAr-type reaction. The potassium cation is too large and therefore not capable to form the corresponding chelate assisted intermediate **II** depicted in **Scheme 7**.[144]

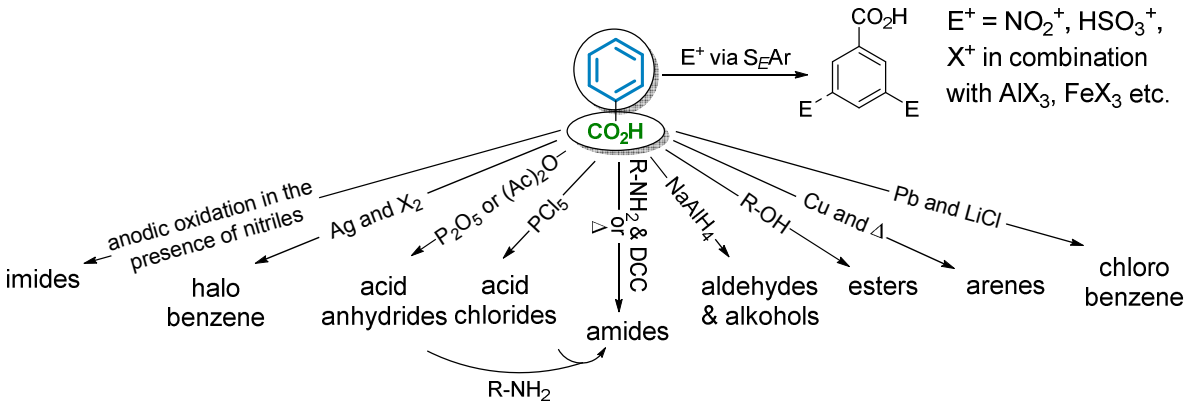


Scheme 7: The Kolbe-Schmitt reaction.

This reaction is generally applicable to various phenols including the ones with polycyclic and even heterocyclic aromatic cores (usually available in considerable structural diversity *via* Hantzsch condensation),[121,124] and is (to this day) the industrially preferred approach to synthesize salicylic acid.[105,142] More modern approaches for the direct implementation of CO_2 into an aromatic C_{sp2}–H or C_{sp2}–Halogen bond that allow more moderate reaction temperatures, broader scope, and higher selectivity, rely on transition metal catalysts such as Rh, Ni, Pd, or strong, Al-, Fe-, Cu- and Au-based Lewis acids.[145–156] Albeit aliphatic carboxylic acids constitute another highly important class of compounds, their preparation as well as their diversification go beyond the scope of this work and are therefore not included in this thesis.

3.2. Classical diversification of aromatic carboxylic acids

Traditional diversifications of aromatic carboxylic acids are mostly governed by transformations of the reactive CO_2H group. Due to the strong polarity of the carbonyl bond and the relatively high acidity of the hydroxyl group, nucleophilic additions/substitutions as well as acid/base reactions are very commonly used synthetic tools to derivatize benzoic acids in a rather straightforward fashion (**Scheme 8**, top).[124,137]



Scheme 8: Overview of classical diversifications of benzoic acids.

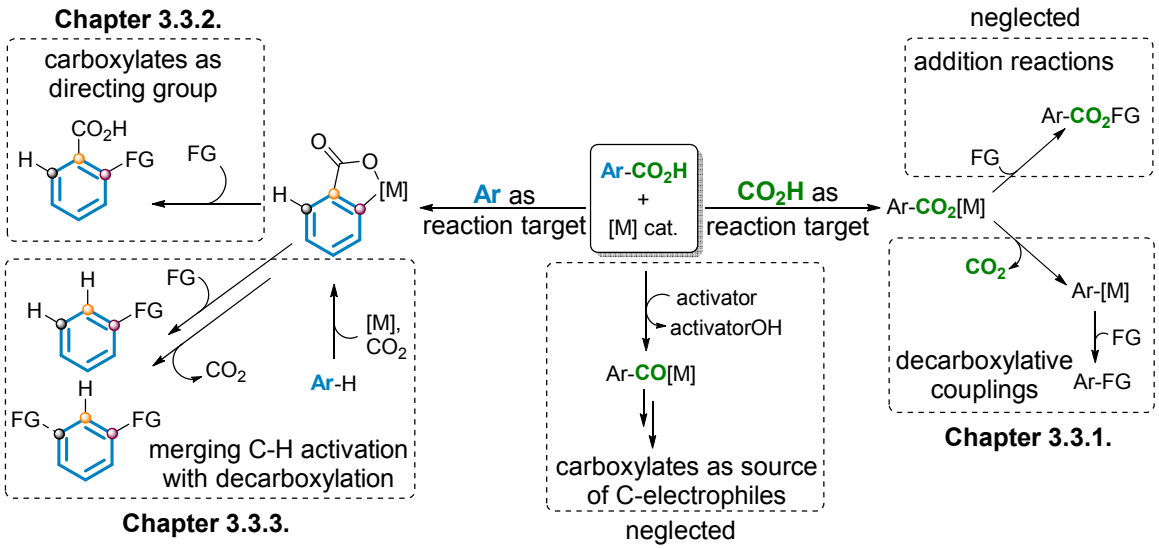
As depicted in **Scheme 8** the carboxyl group offers numerous possibilities for transformations.[131,137] Apart from more conventional reactions, such as esterification, reduction or conversion into more reactive species, e.g. acid chlorides or anhydrates, carboxylic acids can be used as starting materials for other valuable synthons in organic chemistry.[121,122,127] With the Hunsdieker reaction, halo arenes can be formed in a rather efficient radical pathway, in which the halide is installed selectively into the *ipso*-position.[157] Chlorobenzene on the other hand can also be accessed *via* the Kochi reaction.[157] However, due to the stoichiometric amounts of toxic $Pb(OAc)_4$ used as an oxidant the synthetic utility of this reaction is somewhat restricted. Likewise, the direct amidation of acids can be achieved if the acid is activated *in situ via* an active ester with, for instance, dicyclohexylcarbodiimide (DCC). Very often, other additional reagents such as 1–hydroxybenzotriazole (HOBt), are needed for an efficient amidation. Due to the poor atom economical balance, this reaction is highly undesirable, yet it represents one of the most established method for peptide coupling in laboratory to date.[158] Another rather rudimentary way to form amides directly, yet with very restricted functional group tolerance, is the vigorous thermal treatment of the acid and amine precursors. The anodic oxidation of benzoic acid *via* Kolbe electrolysis in presence of

nitriles is one way to prepare imides. However, depending on the nitrile used, the reaction can also lead to the formation of anthranilic acid derivatives. [159–163] Interestingly, in aqueous solution Fichter and Uhl observed that, upon electrochemical oxidation, benzoic acid forms a mixture of hydroxybenzoic acid, hydroquinone and catechol.[164] Another important reaction that will be explicitly discussed within the next chapters, is the metal promoted extrusion of CO_2 to form the corresponding arenes.[28,30]

The aromatic core on the other hand is traditionally functionalized *via* electrophilic aromatic substitutions (S_EAr) (**Scheme 8**, top).[137,157]. A wealth of electrophilic functional groups can be installed this way. As a result of the negative mesomeric effect of the carboxyl moiety, the electrophile is usually directed into the *meta*-position. However, harsh reaction conditions and often poor selectivity with respect to mono- vs disubstitutions regularly occur.

3.3. Transition metal-catalyzed diversifications of aromatic carboxylic acids

Reactions of benzoic acids in the presence of a transition metal catalyst further display how versatile these substrates are. Transformations of the reactive CO_2H groups can be performed much more gently if catalyzed by metals. For that matter, functional group tolerance as well as chemo-, regio-, and enantioselectivity can be highly improved. Furthermore, new synthetic pathways can be accessed, leading to a greater variety of compounds, which were before either inaccessible or only achievable after a laborious multi-step preparation. Another important feature that occurs when metals are involved in the transformation of carboxylic acids is the ability of the CO_2H group to act as a chelating directing group to facilitate C–H bond cleavage reactions in a specified position. An introduced electrophile is then installed into the proximal *ortho*-position, this way overriding the innate *meta*-directing effect of the carboxyl moiety.[165] Finally, the metal-catalyzed extrusion of CO_2 to give aryl–metal species to replace pre-synthesized organometallic compounds further emphasizes how attractive carboxylic acids are in contemporary chemistry.



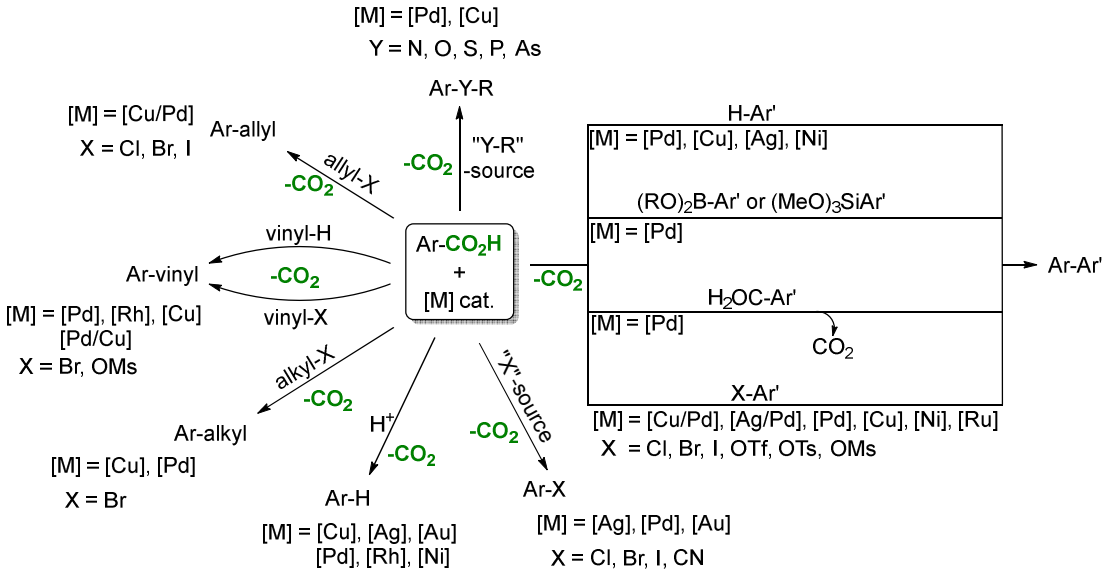
Scheme 9: Multifaceted nature of aromatic carboxylic acids in transition metal catalysis.

Scheme 9 gives an overview on the application of aromatic carboxylic acids in highly topical areas of homogeneous catalysis. This work will mainly focus on the use of the carboxyl moiety as leaving group for decarboxylative cross-couplings (chapter 3.3.1.) and as directing group for the C–H functionalization of the aromatic core (chapter 3.3.2.-3.3.3.). Herein, the different modes of action of the CO_2H group will be elucidated in detail. The combination of carboxylates as directing groups and as leaving groups will be particularly stressed as a new approach for regioselective C–H functionalizations (chapter 3.3.3.). It should be mentioned, that there are also numerous reports on metal-catalyzed addition reactions of the CO_2H group onto unsaturated compounds such as alkenes or alkynes. Likewise, transition metal-catalyzed transformations of acyl–metal species derived from activated carboxylates are described in many literature precedents. However, for the sake of clarity, and since these types of reaction do not play a detrimental role in the present work, both will be omitted.

3.3.1. Carboxylates as leaving groups for catalytic ipso-substitutions (decarboxylative cross-couplings)

Over the past decades carboxylic acids (and their salts) have been intensively studied as a replacement of expensive organometallic reagents in cross-coupling reactions. Carboxylic acids are inexpensive, readily available in great structural diversity, toxicologically unharmful and are easy to store and handle. However, forming carbon nucleophiles from metal–carboxylates *via* CO_2 extrusion is usually energetically disfavored, which makes the

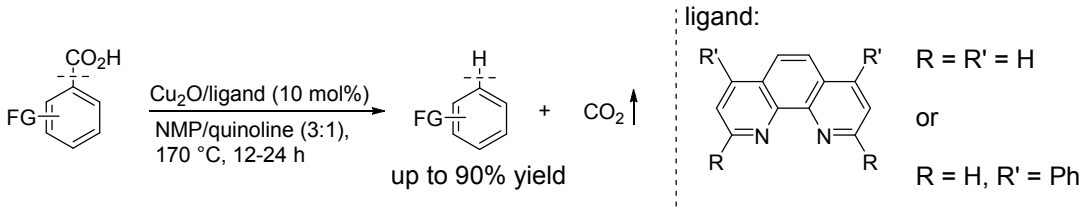
development of catalytic processes highly challenging. Nevertheless, owing to holistic adjustments and tuning of catalyst systems, the chemical community was able to develop numerous efficient reactions to form new C–C and C–heteroatom bonds at the former C–CO_2H position, producing CO_2 as waste instead of stoichiometric metal salts (**Scheme 10**).[23,26–29,47,166–192]



Scheme 10: Overview on decarboxylative cross-coupling reactions of aromatic carboxylic acids.

The simplest decarboxylative cross-coupling reaction is the protodecarboxylation. This reaction is particularly useful as it gives the opportunity to a traceless removal of the CO_2H functionality once it is not required anymore in a molecular scaffold, e.g. for late stage derivatization to enhance the bibliography of biologically active compounds or of Hantzsch esters and analogs.[193–197] As early as 1930 Shepard *et al*. described that halogenated derivatives of furancarboxylic acid are more likely to decarboxylate in the presence of stoichiometric amounts of copper than without a metal presence.[198] Nilsson, Cohen, Sheppard and others extended this reaction type to substituted benzoic acids by combining stoichiometric amounts of copper, bipyridine ligands and nitrogen containing aromatic solvents.[199–205] However, these protocols were efficiently applicable only to “activated” benzoic acids, namely the ones carrying electron-withdrawing *ortho* substituents or few heterocyclic aromatic carboxylates. The decarboxylation of non-activated aromatic carboxylic acids was instead found to be rather difficult. In 2007, Gooßen *et al*. performed intense studies to identify more active decarboxylation catalysts in order to access entire assortment of benzoic acids. Finally, the same group was able to find a suitable copper-based catalyst

system capable of catalytically defunctionalizing non-*ortho*-substituted benzoic acids to give the corresponding arenes at reasonably temperatures (170 °C).[206] Particularly efficient was the implementation of phenanthroline-based ligands for copper, and a specific, carefully deoxygenated solvent mixture composed of NMP and quinoline (**Scheme 11**).

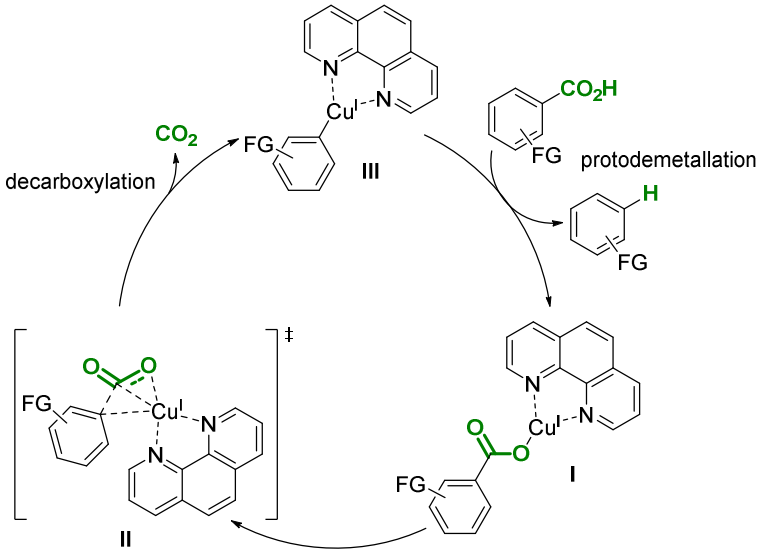


Scheme 11: First truly catalytic protodecarboxylation of unactivated benzoic acids.

Later, long reaction times could be avoided by performing the reaction under microwave irradiation.[207] With a silver(I)-catalyzed protocol, numerous activated benzoic acids were efficiently decarboxylated at temperatures around 80–120 °C, which was 50 °C below previously reported copper-based methods. Moreover, very electron-rich or halide containing benzoic acids, were accessed for the first time, complementing the copper catalyst system.[208,209] Other metals, such as rhodium, nickel or palladium, were found to mediate the CO_2 extrusion to form aryl–metal species, which were *in situ* trapped by protons.[210] Nevertheless, these protocols were still restricted to activated (hetero-)aromatic acids or required reactions performed in gas phase at very high temperatures.[211] More recently, the group of Greaney described a silver-catalyzed radical protodecarboxylation process, which is applicable to both activated and non-activated aromatic acids.[212] Yet, over-stoichiometric amounts of $K_2S_2O_8$ as oxidant are needed. One year later the group of Nolan reported a gold(I)-catalyzed CO_2 extrusion/protodemetallation sequence, in which non-activated *meta*- and *para*-benzoic acids were efficiently converted into the corresponding arenes.[213] Adamantylcarboxylic acids as the right proton source was crucial to achieve protodeauration of the usually stable aryl–gold species.[174,214]

The reason for a reluctant decarboxylation of benzoic acids without activating *ortho* substituents lies within the electronic properties of the substituents. DFT calculations on the copper(I)-catalyzed decarboxylation showed that the decarboxylation is mostly governed by short-range electron-withdrawing inductive effects conducted *via* the σ-backbone, thus most vehemently affected by *ortho* substituents.[206] Moreover, other calculations showed that steric repulsion facilitates the CO_2 extrusion as well.[215] Contrary to this, long-range mesomeric effects transmitted *via* the π-system do not significantly reduce the free reaction energy.[206]

Based on experimental and computational results a catalytic cycle was proposed (**Scheme 12**):[201,206,207,209,216]



Scheme 12: Proposed mechanism for the protodecarboxylation catalyzed by a copper–phenanthroline system.

The copper–phenanthroline–carboxyl complex (**I**) undergoes decarboxylation *via* insertion of the metal into the aryl–CO_2 bond (transition state **II**). CO_2 extrusion gives the aryl–copper species **III** which is protodemetallated by the newly introduced substrate to form again the intermediate **I** along with the arene.

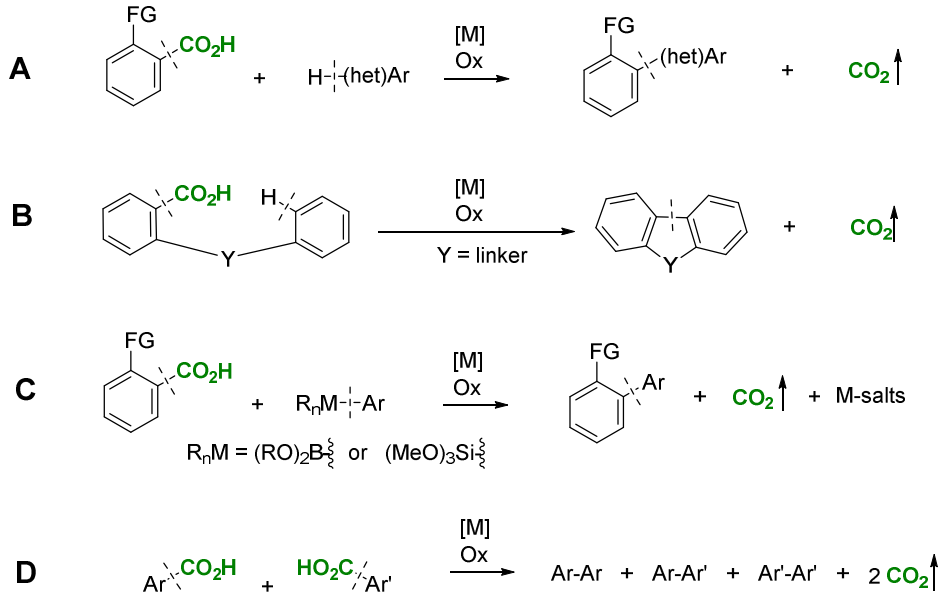
Arguably, a more valuable transformation in the context of decarboxylative couplings is the *ipso*-implementation of other synthons apart from protons. The carboxyl group of activated benzoic acids can be cleaved to form C–halides and pseudo halides, C–N, C–O, C–S, C–P etc. bonds.[47,173,175,177–179,182,184–189] Most of these transformations are catalyzed by copper, silver or palladium combined with stoichiometric amounts of oxidants.

Decarboxylative cross-couplings strategies to form new C–C bonds are particularly interesting because they offer the opportunity for great “synth-tactical” variety for the concise, stepwise construction of organic scaffolds starting from readily available building blocks.[217] The group of Gooßen and many others developed efficient methods for the *ipso*-allylation, -vinylation, -alkylation and -arylation of aromatic carboxylic acids.[168] The latter is particularly important because of the ubiquity of biaryls in pharmaceuticals and functional materials.[218,219] The synthesis of this structural motif *via* transition metal-catalyzed

decarboxylative cross-couplings constitutes a major part of this work and will be therefore elucidated in detail.

3.3.1.1. Biaryl synthesis via decarboxylative oxidative cross-couplings

The groups of Crabtree,[191] Maiti,[172] Larrosa,[220] Glorius,[221,222] and others[27,170,186] reported that under oxidative conditions the aryl–metal species, which is formed by decarboxylation, can be trapped by simple arenes and heteroarenes to form biaryl scaffolds in a rather straightforward fashion. However, these reactions are either restricted to (hetero)arenes bearing C–H acidic positions or require comparatively harsh reaction conditions with over-stoichiometric amounts of silver or copper salts as oxidants. Moreover, most aromatic acids need to be activated for decarboxylation by σ-electron-withdrawing substituents in the *ortho*-position (**Scheme 13A**).



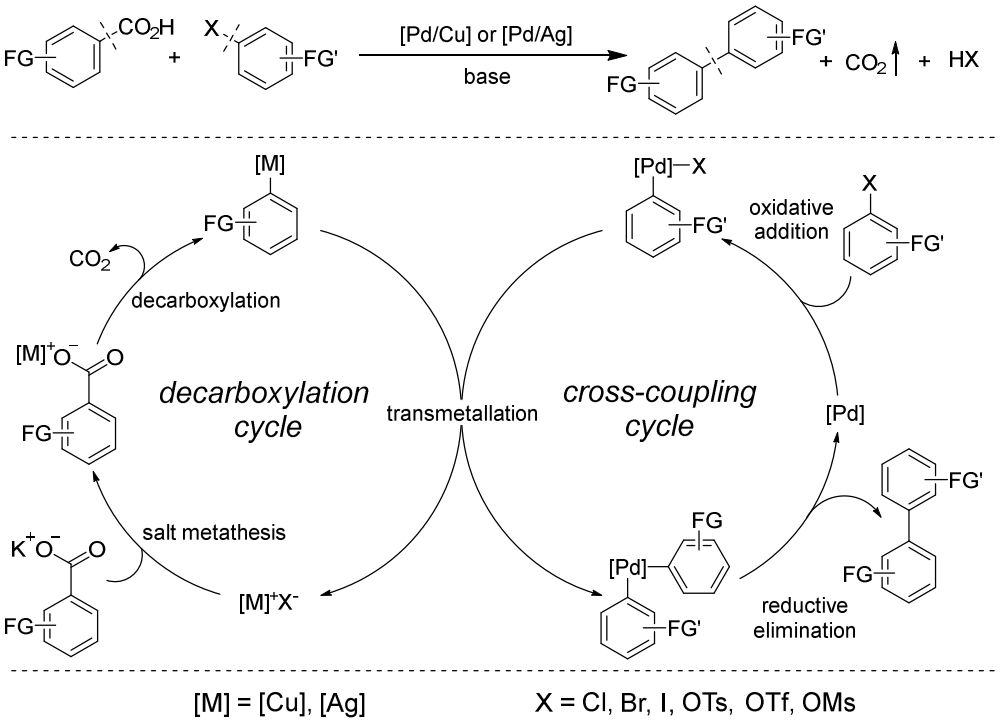
Scheme 13: Decarboxylative biaryl synthesis under oxidative conditions.

The versatility of functional groups is rather narrow and the cross-coupling occurs very seldom intermolecularly (**Scheme 13B**). Oxidative decarboxylative biaryl syntheses can also be conducted between a C–CO_2H moiety and an organometallic reagent (**Scheme 13C**). Yet examples for these types of cross-coupling are rare. The group of Liu reported a decarboxylative Suzuki reaction between highly activated aromatic carboxylic acids and aryl boronic esters.[223] Nevertheless, this reaction is triggered by relatively high loadings of $Pd(TFA)_2$ and over-stoichiometric amounts of expensive silver oxidants. A major challenge was to tune the decarboxylation rate with the transmetallation step. As a result, the choice of

the right organoboron compound was crucial to achieve an efficient coupling with specific benzoic acids. In this context, trialkoxyarylsilanes were also found to be suitable aryl sources for the synthesis of biaryls.[224] This decarboxylative Hiyama coupling is catalyzed by a trimetallic palladium/silver/copper-system, with Pd being the cross-coupling catalyst, silver as the oxidant, and finally copper with a trifold role: as oxidant, as fluoride-source for the silane activation, and as decarboxylation catalyst. Under oxidative conditions the coupling between two aromatic carboxylic acids is possible *via* double-decarboxylation (**Scheme 13D**). The C_{aryl}–C_{aryl} bond is formed at the respective former C–CO_2H bond. Homocouplings as well as heterocouplings are reported in literature.[225–230] In all cases, the efficient conjunction was only achieved with activated (hetero-)aromatic acids and the chemoselectivity for electronically similar acids is rather poor with respect to homo- vs heterocoupling.[27]

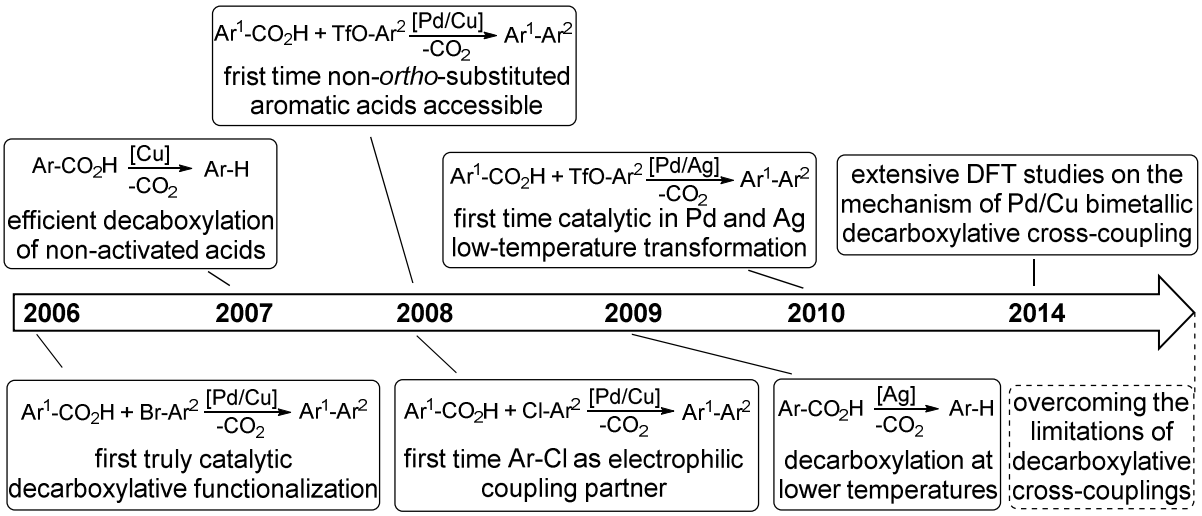
3.3.1.2. Biaryl synthesis via decarboxylative redox-neutral cross-couplings

In contrast, redox-neutral decarboxylative biaryl syntheses have emerged as a particularly preferred reaction strategy because it obviates stoichiometric amounts of oxidants, thus minimizing waste. In this case, *in situ* formed aryl–metal species generated *via* decarboxylation are trapped by aryl electrophiles.



Scheme 14: Bimetallic catalytic decarboxylative biaryl synthesis.

All monometallic catalyst systems reported in literature are restricted to highly activated (hetero-)aromatic acids. Instead, bimetallic catalyst systems, in which a cross-coupling catalyst is combined with a decarboxylation catalyst, are particularly effective (**Scheme 14**). The concept of a bimetallic system offers the unique possibility for an extremely accurate tuning of each catalyst to achieve maximum performance. To date, combinations of Pd as the cross-coupling catalyst with copper or silver as the decarboxylation catalyst are the only reported bimetallic systems to achieve efficient catalytic redox-neutral decarboxylative biaryl couplings. It is highly challenging to achieve perfect synergistic performance of both metals with regard to the two parallel occurring catalytic cycles (exemplified in **Scheme 14**), which coincide at the transmetallation step.



Scheme 15: Timeline of significant advancements of bimetallic decarboxylative biaryl synthesis.

Scheme 15 depicts the evolution of redox-neutral catalytic decarboxylative biaryl syntheses over time. The seminal protocol was reported by Gooßen in 2006.[231] For the first time catalytic decarboxylation was used in cross-coupling catalysis, showing that in fact carbon nucleophiles can be catalytically generated *in situ* and further trapped by electrophiles other than just protons. However, it was mandatory to fine-tune the bimetallic catalyst system for each substrate in order to compensate different decarboxylation propensities of aromatic acids, which considerably alter decarboxylation rates. Moreover, this protocol was limited to *ortho*-nitrobenzoic acids and aryl bromides as the electrophilic coupling partner. A second generation Pd/Cu-bimetallic system extended the scope to the reputedly more challenging aryl chlorides as electrophile source (**Scheme 15**, **2008** bottom).[232] It was crucial to identify a suitable ligand environment on the palladium, without hampering the decarboxylation cycle.

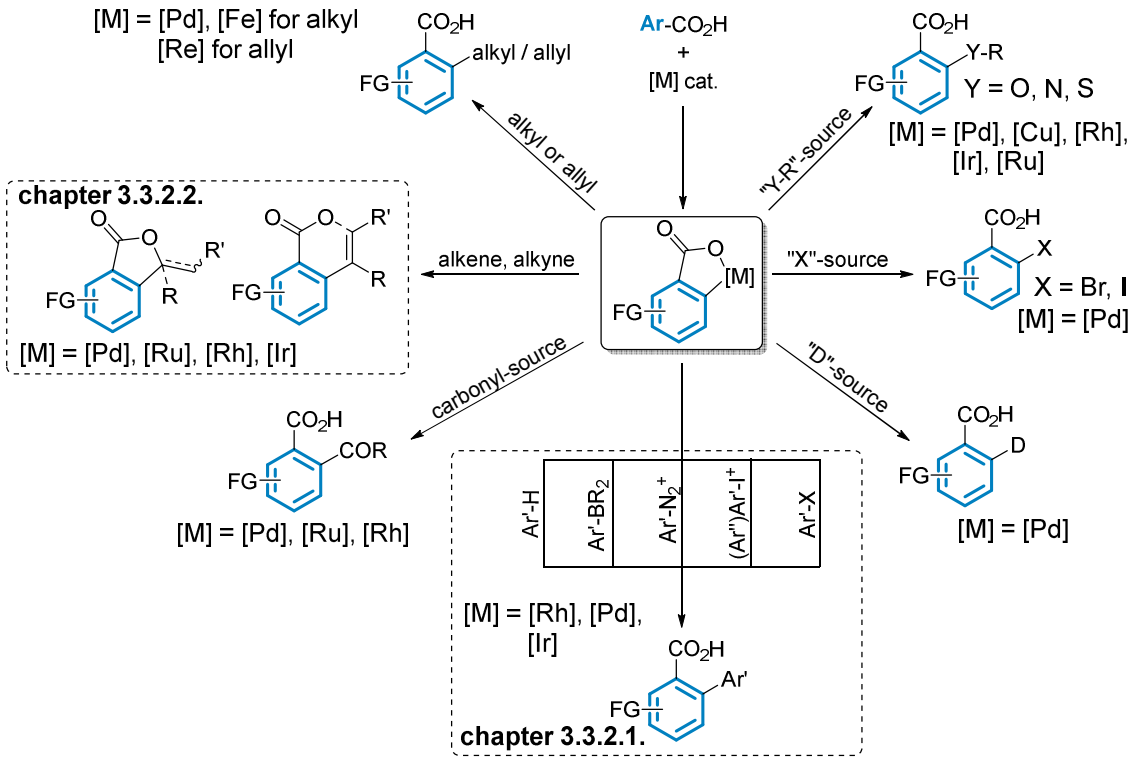
Unfortunately, this protocol was again mainly restricted to *ortho*-nitro benzoic acids. Still, accessing inexpensive and ubiquitous aryl chlorides improved the synthetic utility of decarboxylative cross-couplings and gaining attention as a serious alternative to traditional transformations. In 2007, Gooßen and Thiel explored experimental and computational insights on copper-catalyzed protodecarboxylations, which finally proved to be the key to efficient catalytic transformation of benzoic acids regardless of their substitution patterns (**Scheme 15**). These findings include that the decarboxylation is hampered by additional halide salts, particularly for non-*ortho*-substituted benzoic acids. In the course of a cross-coupling reaction with aryl halides, these anions are increasingly released, forming relatively stable copper halide salts. As a consequence, the formation of the required copper carboxylate *via* salt metathesis (**Scheme 14**) is unfavored. As a matter of fact, non-*ortho*-substituted benzoic acids are efficiently converted solely in the presence of aryl triflates as aryl electrophiles (**Scheme 15**, **2008** top).[233] Hence, weakly coordinating trifluoromethylsulfonate anions do not compete against the formation of the copper carboxylate, which is required to close the decarboxylative catalytic cycle. However, two major drawbacks are the relatively high reaction temperatures (170 °C) and that the reaction is restricted to expensive aryl triflates. With marginal adjustments, this protocol was later extended to more robust and less expensive aryl tosylates.[234] Instead, reputedly less active aryl mesylates required a tailored imidazolyl phosphine ligand on the palladium to ensure an efficient activation and were not suited as coupling partner for non-*ortho*-substituted benzoic acids.[235] For all, high reaction temperatures remained disadvantageous. Shortly thereafter, silver was found to be an efficient decarboxylation catalyst, which is able to truncate the aryl–CO_2H bond at considerably lower temperatures compared to copper-based systems (**Scheme 15**, **2009**). Nevertheless, decarboxylative cross-couplings with aryl halides catalytic in silver remained elusive because stable silver halides are formed during the reaction impeding catalytic turnovers.[181,191,236] This was solved again by implementing aryl electrophiles bearing leaving groups, such as triflates or tosylates, which generate poorly coordinating anions at the transmetallation step (**Scheme 15**, **2010**).[237] In order to shed light on the mechanism of bimetallic catalyst system and to find a recipe to overcome the remaining challenges of efficiently converting non-*ortho*-substituted benzoic acids with aryl halides and lowering the high reaction temperatures, Gooßen and van Wüllen examined the entire Pd/Cu bimetallic catalytic cycle thoroughly (**Scheme 15**, **2014**).[238] They compared the calculated energy barriers for the reaction of *ortho*-fluoro benzoic acid and *para*-fluoro benzoic acid. In accordance to previously reported calculations on the copper-catalyzed

decarboxylation only, the CO_2 extrusion is energetically disfavored for both *ortho*- and *para*-fluoro benzoic acid, but not necessarily the highest in energy for each case in the entire reaction profile. As a matter of fact, when considering the hole bimetallic cycle the highest energy barrier for *para*-fluoro benzoic acid was identified as the transmetallation step and not the decarboxylation. Interestingly, the salt metathesis is, unexpectedly, for both cases equally difficult. This step partially dictates the reaction only because its energy is added to the decarboxylation, which is easier for *ortho*-substituted than for non-*ortho*-substituted benzoates. Concluding, the results show that depending on the substrate, the rate-determinig step lies either at the decarboxylation or at the transmetallation and not, as assumed before, only at the CO_2 extrusion and preceding salt metathesis. Preliminary attempts to facilitate the transmetallation by specifically customized bridging P,N-ligands led to a system, which is able to mediate the reaction at only 100 °C.[239] This demonstrates that holistically optimizing all steps, it should in theory allow to efficiently couple non-activated benzoic acids even in the presence of excess halides at mitigated temperatures. A success would be highly rewarding by showing that the full range of carboxylic acids, as source of carbon nucleophiles, can fully compete in terms of efficiency with organometallic reagents, which are traditionally used in transition metal-catalyzed biaryl synthesis.

3.3.2. Carboxylates as directing group for ortho-C–H activations

Over the past decades, a tremendous progress in directed C–H activations was achieved. This concept has established itself as an efficient tool to create complex molecules in a straightforward fashion and can be regarded as a fundamental synthetic strategy.[240–243] The numerous reported protocols range from the transformation of C_{sp3}–H to C_{sp}–H bonds with pre-functionalized (C–X or heteroatom–X) as well as with non-pre-functionalized (C–H or heteroatom–H) coupling partners, to form new C–C or C–heteroatom bonds, just formally releasing H_2, H_2O, or HX.[31,45,244–249] Arenes are functionalized more efficiently by applying catalyst systems, which are directed by strong chelating directing groups (usually Lewis basic moieties). Moreover, more extended, strong directing groups can be used to regiospecifically and chemoselectively access all positions on the arene.[250,251] However, protocols in which the sole purpose of the directing group is to bring a catalyst into proximity of a C–H bond without being required as a functional group in the final product, become as convenient as or even less convenient than traditional cross-couplings.[153] Frequently, their removal is only possible *via* laborious multi-step procedures and in certain circumstances the directing group even needs to be introduced in an extra step prior to functionalization. For these reasons, it is

a major task in modern-day chemistry to seek for more expedient directing groups to enhance synthetic freedom and step economy in modern transformations.[252,253]

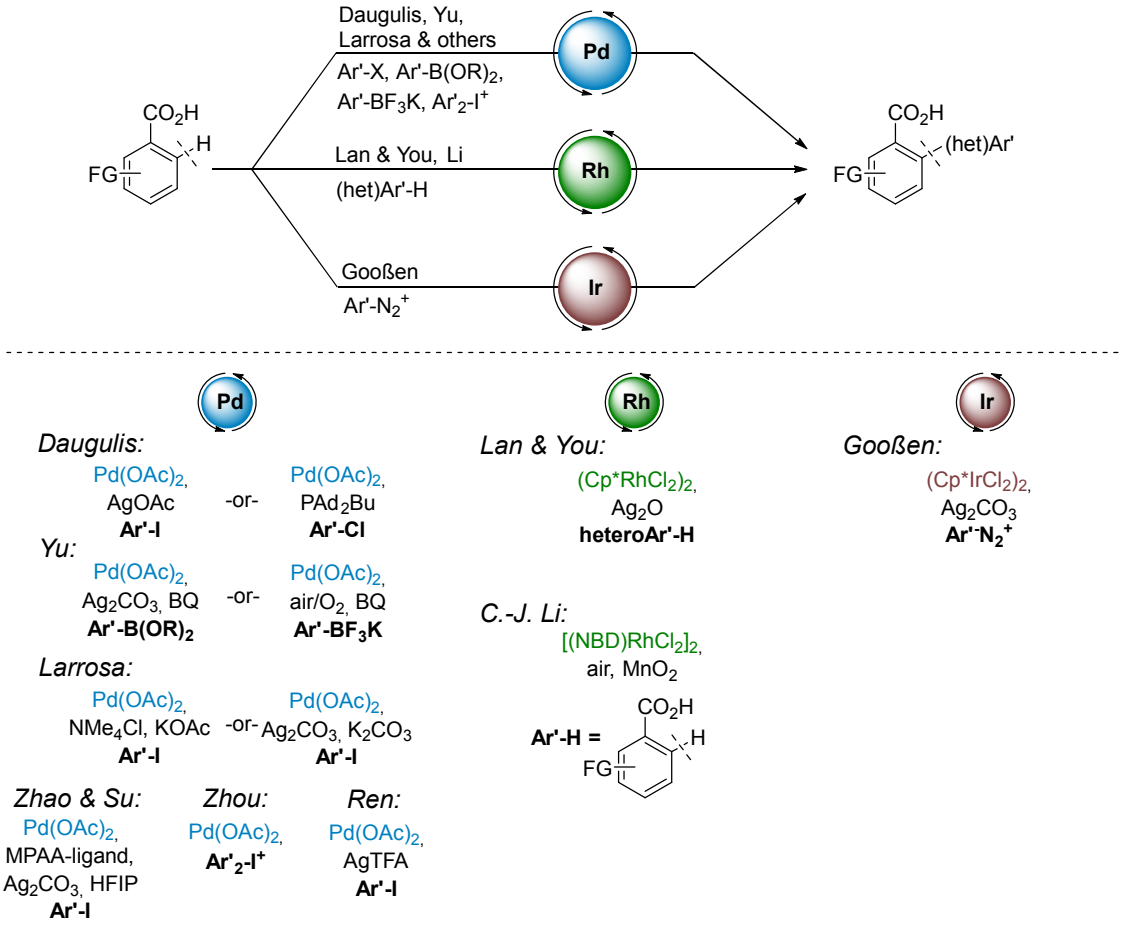


Scheme 16: Overview of carboxylate-directed *ortho*-C–H functionalization of benzoic acids.

In this context, carboxylates fulfill all requirements for an ideal directing group.[254] They are convenient, non-toxic, and commercially available in substantial structural diversity. If the carboxylate group is not required in the final product, it can be truncated and/or replaced by a plethora of functional groups *via* decarboxylative cross-couplings, as shown in chapter 3.3.1. Another argument in favor of carboxylates as starting materials in directed C–H functionalizations is their broad application as potential pharmaceuticals and other functional materials. As a consequence, methods for their step- and waste-minimized atom economic diversification are highly sought-after. **Scheme 16** gives an overview on carboxylate-directed functionalizations of the aromatic core of benzoic acid derivatives, ranging from C–C to C–heteroatom bond formation under oxidative as well as redox-neutral conditions, catalyzed by a number of transition metals. The following chapters will put a strong focus on the state-of-the-art synthesis of biaryls and vinylarenes *via* carboxylate-directed C–H activation. The other transformations depicted in **Scheme 16** move beyond the scope of this work and will therefore not be discussed. Nonetheless, these reactions are outstandingly important and represent useful synthetic tools for the diversification of aromatic carboxylic acids and for the synthesis of complex, otherwise inaccessible building blocks.

3.3.2.1. Carboxylate-directed arylation of aromatic carboxylic acids

C–H arylations are evolving into a greener strategy for the synthesis of biaryls compared to traditional cross-couplings. These systems are particularly effective when aided by Lewis basic directing groups, such as pyridine, pyrimidine, imidazole, and others which guarantee efficient binding of the metal and ease the C–H cleavage process. However, these effective directing groups are rarely needed after the C–H functionalization event and are mostly difficult to remove. In contrast, carboxylates proved to be highly attractive synthons, because of their multipurpose potential. A poor σ-donating tendency and an intrinsic reactive character leading to undesired side reactions, however, create synthetic challenges. Hence, C–H arylations mediated by carboxylates as directing groups are difficult, making expedient methods quite rare. Nonetheless, the groups of Yu, Larrosa, Daugulis, Gooßen, and others, were able to develop protocols for the *ortho*-C–H arylation of benzoic acids (**Scheme 17**).[255–264]



Scheme 17: Overview on carboxylate-directed C–H arylations known in literature.

Pioneering work was achieved by Daugulis and Yu, who disclosed a $Pd(OAc)_2$-catalyzed *ortho*-arylation of benzoic acids with aryl halides and aryl boron reagents, respectively.[255,256,265] Daugulis presented two methods, of which one is applied for aryl iodides, and the second for aryl chlorides as electrophilic coupling partner. For the coupling of aryl iodides, stoichiometric amounts of a silver salt as halophile are needed to achieve sufficient turnover by preventing the formation of catalytically inactive palladium iodide. Aryl chlorides on the other hand present a different challenge. Here, the oxidative insertion of Pd into the reluctantly reactive aryl-chloride bond is facilitated by electron-rich yet bulky phosphine ligands. The scope is strongly restricted to electron-rich benzoic acids and to non-*ortho*-substituted aryl electrophiles. Moreover, in order to avoid that both *ortho*-positions next to the carboxylate group are functionalized, the benzoic acids need at least to be substituted at the *meta*-position. Double-functionalization is often observed for weakly coordinating directing groups, of which carboxylates are inherently included. In contrast, related reactions with strong chelating directing groups usually lead to a selective functionalization at one *ortho*-C–H bond. The group of Yu discovered that under oxidative conditions aryl boronates are also suitable coupling partners for the arylation of benzoic acids.[256,265] An interesting alternative to Daugulis' protocol for the coupling of aryl iodides was described by Larrosa *et al.*[257] There, a combination of a more convenient tetramethylammonium salt with potassium acetate replaced silver as scavenger for halides. This way, intermediary formed PdI_2-species are converted *in situ* to the active $Pd(OAc)_2$ catalyst. $Pd(OAc)_2$ combined with a monoprotected amino acid ligand in HFIP as the solvent boosts the reaction to unlock the coupling of benzoic acids with iodoarenes even at room temperature.[260] Kinetic studies revealed that the amino acid ligand accelerates the reaction rate to ensure higher catalyst longevity. Further improvements include reactions in aqueous solvents either in only water with aryliodonium salts as aryl source or when surfactants are added in a combination with iodoarenes as the electrophile.[259,264] All *ortho*-arylations of benzoic acids, which are catalyzed by expensive palladium precursors, are efficient only with highly activated but expensive aryl sources, such as iodoarenes, aryliodonium salts and aryl boronates. Moreover, most methods require the presence of stoichiometric amounts of expensive silver salts as halide scavengers or oxidants.

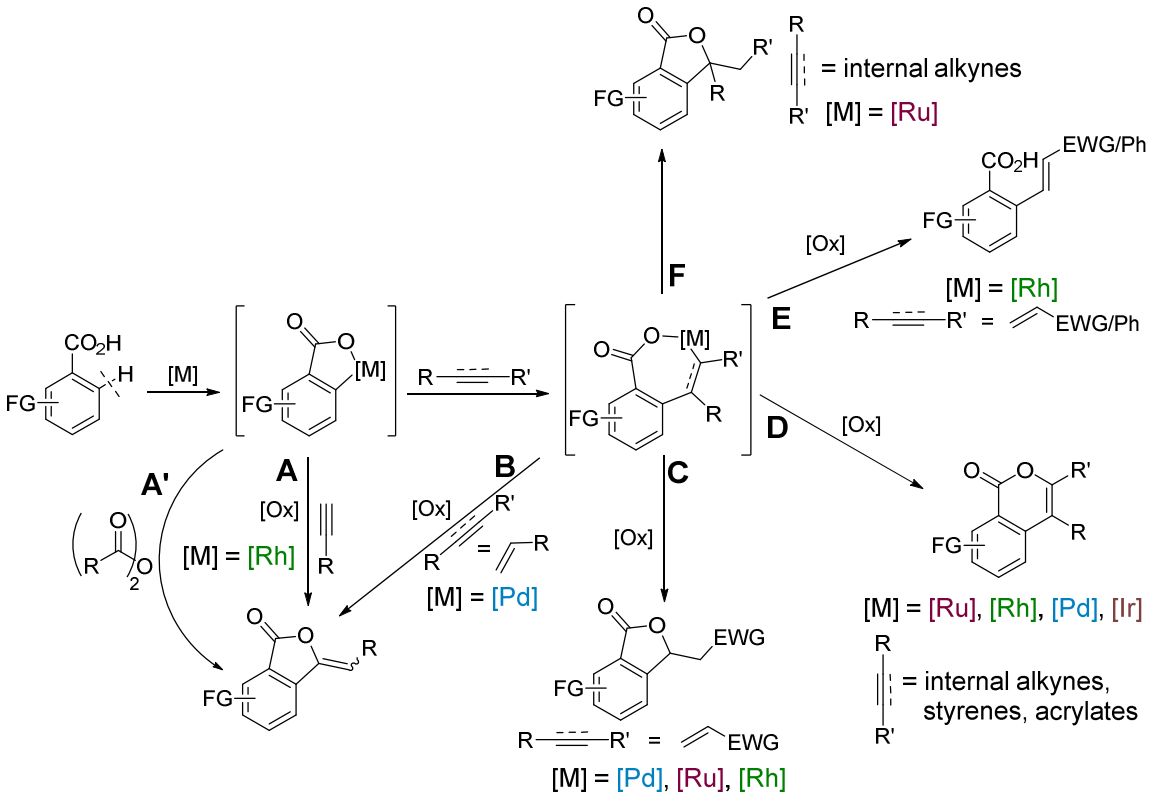
Additionally, biaryls can be formed by carboxylate-directed dehydrogenative couplings, as disclosed by the groups of Lan, You and Li.[261,263] With Rh(III) and overstoichiometric amounts of silver-based oxidants, simple heteroaromatic compounds are coupled with benzoic acids at their most acidic C–H position. On the other hand, Rh(I) couples two benzoic acids to

form diaryl diacids. The reaction is performed in water with air and MnO_2 as oxidants. Unfortunately, homocoupling is always preferred over heterocoupling, deteriorating the synthetic utility of this protocol.

In order to replace expensive aryl iodides or aryl boronates as the aryl source, Gooßen *et al*. developed a method that allows implementing aryl diazonium salts as more convenient surrogates for aryl halides.[262] Aryl diazonium salts are often precursors to synthesize iodoarenes *via* Sandmeyer halogenation, which is also an industrially preferred process. Thus, Gooßen's method formally obviates one additional step compared to the arylation with iodoarenes. Moreover, in the course of the cross-coupling reaction, only gaseous N_2 is released, reducing the amount of heavy waste. The reaction is catalyzed by Ir(III) and performed at remarkably low reaction temperatures (60 °C). Control experiments revealed that the silver salt is likely to play a twofold role in the catalytic cycle. One role is as halide scavenger, to promote dissociation of the Ir-precursor facilitating the formation of the active catalyst species. As a second role, silver is believed to be involved as oxidant in one-electron-transfer steps, for the stepwise oxidation to an Ir(V) intermediate, which should then readily undergo reductive elimination to give the biaryl carboxylate.

3.3.2.2. Carboxylate-directed alkenylation/alkynylation of aromatic carboxylic acids

To introduce C=C double bonds into the *ortho*-position of a carboxylate has been a highly topical area over the past decade. All transformations can be summarized into two main strategies: First, Redox neutral reactions allow introducing an alkyne or alkene onto the aromatic ring with minimum waste. These reactions are extremely rare. In fact, only one example of a transformation, that can be categorized as such, was reported earlier to this work. Second, oxidative Fujiwara-Moritani-type alkenylations, instead, have the advantage to obviate any pre-functionalization of either coupling partner. However, stoichiometric amounts of oxidants are required for a catalytic transformation. The versatility of these strategies is displayed in **Scheme 18**.



Scheme 18: Transition metal-catalyzed reactions of benzoic acids with alkynes and alkenes.

Pioneering work on this field was demonstrated by the group of Miura. In the late 90s they disclosed that in a palladium-catalyzed Fujiwara-Moritani type oxidative coupling of benzoic acids with styrenes or acrylates, a mixture of products formed arising from different demetallative elimination mechanisms (**Scheme 18**, products of pathway **B**, **C** and **D**).[266] With acrylates, intramolecular hydroacetoxylation of the vinylarene, which is formed after reductive elimination, is preferred over β–hydride elimination. Products arising from the β–hydride elimination are observed when styrenes are used as coupling partners. The choice of which specific β–hydride is eliminated to finally give the 5- or the 6-membered ring, respectively, is apparently controlled by steric factors. As a consequence of poor chemoselectivity, this protocol lacks synthetic utility. Nevertheless, this is an early example of a direct *ortho*-olefination of benzoic acids in catalytic Fujiwara-Moritani reactions and inspired many groups to further improve this reaction mode.[267–270] Before that, a comparable reaction was only possible *via* the palladium-catalyzed coupling of preformed toxic arylthallium reagents with olefins to give the corresponding isocoumarins.[271] Over the last decade many groups focused their research on accessing this class of compounds *via ortho*-C–H functionalization of benzoic acids. The hydroarylation of internal alkynes with concomitant intramolecular reductive C–O bond formation crystallized as a preferred strategy

and was first published by Miura and Satoh in 2007 (**Scheme 18D**).[272,273] Rhodium and iridium were found to be particularly efficient catalysts allowing the reaction for a number of internal alkynes even in water and with reduced reaction times by microwave irradiation.[274–277] More recently, ruthenium was used as a cheaper surrogate of Rh, Ir and Pd for the *ortho*-C–H olefination of benzoic acids.[278–280] It is worth mentioning that the tendency of the acid group to undergo Ru-catalyzed acetoxylation across the C,C triple-bond yielding enolesters makes the combination of alkynes with acids and ruthenium as catalyst to aim at a competing *ortho*-functionalization particularly challenging.[281–283] Nevertheless, the group of Ackermann were the first to disclose a ruthenium-catalyzed protocol in which diaryl as well as dialkyl alkynes were efficiently coupled to yield substituted isocumarins.[278] In order to achieve efficient turnover, it was essential to add stoichiometric amounts of copper acetate to the reaction medium. Another drawback is that unsymmetrically substituted alkyl,aryl alkynes reacted sluggishly and with poor regioselectivity. In the same year, the group of Jeganmohan reported that the amount of copper can be reduced to 20 mol% when the reaction is performed under aerobic conditions. Moreover, the regioselectivity of the reaction with unsymmetrical alkynes was completely controlled when aided by a silver salt.[279] Finally, with a designed ruthenium catalyst bearing mesitylene carboxylate as ligands, the group of Ackermann was able to replace the copper salt as terminal oxidant entirely by O_2, formally producing environmentally innocuous water as waste.[284] The strong tendency of the carboxylate group to undergo intramolecular acetoxylation onto an alkene, impedes the *ortho*-C–H alkenylations/alkynylations without cyclization immensely (**Scheme 18E**). Only a handful of aromatic acids, mostly heterocyclic, are reported not to undergo cyclization. These reactions are catalyzed by rhodium combined with stoichiometric silver salts as oxidants and use Michael-acceptors, such as acrylates, as coupling partners.[285,286] In all cases, the scope is restricted to *ortho*-substituted benzoic acids to avoid double-functionalization. Very recently, Shishido disclosed an entirely waste-free C–C bond formation *via* carboxylate-directed *ortho*-hydroarylation of internal alkynes followed by intramolecular hydroacetoxylation (**Scheme 18F**). The reaction is aided by only catalytic amounts of base, is catalyzed heterogeneously by ruthenium coated on a ZrO_2 surface, and represents the first example of an oxidant-free carboxylic acid directed functionalization with internal alkynes.[282]

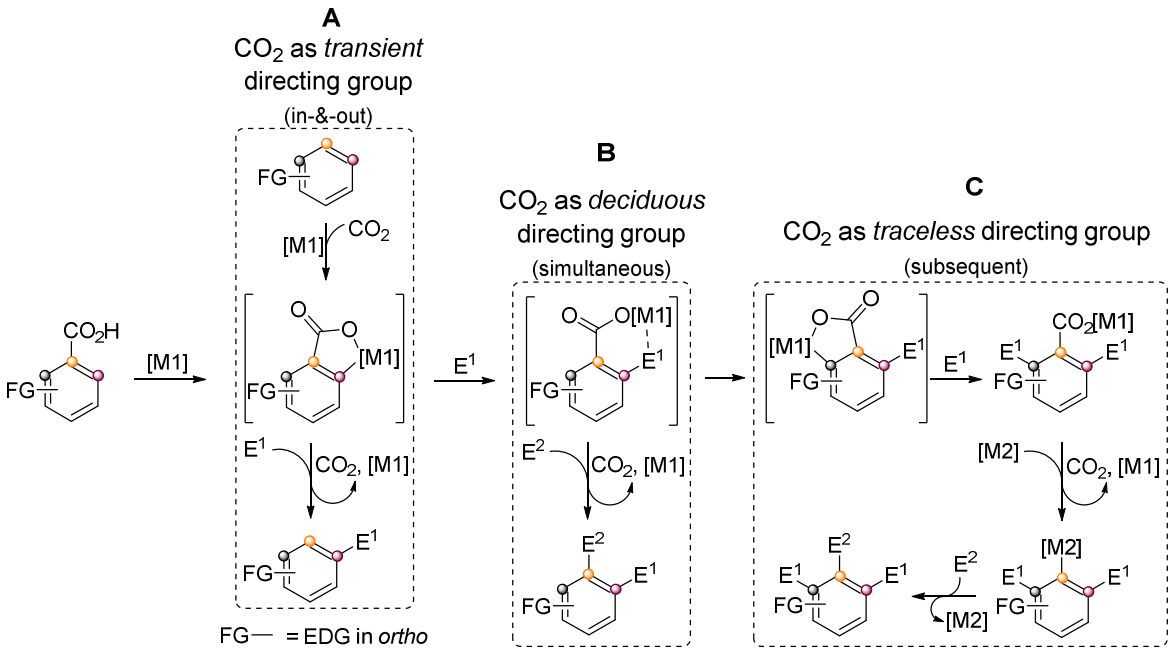
Another mentionable redox neutral carboxylate-directed alkenylation to form 3–alkylidenephthalides from benzoic acids (product of **Scheme 18**, pathway **A'**), was reported by Gooßen and coworkers. The corresponding product is formed *via* a rhodium-

catalyzed acylation[287] with anhydrides followed by cyclizing acylalization and consecutive elimination.[288]

Literature clearly shows that waste-free and oxidant−free carboxylate-directed C–C bond formations are highly needed. However, one major challenge is to overcome the poor selectivity towards mono- vs difunctionalization on both *ortho*-positions, to allow accessing also simple, unfunctionalized aromatic carboxylic acids.

3.3.3. Merging C–H activation with decarboxylation

The major advantage of carboxylates as directing groups is that, after the C–H activation, the CO_2H moiety constitutes a predetermined breaking point either for defunctionalization by protodecarboxylation or for functionalization by decarboxylative cross-couplings. This characteristic allows the potential regio- and chemoselective installation of a wealth of functional groups, accessing diversely multi-decorated arenes. As a matter of fact, this approach was successfully applied by chemists in a number of cases under different strategies (**Scheme 19**).



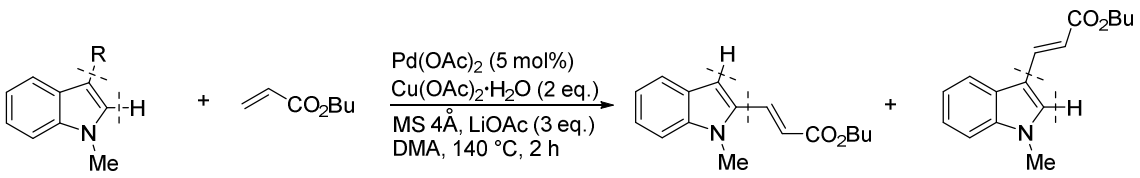
Scheme 19: Different approaches for merging both C–H activation and decarboxylation for the regioselective multi-functionalization of benzoic acids.

The strategy depicted in **Scheme 19C** is the most commonly used approach for the decoration of benzoic acid *via* subsequent C–H and C–CO_2H bond cleavage events. In contrast, the strategy depicted in **Scheme 19A** represents a special feature of CO_2. It is

transiently introduced prior to the C−H activation and removed from the aromatic skeleton after functionalization. These two strategies will be outlined in detail in the following two subchapters. The third strategy, depicted in **Scheme 19B**, was developed within this work and will be explained in detail in the "results and discussion" section. Nevertheless, the subchapter in this section aims at giving the conceptual background and to show the potential utility of carboxylates as *deciduous* directing groups.

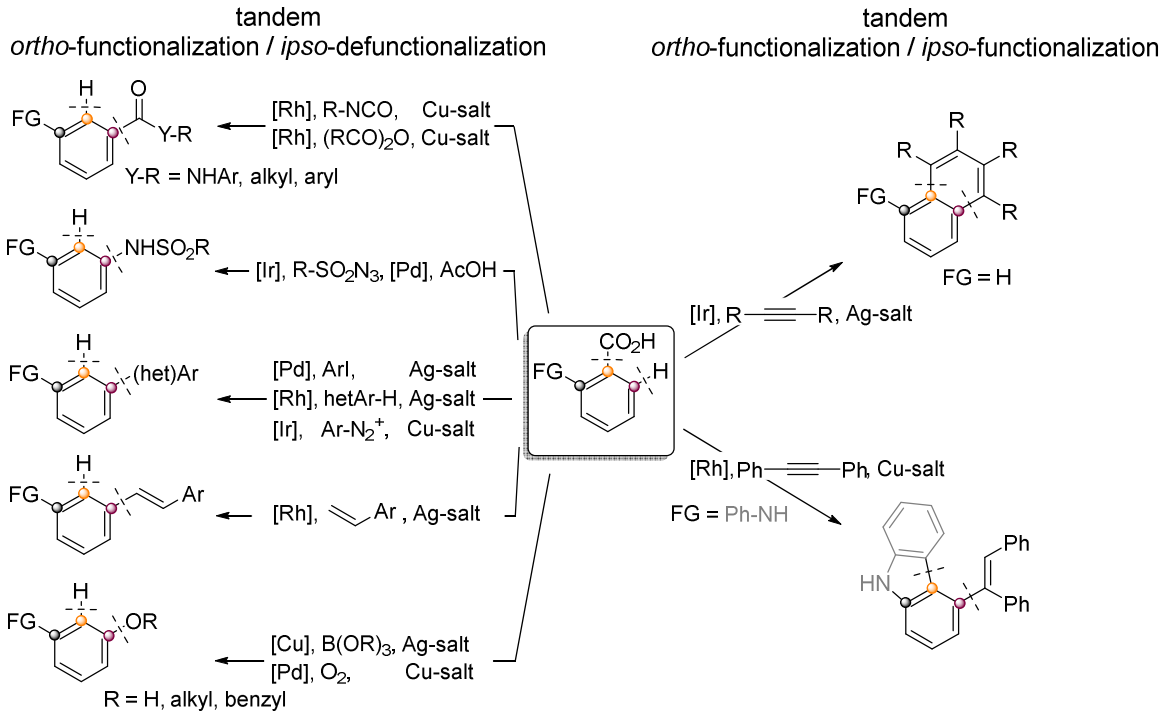
3.3.3.1. Carboxylates as traceless directing group

The concept of a traceless directing group established itself as a powerful tool to formally invert the intrinsic reactivity of a substrate towards a nucleophile or an electrophile by overriding inherent electronic effects.[253] In this context, carboxylates are privileged synthons because they can be installed and removed with particular ease to form an new organic framework, releasing gaseous CO_2. Miura was the first to show that the carboxylic acid functionality can trigger the C2-selective alkenylations of indoles with acrylic acids. In a control experiment in which the carboxylate directing group is omitted, the acrylate reacts selectively at the preferred C3-position (**Scheme 20**).[289] The carboxylic acid thus affects the inherent reactivity of indoles.[290]



Scheme 20: Effect of the carboxylate directing group on the regioselectivity of the vinylation.

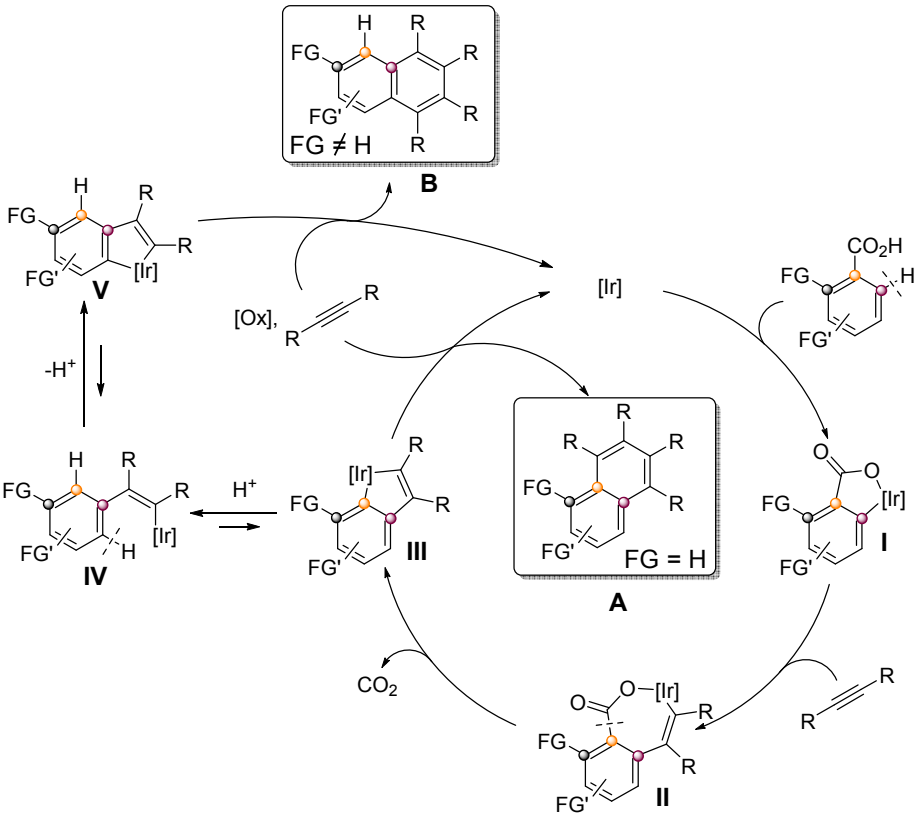
The groups of Larrosa, Li, Chang, Su, Gooßen and others, which are particularly active on the field of carboxylate-directed C–H functionalizations, disclosed examples for the subsequent, and in some cases concomitant, protodecarboxylation of benzoic acids, which takes place after the C–H activation event (**Scheme 21**, left).[48,291] Moreover, Miura and others showed examples of *ortho*-functionalization with subsequent *ipso*-functionalization without the need for an interposed isolation (**Scheme 21**, right).[272,292,293]



Scheme 21: Examples for carboxylate-directed *ortho*-C–H functionalizations of benzoic acids combined with decarboxylative couplings.

In most cases, the CO_2H group is replaced by a proton consecutive to the C–H functionalization step. An early example was reported by Miura and Satoh, in which in a Fujiwara-Moritani type reaction the carboxylate group guides the terminal alkene into the *ortho*-position before being removed by the excess silver, present as oxidant and decarboxylative mediator.[285] However, the CO_2 extrusion is so slow that the second *ortho*-position needs to be blocked to avoid double alkenylation. This is also an issue in nearly all tandem *ortho*-functionalization / *ipso*-defunctionalizations of benzoic acids. Nevertheless, the potential of this reaction sequence unfolds when benzoic acids bearing electron donating *ortho* substituents are coupled with electrophiles. The group of Larrosa disclosed the *ortho*-arylation of 2-substituted benzoic acids and aryl iodides with concomitant Ag-mediated decarboxylation.[294,295] The formed *meta*-substituted arenes, which are difficult to obtain by the use of conventional synthetic approaches, are generated in good to excellent yields regardless of their electronic properties. This strategy was later extended to the cross-dehydrogenative coupling with simple heteroarenes.[296,297] Gooßen *et al.* showed that the iridium-catalyzed *ortho*-arylation of aromatic carboxylates with arene diazonium salts can be combined with a subsequent copper mediated protodecarboxylation in one pot.[262] Other functionalities such as amides or sulfonamides were also found to be accessible coupling products which survive the subsequent protodecarboxylation step.[287,298,299]

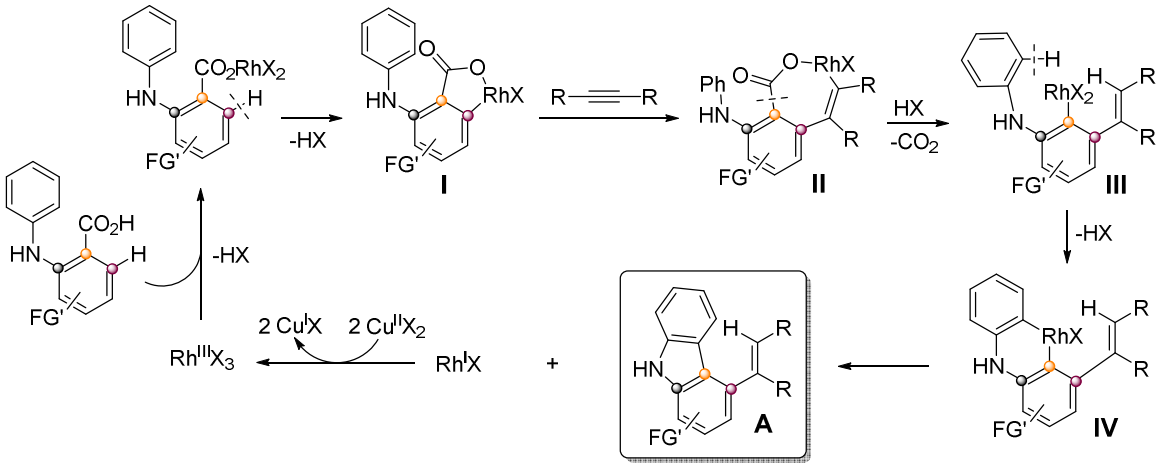
Examples for the tandem *ortho*-functionalization / *ipso*-functionalization are very rare. An excess of protons available in the reaction medium needs to be avoided in order to prevent fast protodecarboxylation. This is a difficult task, taking in consideration that the starting material itself can act as a proton source. Moreover, the literature exclusively contains intramolecular examples of this reaction mode as, intermolecularly, chemoselectivity as well as the regioselectivity are rather hard to control. As a matter of fact, in the iridium-catalyzed oxidative hydroarylation of benzoic acids with alkynes, the product formed is strongly dependent on the *ortho* substituent present on the aromatic acid (**Scheme 22**).[272,274,292]



Scheme 22: Iridium-catalyzed oxidative coupling of benzoic acids with alkynes reported by Miura and Satoh.[272]

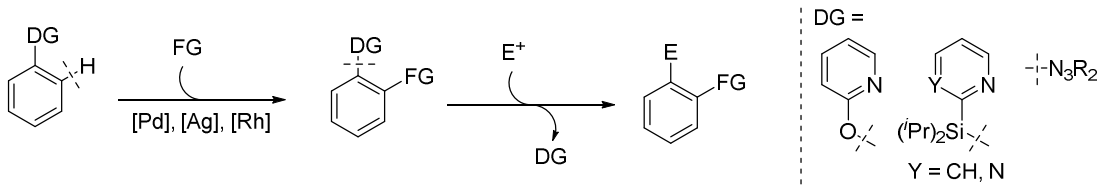
The reaction is presumed to occur *via* initial carboxylate-directed *ortho*-C–H metallation to give intermediate **I** (**Scheme 22**). The following alkyne insertion gives the seven-membered metallacycle **II** (**Scheme 22**). The concomitant decarboxylation gives intermediate **III**, which can undergo two competing pathways. The first pathway is another prompt alkyne insertion, which gives the corresponding naphthalene after reductive C–C bond formation, deriving from a tandem *ortho*-functionalization / *ipso*-functionalization sequence (**Scheme 22**, product **A**). However, this is only possible when no functional groups are adjacent to the carboxylate directing group. The second competing reaction is the protodemetallation to give intermediate

IV. The steric pressure induced by a substituent at the *ortho*-position triggers a second C–H activation step, which is directed *meta* to the former C–CO_2H group and leads to the five-membered metallacycle **V**. An additional alkyne insertion followed by reductive elimination gives the product **B** depicted in **Scheme 22**, which results from a tandem *ortho*-functionalization / *ipso*-defunctionalization process. More recently, Miura and Satoh reported the tandem *ortho*-functionalization / *ipso*-functionalization of diphenylmine–2–carboxylic acid with internal alkynes (**Scheme 23**).[293] They proposed a reaction mechanism that starts with the *ortho*-C–H metallation at the benzoic acid residue to give intermediate **I** in **Scheme 23**. The alkyne insertion into the aryl–metal bond forms the seven membered rhodacycle **II**. Protodemetallation of the Rh–alkenyl bond with concomitant decarboxylation give rise to the aryl–rhodium intermediate **III**. This then undergoes intramolecular oxidative arylation, finally yielding the alkenylated carbazole (**Scheme 23A**). The resulting Rh(I)-species is then re-oxidized by copper to give the active catalyst species Rh(III).



Scheme 23: Tandem *ortho*-hydroarylation / decarboxylative intramolecular *ipso*-arylation reported by Miura and Satoh.

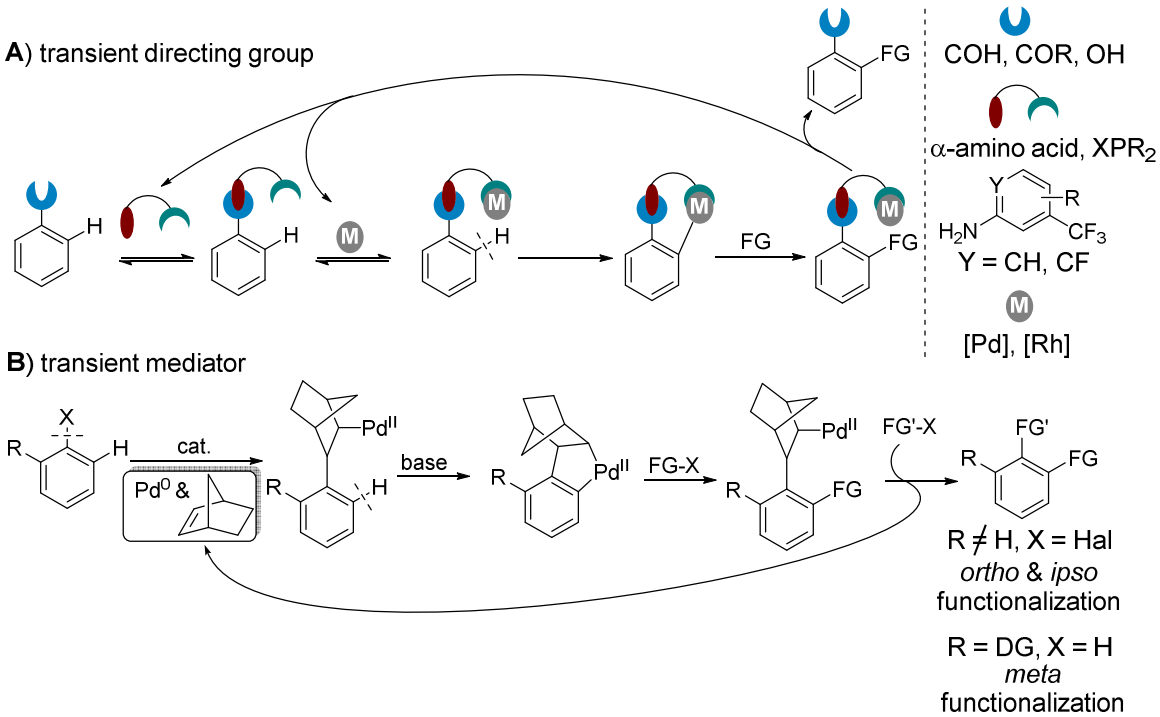
Interestingly, other directing groups such as 2–(diisopropylsilyl)–pyridines and –pyrimidines, 2–pyridyloxy groups and substituted triazenes are also able to mediate tandem *ortho*-functionalization / *ipso*-functionalization (**Scheme 24**).[300–306] However, these groups need to be installed onto the aromatic backbone before they react with the corresponding coupling partners. Moreover, their molecular weight is much higher than simple CO_2 decreasing the total atom economy.



Scheme 24: Tandem *ortho*-functionalization / *ipso*-functionalization with other directing groups.

3.3.3.2. Carboxylates as transient directing group

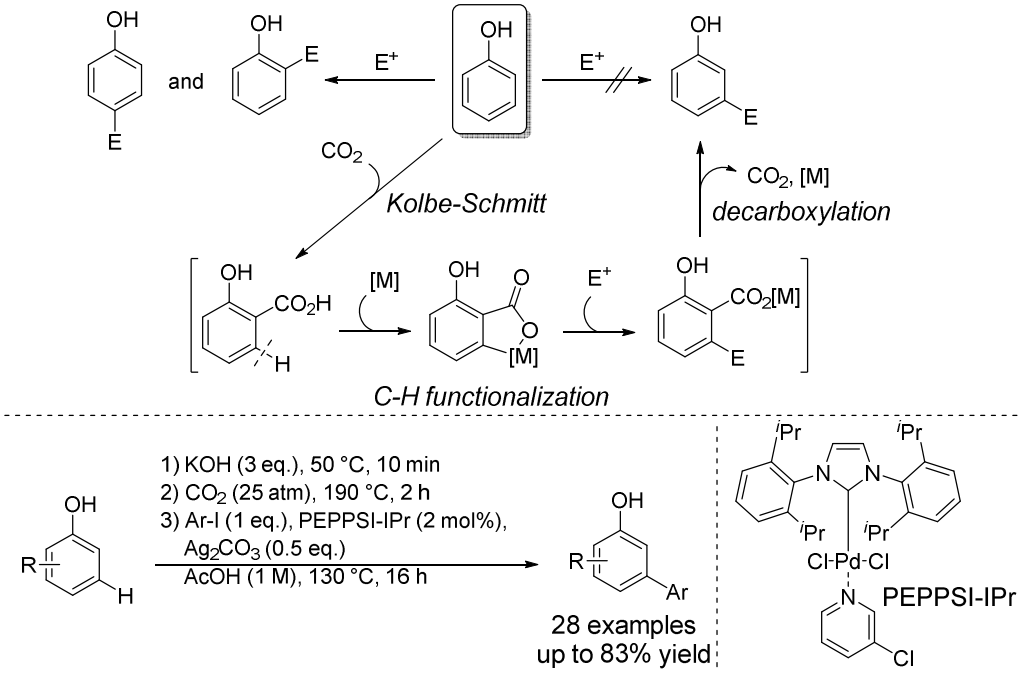
The strategy of transient directing groups has recently emerged as a powerful tool to avoid permanent covalently bonded directing groups, which in most cases need to be installed and later on removed under conditions that are frequently not compatible with labile yet important functionalities.[307,308] Transient directing groups are usually formed by condensing carbonyl groups with amines to give reversibly linked imines or enamines. The Schiff-base is a strong directing group, which is then able to guide the metal to the adjacent C–H position.[309–311] Another example of transient directing groups is given by the reversible transesterification of phenols with phosphinites (**Scheme 25A**).[312,313]



Scheme 25: Two different strategies to apply transient directing groups.

Transient directing groups can also be introduced into simple arenes as shown by the cooperative catalysis of norbornene and palladium, the so-called Catellani reaction.[314–316]

Norbornene can also be regarded as a transient mediator since in this case the substrate does not have a predetermined anchor point such as carbonyl group on which the transient group is condensed (**Scheme 25B**). With extended directing groups it is also possible to directly install functional groups in the *meta*-position.[317–319] In the context of carboxylate-directed C–H functionalization reactions, the group of Larrosa combined a Kolbe-Schmitt reaction with CO_2H directed C–H functionalization. CO_2 is added to the aromatic backbone, triggers the C–H cleavage process, and is then again removed after the functionalization event is fully completed.[320] This is the first example of CO_2 as a transient mediator / directing group and in this way the usual selectivity of the reaction of phenols with electrophiles to give *ortho*- and *para*- instead of *meta*-substituted products has been overridden (**Scheme 26**).



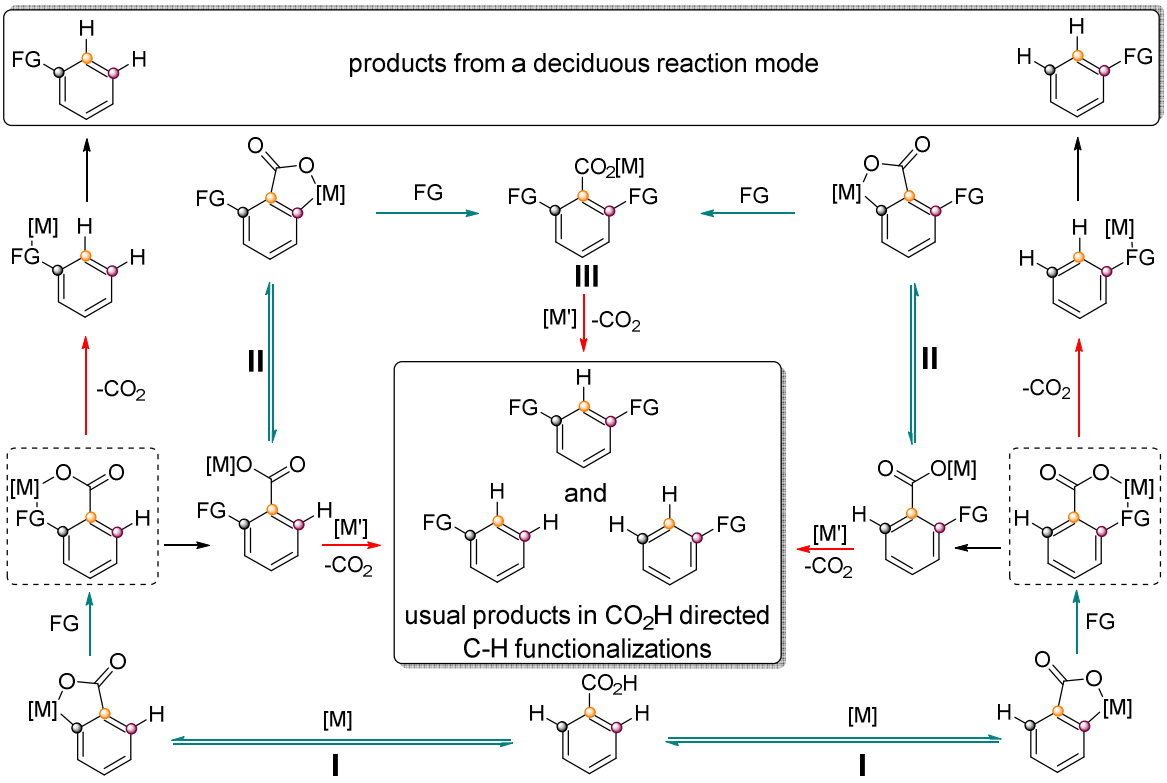
Scheme 26: Larrosa's strategy to use CO_2 as transient directing group to access *meta*-substituted phenols.

The reaction is performed in a three-step one-pot sequence. It tolerates phenols bearing a wealth of functional groups including electron withdrawing and donating moieties, which are coupled with various aryl iodides as well as heteroaryl iodides. Later, the same group reported a related transformation, in which salicylaldehydes are converted into *meta*-arylated phenols.[321] Instead of introducing CO_2, the aldehyde is first oxidized to the corresponding salicylic acid, which then guides the transition metal-catalyzed *ortho*-arylation. Subsequent protodecarboxylation gives the final product.

3.3.3.3. Carboxylates as deciduous directing group

The deciduous reaction mode of carboxylates as directing group has been developed within the present doctoral work, and will be therefore explained in detail in the "results and discussion" sections 5.3-5.4. This part is meant to give a short conceptual overview on this reaction mode.

Apart from the generally challenging activation of inertial C–H bonds, the major issue of carboxylate-directed C–H cleavages is the poor selectivity toward mono- vs difunctionalization (**Scheme 27**, turquoise pathway).



Scheme 27: Reaction modes of a carboxylate-directed C–H functionalization combined with decarboxylation.

This results from the weak σ-donating ability of the carboxy group, which destabilizes the metallacycle formed after the C–H cleavage, making it a reversible event (**Scheme 27**,**I**).[252] In the presence of a coupling partner on the other hand, the metallacycle shows high reactivity resulting in an irreversible insertion of a functional group. Once one functionalization is completed, the carboxylate group can then direct another reversible C–H cleavage event (**Scheme 27**,**II**), leading to usually unwanted doubly functionalized carboxylates. The C–H activation process stops only at this point, more precisely, when no other adjacent C–H bonds

are present (**Scheme 27**,**III**). However, carboxyl groups constitute a predetermined breaking point, which in theory could be cleaved *via* decarboxylation after each completed C–H functionalization step (**Scheme 27**, red pathway). Hence, the extrusion of the DG causes this step to become irreversible as the metal cannot be guided to the next proximal C−H position anymore. However, the decarboxylation rate needs to be fast in order to cleave the directing group before a second C–H activation can take place. This is a very challenging task and can be achieved only when aided by strong decarboxylation catalysts. One rare example was reported by Gooßen *et al*. for the decarboxylative C–H etherification.[46] The insertion of an alkoxy group further facilitates the decarboxylation, occurring in perfect synchrony to the C–H functionalization. Theoretically, the C–H cleavage of the second *ortho*-position can also be avoided by a decarboxylation occurring concertedly with inserting a functional group into the aryl–metal bond of the preceding five membered metallacycle (**Scheme 27**, intermediate in dotted line). This pathway was already proposed by Miura and others for the iridium-catalyzed naphthalene formation (**Scheme 22**). However, in his case the vinyl metal species immediately undergoes cyclization steps before either reductive elimination or protonolysis can take place. Forcing the intermediate in the dotted line depicted in **Scheme 27** to undergo direct decarboxylation and protonolysis would obviate the formation of doubly functionalized arenes without the assistance of an additional decarboxylation mediator. We refer to this possible reaction mode as deciduous, because the carboxylate group is shed from the intermediate after it fulfilled its task. This sequence can be compared to a leaf of a tree in fall, which is cast off because it has served its purpose and is no longer required.

4. Research objectives

The aim of this research was to rationally develop expedient methods for a concise and especially regioselective assembly of synthetic relevant products from readily available aromatic carboxylic acids. C–H activation and decarboxylative cross-couplings were the two main strategies applied to ensure that our objectives of high atom efficiency and a minimum amount of waste are achieved. The major challenge was to overcome the abovementioned intrinsic limitations of these concepts, which are encountered when dealing with aromatic carboxylic acids as starting materials in homogeneous catalysis. These framework conditions define the following specified objectives:

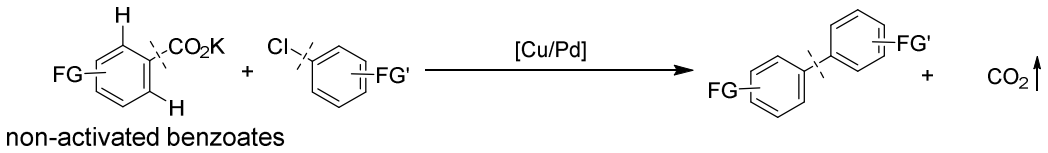
- The first goal was to unlock the last missing piece in the context of decarboxylative biaryl couplings. The efficient redox neutral biaryl formation starting from aryl chlorides and benzoates, without activating *ortho* substituents, should be achieved for the first time by holistic optimization of a bimetallic catalyst system. It is a particularly challenging target because both aryl chlorides and non-activated benzoic acids are reluctantly reactive in cross-coupling reactions and because decarboxylative couplings are reputedly additionally hampered by the presence of excess halides.
- The second goal was the redox neutral *ortho*-arylation of benzoic acids with aryl chlorides and bromides catalyzed by ruthenium. Such a protocol would shift the biaryl coupling from the *ipso*- to the *ortho*-position highlighting the perfect orthogonality to decarboxylative couplings. It is therefore important that the carboxylate group remains untouched after the reaction to give the potential opportunity for a stepwise synthesis of multi-functionalized arenes *via* a conceivable subsequent *ipso*-substitution.
- The second goal was to circumvent the weak coordinating ability of carboxylic acids and diminish the issues that come with it in a straightforward fashion. Our vision was to embed the decarboxylation within the C–H functionalization to unlock the deciduous reaction mode of the carboxylate group. That means that the usually observed, but unwanted, double-functionalization on both *ortho*-positions will be avoided by concertedly extruding CO_2 during one C–H functionalization event. Additionally, this reaction mode would override natural regioselectivity driven by intrinsic electronic properties commanded by already installed substituents.

5. Results and discussion

The following chapters comprise a short overview of the aims and challenges of each project. Due to the cumulative form, every section contains a depicted copy of the corresponding original publication in which all citations and experimental data are included, respectively. Moreover, strongly related work, which has been published by other groups simultaneously to or after the own projects, are shown for comparison and as support for conducted preliminary mechanistic experiments.

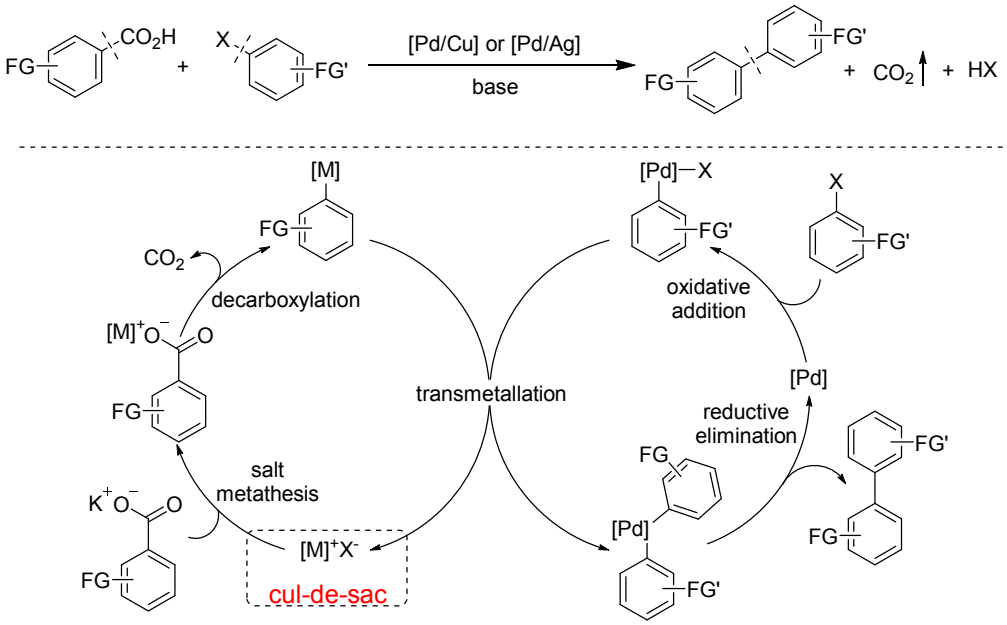
5.1. Catalytic Decarboxylative Cross-Coupling of Aryl Chlorides and Benzoates without Activating *ortho* Substituents

In continuation with the development of decarboxylative cross-couplings for the synthesis of biaryls, this project targeted at the elaboration of an extremely potent Cu/Pd bimetallic catalyst system that would allow the efficient coupling of aryl chlorides with non-activated benzoates (**Scheme 28**). To date, such a transformation was not possible with state-of-the-art catalyst systems yet highly desirable, because it would represent a serious alternative to traditional cross-couplings.



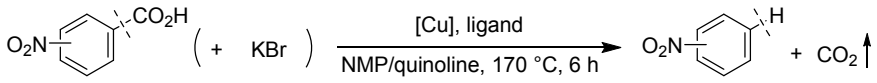
Scheme 28: Decarboxylative biaryl synthesis from aryl chlorides and benzoates without activating *ortho* substituents.

Highly active protodecarboxylation catalysts developed by Gooßen *et al*. proved that the energy required to decarboxylate benzoic acids without activating *ortho* substituents can be surmounted at acceptably low temperatures. However, in a cross-coupling reaction with aryl halides, the halide salts formed after the transmetallation step would hamper the decarboxylation because of the difficult preceding salt metathesis, formally impeding the benzoate to enter the catalytic cycle (**Scheme 29**).



Scheme 29: General decarboxylative cross-coupling reaction for the biaryl synthesis and proposed reaction mechanism for a bimetallic catalyst system.

Based on the postulated mechanism displayed in **Scheme 29** it was tentatively assumed that efficient turnover can only be achieved when the salt metathesis between halide salts and benzoates is aided by coordinating *ortho* substituents. This hypothesis is supported by comparative protodecarboxylation experiments of *o*–nitrobenzoic acid and *p*–nitrobenzoic acids, in which the reaction is shut down by added halide salts, in the case of *p*–nitrobenzoic acid exclusively (**Scheme 30**).[322]



O_2N— = *ortho*-NO_2 : 100% without KBr; 95% with KBr

O_2N— = *para*-NO_2 : 52% without KBr; 0% with KBr

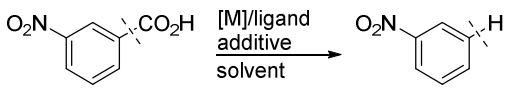
Scheme 30: Influence of halides and substitution patterns on protodecarboxylations.

Another result which supports the theory of a disfavored anion exchange is the efficient coupling of non-*ortho*-substituted benzoic acids with aryl electrophiles bearing non-coordinating leaving groups such as triflates or tosylates, for which the salt metathesis is reputedly unproblematic.[233–235,237] Yet, these aryl sources are expensive and only available in limited functional diversity. A connatural reaction with substantially lower-priced and more diverse aryl halides is therefore a main target in the context of decarboxylative biaryl synthesis.

Extensive mechanistic investigations confirmed the disfavored salt metathesis. However, in strong contrast to experimental results, the substitution patterns were found to be surprisingly uninvolved in this step and the energy barriers are for both *ortho*- and *para*-substituted benzoic acids almost identical.[238] The difference in reactivity lies within the rate determining energy span which is only revealed when taking in consideration the entire catalytic cycle and not each single step alone. The energy span for *ortho*-substituted benzoic acid is between the starting materials and the decarboxylation transition state, whereas for non-*ortho*-substituted benzoic acids the rate determining energy span lies between the starting materials and the transmetallation transition state. This energy span is found to be 4–8 kcal mol^{-1} higher than in the *ortho* case, just enough to enable decarboxylative couplings at manageable temperatures. Nevertheless, the energy barriers for the transmetallation and decarboxylation are so similar for both substitution patterns that the actual rate determining step of a decarboxylative cross-coupling is probably depending on each individual substrate, but not as originally assumed on intrinsic decarboxylation propensities. The halide effect observed is probably due to the higher stability of copper or silver halides shifting the equilibrium so that less copper or silver carboxylate is present, decreasing the entire decarboxylation rate by additionally increasing its energy span. These computational studies indicate that an efficient decarboxylative arylation of benzoates without activating *ortho* substituents with inexpensive aryl chlorides can only be achieved by thoroughly optimizing each elementary catalytic step that is involved. The objective of this project was to develop an efficient catalyst system, which would confirm the postulated feasibility of this transformation.

Thus, we started our investigation by optimizing the decarboxylation catalyst. It was soon demonstrated that the CO_2 extrusion of non-*ortho*-substituted benzoic acids can even be done in the presence of excess halides (**Table 1**).

Table 1: Optimization of the decarboxylation catalyst in the presence of excess halides.



#	[M]	ligand	additive	solvent	T/°C	yield/%
1	Cu_2O	phen	-	NMP/quin=3/1	190	99
2	"	"	KCl	"	"	14
3	"	Me_4phen	"	"	"	99
4	Ag_2CO_3	-	"	"	"	-

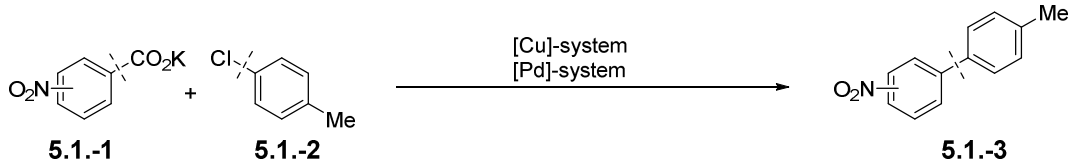
Reaction conditions: 3–nitro–benzoic acid (0.5 mmol), Cu_2O (5 mol %), ligand (10 mol %), additive (0.5 mmol), 3 mL of solvent, 190 °C, 16 h. quin = quinoline; NMP = N–methyl–2–pyrrolidone. Yields determined by GC analysis using n-tetradecane as the internal standard.

The cross-coupling was examined by thoroughly optimizing the palladium co-catalyst system in the presence of the copper co-catalyst system. State-of-the-art palladium cross-coupling catalyst systems were found inefficient, leading to higher levels of unwanted protodecarboxylated product instead of the desired biaryl. Further extensive optimization revealed that combining cationic palladium species with bulky phosphines, such as XPhos which reputedly activate aryl chlorides, gave the best results. With the best conditions in hands, benzoates, regardless of their substitution patterns, were smoothly coupled with numerous readily available aryl chlorides.

We realized that it was difficult to steer the reaction in favor of the desired biaryl product when electron-rich aryl chlorides were implemented. Instead, protodecarboxylation was found to be the predominant pathway, leading to a more selective formation of the corresponding decarboxylated arene. The observation that the oxidative addition negatively affects the selectivity between cross-coupling and protonolysis can be rationalized by the energy span model.[323] By assuming that 1) for non-*ortho*-substituted benzoic acids the transmetallation transition state is the highest in energy but 2) is not effected by the nature of the Pd-bound aryl group, and 3) that the protodecarboxylation always proceeds with the same rate, a preceding oxidative addition of electron-rich substrates, which occurs with lower rate compared to electron poor electrophiles, would further enhance the rate-determining energy span. As a consequence, the protodecarboxylation outbalances the transmetallation, leading to simple arenes instead of the desired biaryls.

Despite this limitation it should be mentioned, that this method is applicable to the full range of benzoic acids and it considerably surpasses previously reported protocols for the coupling of activated benzoic acids with aryl chlorides (**Table 2**). The reason for the high performance of this catalyst system is probably a result of a thorough optimization of each elementary catalytic step. Whereas in previously reported protocols the focus was to optimize the decarboxylation alone, which was thought to be the only possible rate limiting step.

Table 2: Direct comparison of this method with two other previously reported protocols for the exemplary coupling of *ortho*-, *meta*- or *para*-nitrobenzoic acid with *para*-tolyl chloride.

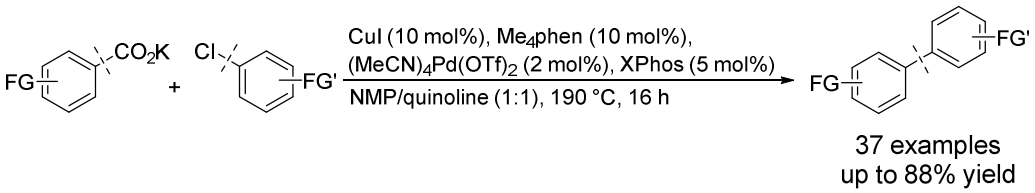


5.1.-1 **5.1.-2** **5.1.-3**

#	**5.1.-1**	**yield of biaryl 5.1.-3 for each method**		
		CuI/Me_4Phen $(MeCN)_4Pd(OTf)_2/XPhos$ **(this method)**	CuI/Phen PdI_2/JohnPhos[232]	CuI/Phen $Pd(acac)_2$/JohnPhos[324]
1	2–NO_2	80%	71%	57%
2	3–NO_2	61%	-	-
3	4–NO_2	51%	-	-

Me_4Phen = 3,4,7,8-tetramethyl-1,10-phenanthroline; XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; Phen = 1,10-phenanthroline; JohnPhos = (2-biphenyl)di-tert-butylphosphine.

To summarize, the customized Cu/Pd bimetallic catalyst system depicted **Scheme 31** in was found to enable the decarboxylative cross-coupling of non-*ortho*-substituted benzoates with aryl chlorides, proving that the limitations are not intrinsic. This system is highly performing and can be regarded as a true alternative to traditional cross-coupling reactions for the redox neutral synthesis of biaryls.



Scheme 31: Reaction conditions elaborated during this project.

Authors' contributions:

This work was performed in collaboration with Mr. J. Tang. He performed the initial screening and optimization. I supported him during the final screening by synthesizing the palladium catalysts and testing the robustness of the developed reaction conditions. I isolated half of the scope and corrected the first draft of the manuscript and supporting information that Mr. J. Tang wrote. The final submission process, which includes further improvements of the manuscript, was performed by me and Prof. Dr. L. J. Gooßen.

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Decarboxylative Cross-Coupling

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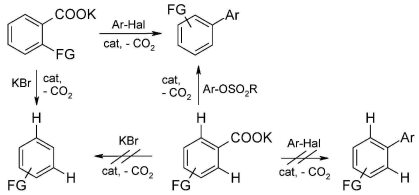
Catalytic Decarboxylative Cross-Coupling of Aryl Chlorides and Benzoates without Activating *ortho* Substituents

*Jie Tang, Agostino Biafora, and Lukas J. Goossen**

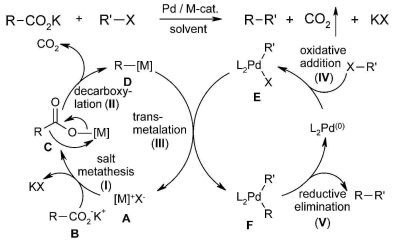
Abstract: *The restriction of decarboxylative cross-coupling reactions to ortho-substituted or heterocyclic carboxylate substrates was overcome by holistic optimization of a bimetallic Cu/Pd catalyst system. The combination of a CuI/Me$_4$phen decarboxylation catalyst and a [(MeCN)$_4$Pd](OTf)$_2$/XPhos cross-coupling catalyst enables the synthesis of biaryls from inexpensive aryl chlorides and potassium benzoates regardless of their substitution pattern.*

The past decade has witnessed tremendous progress in the development of decarboxylative cross-coupling reactions.[1] The key advantage of this reaction concept is that it is based on inexpensive carboxylate salts as the source of carbon nucleophiles instead of preformed organometallic reagents. Various synthetic transformations have been developed based on this strategy, including decarboxylative Heck-type vinylations,[2] redox-neutral cross-coupling reactions,[3] allylations,[1a,4] oxidative coupling reactions,[5] C–H arylations and acylations,[6] and addition reactions.[7] Whereas aromatic carboxylates are usually coupled through two-electron steps, one-electron steps predominate in the activation of aliphatic carboxylates.[8] A particularly topical development in this field is the implementation of photoredox catalysts that permit decarboxylatively coupling, for example, of aliphatic carboxylic and amino acids.[9]

The discovery of bimetallic Cu/Pd or Ag/Pd catalysts has enabled the efficient coupling of various aromatic and heteroaromatic carboxylates with aryl electrophiles.[3b,10] Initially, the reaction concept appeared to be limited to certain heterocyclic and mono- or di-*ortho*-substituted carboxylates. In protodecarboxylations, improved catalysts soon allowed the energetic barrier to decarboxylation to be surmounted, even for *meta*- and *para*-substituted benzoates.[11] Unfortunately, the addition of halide salts, as they form in cross-coupling reactions with aryl halides, completely suppresses protodecarboxylations of such non-activated benzoates (Scheme 1).[3b] Based on the mechanistic outline depicted in Scheme 2, it was initially hypothesized that the thermodynamically disfavored salt metathesis between copper or silver halides (**A**) and the potassium carboxylate



Scheme 1. Scope and limitations of known decarboxylative coupling reactions. FG = functional group.



Scheme 2. Decarboxylative cross-coupling reaction. M = Cu, Ag; R = (hetero)aryl, vinyl, acyl; R′ = (hetero)aryl; alkenyl.

(**B**) proceeds only when aided by coordinating groups in the *ortho* position. This theory appeared to be supported by the successful coupling of non-*ortho*-substituted carboxylates with carbon electrophiles with noncoordinating sulfonate leaving groups,[10d,e] for which the salt metathesis step (I) should be favorable. Unfortunately, the price and availability of these electrophiles somewhat limit the practical utility of these procedures.

Overcoming the restriction to *ortho*-substituted benzoates for aryl halide substrates remained a prime target in the development of decarboxylative arylations, because *meta*- and *para*-substituted biaryls are otherwise difficult to access from inexpensive precursors, whereas *ortho*-substituted biaryls can be synthesized in increasing diversity through *ortho*-C–H arylation.

In-depth mechanistic studies confirmed the unfavorable position of the upstream salt metathesis equilibrium (I), but surprisingly revealed that it is almost unaffected by the substitution pattern of the benzoates.[12] Instead, the presence of σ-withdrawing groups in the *ortho* position enables decarboxylative coupling reactions by reducing their rate-determining energy span by 4–8 kcal mol^{-1} overall, thus

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making them just feasible at manageable reaction temperatures.[13] The transmetalation step (III) was found to have an energy barrier in the same high range as the salt metathesis/decarboxylation process. Improving the decarboxylation catalysts by introducing ligands that strongly stabilize intermediate **D** would facilitate its formation but reduce its reactivity in step III, once again disabling the overall process. Only a holistic optimization of all reaction steps together might enable the desired decarboxylative cross-coupling of non-activated benzoates with aryl halides using metal mediators only in catalytic amounts.

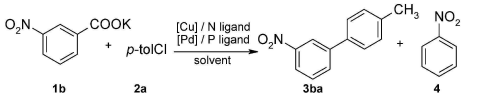
For the development of a decarboxylative arylation of benzoates without activating *ortho* substituents, we set the focus on aryl chloride substrates, the most available and inexpensive of the aryl halides. Thus, we started by investigating the protodecarboxylation of 3-nitrobenzoic acid. At 190 °C, quantitative conversion was observed in the presence of the standard Cu_2O/1,10-phenanthroline catalyst, but when 1 equiv of potassium chloride was added, the yield dropped to 14 %. The addition of other salts, for example, NaCl, nBu$_4$NCl, or CsCl, suppressed the protodecarboxylation to a comparably strong extent, whereas it was unaffected by the presence of potassium salts with weakly coordinating anions such as KOTf. This confirms that it is mostly the anion and not the cation that affects the decarboxylation step. However, after in-depth optimization, a quantitative yield was finally achieved using a 3,4,7,8-tetramethyl-1,10-phenanthroline ligand in quinoline as the solvent (see the Supporting Information). This result demonstrates that the decarboxylation barrier of non-activated carboxylates can be overcome with customized catalysts, even when excess halide salt reduces the availability of copper carboxylate intermediates.

Silver-based catalysts were ineffective under these conditions. The proverbial stability of silver chloride shifts the salt exchange equilibrium away from the silver carboxylates. Furthermore, the influence of *ortho* substituents is particularly strong for silver, which catalyzes the decarboxylation of 2,6-dimethoxybenzoates under very mild conditions but is inactive for non-*ortho*-substituted benzoates.[10a,14]

Encouraged by the protodecarboxylation results, we searched for an effective decarboxylative cross-coupling catalyst for the model reaction of potassium 3-nitrobenzoate (**1b**) with 4-chlorotoluene (**2a**). Using a combination of the optimal protodecarboxylation catalyst (Cu_2O/Me$_4$phen) with a state-of-the-art cross-coupling system ($PdBr_2$/JohnPhos), only 15 % yield of the desired product was detected (Table 1, entry 1). The yield of **3ba** was even lower with other phenanthroline derivatives (entries 2–4). Remarkably, large amounts of protodecarboxylation product **4** were formed. This indicates that the decarboxylation step proceeds efficiently and suggests that the transmetalation step has become limiting. The ratio of **3ba** to **4** improved when shifting to a more polar solvent mixture of quinoline/NMP and to CuI as the copper source (entries 5 and 8).

The key improvement in the overall yield was achieved by optimizing the palladium co-catalyst. Among the electron-rich, bulky phosphines known to activate aryl chlorides, XPhos was by far the most effective (entry 13). Another major improvement resulted from the use of palladium

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



1b 2a 3ba 4

Entry	[Cu]	N ligand	[Pd]	P ligand	Yield [%] 3ba	4
1[b]	Cu_2O	Me$_4$phen	$PdBr_2$	JohnPhos	15	70
2[b]	Cu_2O	phen	$PdBr_2$	JohnPhos	4	60
3[b]	Cu_2O	Ph$_2$phen	$PdBr_2$	JohnPhos	5	72
4[b]	Cu_2O	(MeO)$_2$phen	$PdBr_2$	JohnPhos	0	18
5	Cu_2O	Me$_4$phen	$PdBr_2$	JohnPhos	16	40
6	CuBr	Me$_4$phen	$PdBr_2$	JohnPhos	12	42
7	CuCl	Me$_4$phen	$PdBr_2$	JohnPhos	14	38
8	CuI	Me$_4$phen	$PdBr_2$	JohnPhos	19	30
9	CuI	Me$_4$phen	$PdBr_2$	tBu$_3$P·HBF$_4$	17	28
10	CuI	Me$_4$phen	$PdBr_2$	PCy$_3$	8	28
11	CuI	Me$_4$phen	$PdBr_2$	SPhos	14	34
12	CuI	Me$_4$phen	$PdBr_2$	DavePhos	17	25
13	CuI	Me$_4$phen	$PdBr_2$	XPhos	36	23
14	CuI	Me$_4$phen	PdI_2	XPhos	37	24
15	CuI	Me$_4$phen	$Pd(OAc)_2$	XPhos	42	40
16	CuI	Me$_4$phen	$[Pd_2(dba)_3]$	XPhos	7	25
17	CuI	Me$_4$phen	$[Pd(allyl)_2Cl_2]$	XPhos	29	32
18	CuI	Me$_4$phen	XPhos-Pd-G2	XPhos	12	27
19	CuI	Me$_4$phen	$[(MeCN)_4Pd](OTf)_2$	XPhos	58	50
20[c]	CuI	Me$_4$phen	$[(MeCN)_4Pd](OTf)_2$	XPhos	67	38

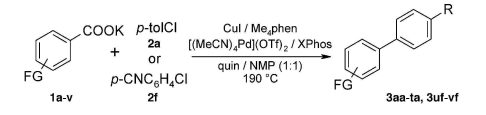
[a] Reaction conditions: **1b** (0.6 mmol, 1.2 equiv), **2a** (0.5 mmol), Cu source (10 mol %), N ligand (10 mol %), Pd source (2 mol %), P ligand (5 mol %), 3 mL of solvent (quinoline/NMP = 1:1), 190 °C, 16 h, yields determined by GC analysis using *n*-tetradecane as the internal standard based on **2a**, for abbreviations see Ref. [15]. [b] In quinoline. [c] 5 mL of solvent.

precursors with weakly coordinating counterions, that is, $[(MeCN)_4Pd](OTf)_2$ (entry 19). Finally, the cross-coupling catalyst was found to preserve its activity better at greater dilution (entry 20). Control experiments showed that both metals are essential for this transformation and that the yields sharply decrease at lower temperatures (38 % at 180 °C, 30 % at 170 °C, and 0 % at 150 °C; see the Supporting Information for details).

By using the optimal catalyst, a mixture of CuI, Me$_4$phen, $[(MeCN)_4Pd](OTf)_2$, and XPhos in 1:1 quinoline/NMP, the desired product **3ba** was obtained in close to 70 % yield after 16 h at 190 °C, along with unreacted aryl chloride and the protodecarboxylation product **4**.

Under these conditions, a wide variety of benzoic acids were coupled with the model substrate 4-chlorotoluene (**2a**) in good yields (Table 2). The yields obtained for *ortho*-substituted carboxylates are significantly higher than those previously reported, thus confirming the superiority of the new procedure. *ortho*-Methyl benzoate and *ortho*-phenyl benzoate (**3uf**, **3vf**), which have never before been converted in decarboxylative coupling reactions, gave reasonable yields. Electron-withdrawing substituents, such as nitro, cyano, fluoride, trifluoromethyl, trifluoromethoxy, sulfonyl, and sulfonamide may be present in any position of the aromatic ring. The catalyst reaches its performance limit for 3-phenoxy

Table 2: Scope with regard to the aromatic carboxylates.[a]



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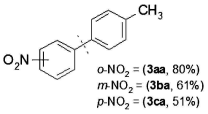
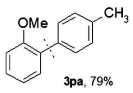
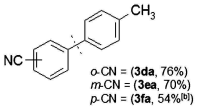
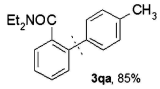
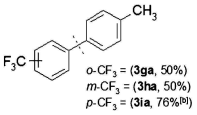
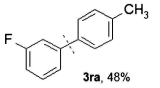
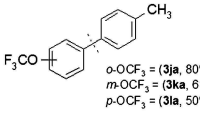
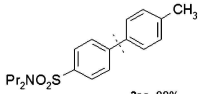
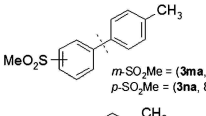
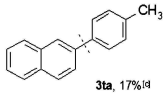
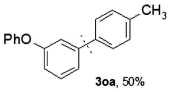
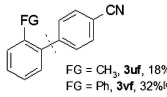
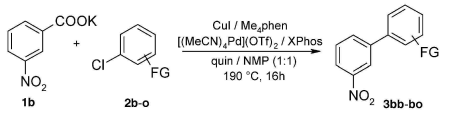
 o-NO_2 = (**3aa**, 80%) m-NO_2 = (**3ba**, 61%) p-NO_2 = (**3ca**, 51%)	 **3pa**, 79%
 o-CN = (**3da**, 76%) m-CN = (**3ea**, 70%) p-CN = (**3fa**, 54%[b])	 **3qa**, 85%
 o-CF_3 = (**3ga**, 50%) m-CF_3 = (**3ha**, 50%) p-CF_3 = (**3ia**, 76%[b])	 **3ra**, 48%
 o-OCF_3 = (**3ja**, 80%) m-OCF_3 = (**3ka**, 61%) p-OCF_3 = (**3la**, 50%)	 **3sa**, 88%
 m-SO_2Me = (**3ma**, 60%) p-SO_2Me = (**3na**, 88%[b])	 **3ta**, 17%[c]
 **3oa**, 50%	 FG = CH_3, **3uf**, 18%[d] FG = Ph, **3vf**, 32%[d]

[a] Reaction conditions: **1a–v** (0.6–0.75 mmol), **2a** or **2f** (0.5 mmol), CuI (10 mol%), 3,4,7,8-tetramethyl-1,10-phenanthroline (10 mol%), $[(MeCN)_4Pd](OTf)_2$ (2 mol%), XPhos (5 mol%), 5 mL of solvent, 190°C, 16 h. Yields of isolated products. [b] 32 h. [c] GC yield. [d] 4-Chlorobenzonitrile (**2f**) used as coupling partner.

Table 3: Scope with regard to the aryl chlorides.[a]



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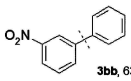
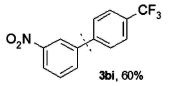
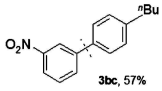
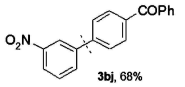
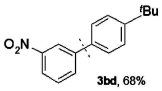
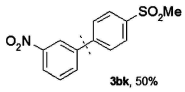
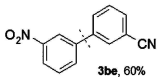
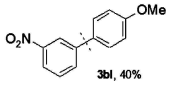
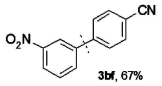
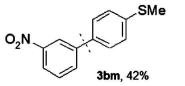
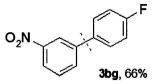
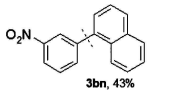
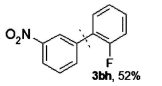
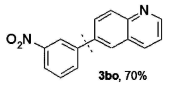
 **3bb**, 63%	 **3bi**, 60%
 **3bc**, 57%	 **3bj**, 68%
 **3bd**, 68%	 **3bk**, 50%
 **3be**, 60%	 **3bl**, 40%
 **3bf**, 67%	 **3bm**, 42%
 **3bg**, 66%	 **3bn**, 43%
 **3bh**, 52%	 **3bo**, 70%

[a] Reaction conditions: **1b** (0.6 mmol), **2b–o** (0.5 mmol), CuI (10 mol%), 3,4,7,8-tetramethyl-1,10-phenanthroline (10 mol%), $[(MeCN)_4Pd](OTf)_2$ (2 mol%), XPhos (5 mol%), 5 mL of solvent, 190°C, 16 h. Yields of isolated products.

benzoate (**3oa**). Substrates that were even more electron rich gave unsatisfactory yields. However, the formation of protodecarboxylation by-products indicates that the decarboxylation step is not limiting for any of the substrates.

The scope with regard to the electrophilic coupling partner was explored with potassium 3-nitrobenzoate (**1b**). As shown in Table 3, various aryl chlorides with common functionalities such as cyano, fluoro, trifluoromethyl, ether, sulfonyl, and ketone groups, as well as heterocyclic derivatives react smoothly. Notably, electron-rich derivatives gave lower ratios of decarboxylative coupling to protodecarboxylation than electron-poor substrates. A rationale for the observation that the oxidative addition becomes the selectivity-determining step can be derived from the energy span model, if one assumes that 1) the transmetalation proceeds via the highest-energy transition state in the reaction profile, 2) the protodecarboxylation always proceeds with the same speed, and 3) the transmetalation is unaffected by the substituent on the Pd-bound aryl group. The oxidative addition equilibrium, which should lie more on the side of the starting materials for electron-rich compared to electron-poor substrates, increases the rate-determining energy span for the former, so that the decarboxylative cross-coupling is more selective for the latter.

In conclusion, a customized bimetallic Pd^{II}/Cu^{I} catalyst system was found to enable the decarboxylative cross-coupling of non-*ortho*-substituted aromatic carboxylates with aryl chlorides. This confirms predictions by DFT studies that the previously observed limitation to certain activated carboxylates is not intrinsic. Since the decarboxylation step is no longer limiting, further studies can now be directed towards the development of a new generation of catalysts with bridging ligands designed to facilitate the transmetalation and allow catalytic turnover at strongly reduced temperatures.

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[15] dba = dibenzylideneacetone; NMP = *N*-methyl-2-pyrrolidone; phen = 1,10-phenanthroline; Me_4phen = 3,4,7,8-tetramethyl-1,10-phenanthroline; Ph_2phen = 4,7-diphenyl-1,10-phenanthroline; $(MeO)_2$phen = 4,7-dimethoxyl-1,10-phenanthroline; JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl; SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; DavePhos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl; XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; XPhos-Pd-G2 = chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II); Ts = 4-toluenesulfonyl; Tf = trifluoromethylsulfonyl.

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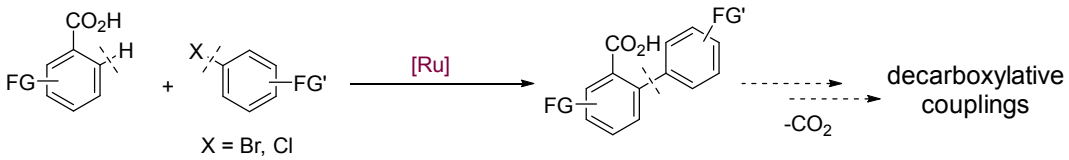
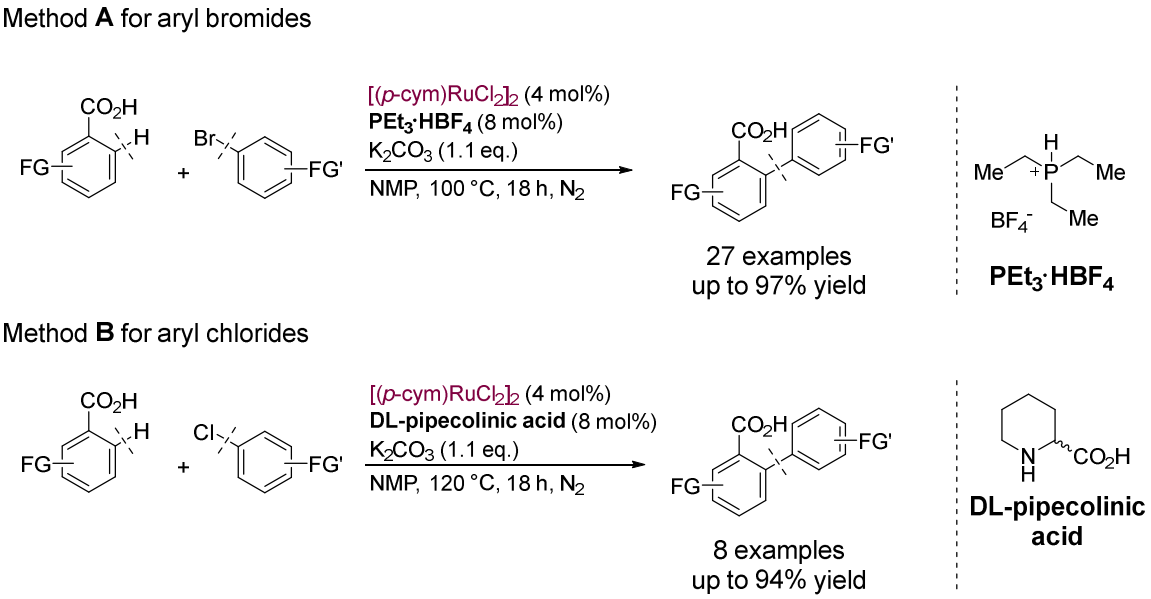
5.2. *ortho*-C-H Arylation of Benzoic Acids with Aryl Bromides and Chlorides Catalyzed by Ruthenium

For this project we envisioned to switch the arylation of benzoic acids from the *ipso*- to the *ortho*-position with retention of the carboxylate group for potential orthogonal decarboxylative cross-couplings. As shown in chapter 3.3.2.1., carboxylate-directed C–H arylations are catalyzed by expensive Pd-, Rh- or Ir-catalysts and rely mostly on costly aryl iodides or aryl boronates as the aryl source. Moreover, oxidative protocols require stoichiometric amounts of silver-based oxidants. We therefore aimed at the challenging redox neutral transformation of aryl bromides and aryl chlorides, the most inexpensive and most available of the aryl electrophiles. This transformation should be mediated by a more affordable ruthenium catalyst, outperforming known protocols and able to compete with traditional biaryl syntheses *via* cross-coupling of preformed organometallic reagents (**Scheme 32**).



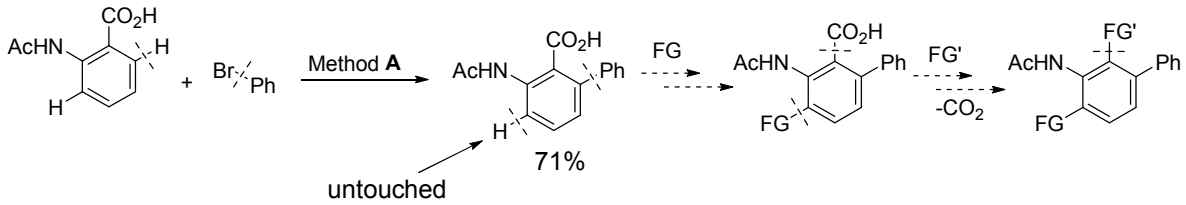
Scheme 32: Ruthenium-catalyzed *ortho*-C–H arylation of benzoic acids with aryl bromides and aryl chlorides.

The decisive breakthrough was to implement a ligand, which is capable of facilitating the oxidative insertion of the ruthenium into the aryl halogen bond. Electron-rich phosphines and, in rare cases, amino acids were already found beneficial in analogous C–H arylations of arenes bearing strong directing groups.[326–329] Intensive optimizations revealed that in fact the ligands play a detrimental role.



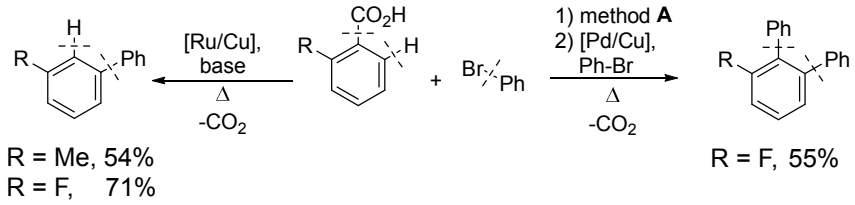
Scheme 33: Optimized conditions for the ruthenium-catalyzed *ortho*-C–H arylation of benzoic acids with both aryl bromides (method **A**) and aryl chlorides (method **B**).

Bromoarenes are efficiently coupled when the ruthenium catalyst is potentiated by small electron-rich alkyl phosphines. Among them, triethyl phosphine particularly outperformed other ligands and can conveniently be applied in its HBF_4 salt (**Scheme 33**, method **A**). Instead, aryl chlorides are preferentially converted when the non-proteinogenic amino acid DL–pipecolinic acid was used as ligand at slightly elevated reaction temperatures (**Scheme 33**, method **B**). Control experiments revealed that the optimal conditions for aryl chlorides are not efficient for aryl bromides, suggesting that different reaction pathways might be involved in this case. In contrast, the reaction conditions elaborated for bromoarenes are applicable to aryl chlorides. However, comparable yields can only be achieved after substantially longer reaction times of 48 h instead of 18 h. These two methods showed broad applicability and comparable yields for both aryl bromides and aryl chlorides. As expected, double-arylation on both sides of the carboxylate group could only be avoided when one *ortho*-position is blocked either by an *ortho*- or sterically by a *meta* substituent. Interestingly, a competitive experiment in which an acetamido group is additionally present in the benzoic acid revealed that the *ortho*-C–H metallation is selectively guided by the carboxylate rather than by the amide group (**Scheme 34**). This feature is particularly remarkable because the C–H directing ability of the amide groups reputedly exceeds that of carboxylic acids and could give the possibility for orthogonal transformations *via* amide directed C–H functionalizations and even further *via* decarboxylative *ipso*-functionalizations.



Scheme 34: Selective *ortho*-C–H arylation in the presence of two competing directing groups and potential further regioselective transformations.

To show the versatility of this reaction concept, the elaborated biaryl synthesis was combined with a concomitant protodecarboxylation and in another with a subsequent decarboxylative *ipso*-arylation (**Scheme 35**).



Scheme 35: Tandem *ortho*-arylation / *ipso*-defunctionalization (left); tandem *ortho*-arylation / *ipso*-arylation (right).

To our delight, only by adding catalytic amounts of copper as one of the reaction ingredients and increasing the temperature to 190 °C, the corresponding decarboxylated biaryls were formed in good yields without any additional steps or ligands (**Scheme 35**, left). This route can therefore be regarded as complementary to a decarboxylative cross-coupling of aryl halides with benzoates without activating *ortho* substituents because it yields the same products, but circumvents low decarboxylation propensities of non-*ortho*-substituted benzoic acids. On the other hand, the combination of *ortho*-arylation with decarboxylative cross-couplings was only possible in a two-step, one-pot procedure (**Scheme 35**, right). Nevertheless, this is the first example for the synthesis of a terphenyl *via* an intermolecular tandem *ortho*-arylation / *ipso*-arylation.

The method developed within this project highlights the multifaceted potential of aromatic carboxylic acids in catalytic regioselective transformations. With the implementation of inexpensive aryl bromides and chlorides and a cost-effective ruthenium catalyst, this reaction can be regarded as a serious alternative to traditional transition metal-catalyzed biaryl syntheses.

Authors' contributions:

This work was performed in collaboration with Mr. T. Krause, Mrs. D. Hackenberger and Mr. F. Belitz. I developed the reaction and performed the major part of the screening experiments. Mr. F. Belitz supported me in the laboratory as an intern during his practical course. Mr. T. Krause and Mrs. D. Hackenberger supported me in the final optimization of the reaction conditions. Mr. T. Krause, Mrs. D. Hackenberger and I contributed equally on both, isolation of the products, as well as optimizing the decarboxylative conditions. The analytical data was processed by Mr. F. Belitz, Mr. T. Krause and Mrs. D. Hackenberger. I wrote the first draft of the manuscript which was revised by Mr. T. Krause and Mrs. D. Hackenberger. Mechanistic experiments were done by me. The final submission process, which includes further improvements of the manuscript, was performed by Prof. Dr. L. J. Gooßen, Mrs. D. Hackenberger and I. The supporting information was authored by Mr. T. Krause, Mrs. D. Hackenberger and I.

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ortho-C–H Arylation of Benzoic Acids with Aryl Bromides and Chlorides Catalyzed by Ruthenium

*Agostino Biafora, Thilo Krause, Dagmar Hackenberger, Florian Belitz, and Lukas J. Gooßen**

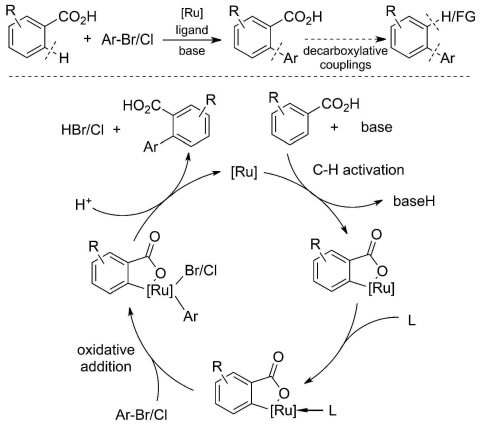
Abstract: *A system consisting of catalytic amounts of $[(p\text{-cym})RuCl_2]_2$/$PEt_3{\cdot}HBF_4$, K_2CO_3 as the base, and NMP as the solvent efficiently mediates the ortho-C–H arylation of benzoic acids with aryl bromides at 100 °C. Replacing the phosphine ligand with the amino acid* DL*-pipecolinic acid enables the analogous transformation with aryl chlorides. The key advantage of this broadly applicable transformation is the use of an inexpensive ruthenium catalyst in combination with simple carboxylates as directing groups, which can either be tracelessly removed or used as anchor points for decarboxylative ipso substitutions.*

Biaryls are ubiquitous in pharmaceuticals, agrochemicals, and functional materials, and efficient methods to access these substructures are constantly sought after.[1] Traditionally, these structures are accessed by cross-coupling of preformed organometallic reagents with aryl halides[2] or by oxidative or reductive couplings of prefunctionalized substrates.[3]

The discovery of directing groups that efficiently control the regioselectivity of C–H arylations has recently revolutionized this field, enabling the regiospecific introduction of aryl groups in unfunctionalized positions.[4] However, this great conceptual advantage is often offset by the structural complexity of the required directing groups.[5] Their introduction and subsequent removal adds several steps to the overall synthetic process. Only recently, abundant functional groups with low coordinating ability, such as carboxylates, have successfully been used as directing groups for *ortho*-C–H arylations.[6] The key benefit of carboxylate groups is that they can be tracelessly removed by protodecarboxylation or utilized as leaving groups in a rapidly growing number of decarboxylative coupling reactions, with formation of C–C, C–O, C–N, C–S, C–P, and C–halogen bonds, for example.[7]

The development of transformations based on carboxylate directing groups is highly challenging. The low σ-donating ability of the carboxylate limits their ability to direct metal centers to one specific C–H bond and reduces the activity of the resulting metallacycle towards aryl electrophiles. *ortho* Arylations of benzoic acids were first reported by the groups of Daugulis,[8] Larrosa,[9] Su,[10] and Yu,[11] who employed expensive palladium catalysts.[12] With aryl iodides, these transformations proceeded smoothly even at room temperature.[10] The conversion of aryl bromides is possible only under rather harsh conditions, and the coupling of aryl chlorides has thus far required such high temperatures that selective monoarylation could not be achieved.[8] With arenediazonium salts as electrophiles, *ortho* arylation proceeds under mild conditions, but requires expensive iridium catalysts.[13] Oxidative arylations have been reported with expensive aryl boronic acids and a limited set of heteroarenes as arylating agents.[14]

Despite the remarkable progress achieved in this highly topical area, a broadly applicable carboxylate-directed C–H arylation that is based on readily available aryl bromides or chlorides and the use of a reasonably priced catalyst[15] has not yet been described. Ackermann and co-workers as well as our group have recently demonstrated that simple and affordable ruthenium catalysts efficiently promote regioselective hydroarylations of carboxylates.[16] We reasoned that the addition of electron-rich ligands might activate the intermediary ruthenacycle towards oxidative insertion into Ar–Br or Ar–Cl bonds by increasing its electron density, as outlined in Scheme 1. This hypothesis was supported by results of Dixneuf,[17] Larrosa,[18] Ackermann,[19] and others,[20] who demonstrated that ruthenium catalysts can activate aryl chlorides or bromides, and the observations by Daugulis,[8] Dixneuf,[21]



Scheme 1. Carboxylate-directed C–H arylation of arenes with aryl electrophiles assisted by electron-rich ligands.

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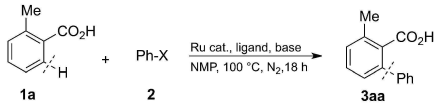
and Ackermann[22,19b] that such processes are facilitated by electron-rich phosphine and amino acid ligands.

To confirm our hypothesis, we chose the reaction of 2-methylbenzoic acid (**1a**) and bromobenzene (**2a**) as a model system and investigated various catalysts and conditions (Table 1). Encouragingly, traces of the desired product **3a** were detected when $[(p\text{-cym})RuCl_2]_2$ was used as

Table 1: Optimization of the *ortho* arylation reaction.[a]



1a **2** **3aa**

Entry	Catalyst	PhX	Base	Ligand	Yield[b] [%]
1	$[(p\text{-cym})RuCl_2]_2$	PhBr	$GuanCO_3$	–	trace
2	$[(p\text{-cym})RuCl_2]_2$	PhBr	K_2CO_3	–	13
3	$[(p\text{-cym})RuCl_2]_2$	PhBr	K_2CO_3	PPh_3	35
4	$[(C_6H_6)RuCl_2]_2$	PhBr	K_2CO_3	PPh_3	34
5	$[(C_6Me_6)RuCl_2]_2$	PhBr	K_2CO_3	PPh_3	0
6	$[(p\text{-cym})RuI_2]_2$	PhBr	K_2CO_3	PPh_3	35
7	$[(p\text{-cym})RuCl_2]_2$	PhBr	K_2CO_3	$PPhCy_2$	59
8	$[(p\text{-cym})RuCl_2]_2$	PhBr	K_2CO_3	PCy_3	76
9	$[(p\text{-cym})RuCl_2]_2$	PhBr	K_2CO_3	P^iPr_3	80
10	$[(p\text{-cym})RuCl_2]_2$	PhBr	K_2CO_3	$PMe_3{\cdot}HBF_4$	73
11	$[(p\text{-cym})RuCl_2]_2$	PhBr	K_2CO_3	$PEt_3{\cdot}HBF_4$	90
12[c]	$[(p\text{-cym})RuCl_2]_2$	PhBr	K_2CO_3	$PEt_3{\cdot}HBF_4$	93 (**93**)
13[c]	$[(p\text{-cym})RuCl_2]_2$	PhCl	K_2CO_3	$PEt_3{\cdot}HBF_4$	12
14[d]	$[(p\text{-cym})RuCl_2]_2$	PhCl	K_2CO_3	$PEt_3{\cdot}HBF_4$	12/75[e]
15[d]	$[(p\text{-cym})RuCl_2]_2$	PhCl	K_2CO_3	L-proline	47
16[d]	$[(p\text{-cym})RuCl_2]_2$	PhCl	K_2CO_3	DL-pipecolinic acid	80 (**75**)

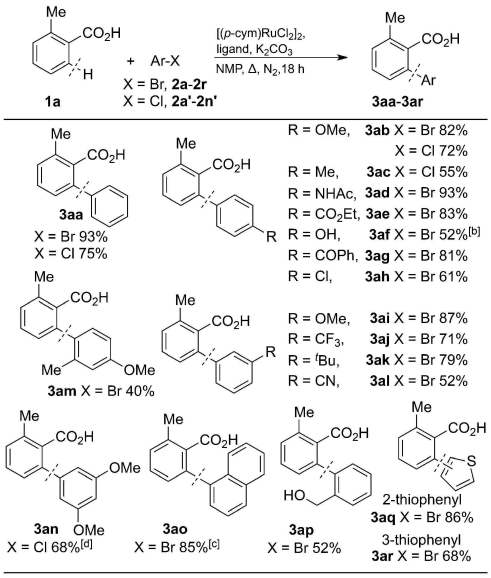
[a] Reaction conditions: **1a** (1 equiv), **2a** (4 equiv), [Ru] (4 mol%), ligand (8 mol%), base (1.1 equiv), NMP (3 mL), 100°C, 18 h, N_2 atmosphere. [b] Yields of the corresponding methyl esters determined by GC analysis after esterification with K_2CO_3 (2 equiv) and MeI (5 equiv) in NMP using *n*-tetradecane as the internal standard; yields of isolated products are given in parentheses. [c] PhX (1 equiv). [d] 120°C. [e] After 48 h. Cy = cyclohexyl, $GuanCO_3$ = guanidine carbonate, NMP = *N*-methylpyrrolidone, *p*-cym = *para*-cymene.

the catalyst in combination with guanidine carbonate at 120°C (entry 1), conditions that had been highly effective for our hydroarylation reaction.[16b] A major increase in yield was achieved upon switching to potassium carbonate as the base (entry 2). As anticipated, the yields improved substantially upon addition of a phosphine ligand (entry 3). Systematic variation of the ruthenium precursor confirmed that $[(p\text{-cym})RuCl_2]_2$ is the optimal precatalyst (entries 4–6). The nature of the ligand had a decisive influence on the reaction outcome. Among the ligands tested, electron-rich alkyl phosphines turned out to be superior. The best yields were achieved with triethylphosphine (entry 11), which can be conveniently administered in the form of its HBF_4 salt. After optimization of the reaction conditions (4 mol% $[(p\text{-cym})RuCl_2]_2$, 8 mol% $PEt_3{\cdot}HBF_4$, and 1.1 equiv K_2CO_3 in 3 mL NMP at 100°C), high yields were obtained even when using only one equivalent of the aryl bromide (entry 12). NMP is uniquely effective as the solvent (see the Supporting Information).

When chlorobenzene was used as the electrophile, only modest yields were observed under these conditions (entry 13), even upon increasing the temperature to 120°C (entry 14). Once again, the ligand turned out to be the decisive factor in the reaction development. Phosphine ligands were almost ineffective whereas amino acids strongly promoted the desired transformation (entry 15). After increasing the amount of aryl chloride, the monoarylated product **3a** was obtained in 80% yield. Although pipecolinic acid is a more efficient ligand than $PEt_3{\cdot}HBF_4$, the latter gave high yields when the reaction time was extended to 48 h, indicating that the reaction proceeds through a similar mechanism for aryl chlorides and bromides. Control experiments revealed that the optimal system for aryl chlorides is less effective for aryl bromides (33% yield, see the Supporting Information).

With effective methods in hand for the conversion of both aryl bromides and chlorides, we investigated the scope of the transformation. The model substrate 2-methylbenzoic acid (**1a**) was successfully coupled with various aryl bromides using method A (Table 2). Electron-rich and electron-poor substrates reacted similarly, and common functional groups, such as CF_3, CN, ester, halo, keto, alkyl, and methoxy moieties as well as unprotected phenolic and benzylic hydroxy groups,

Table 2: Substrate scope of the direct arylation with various aryl bromides and chlorides.[a]

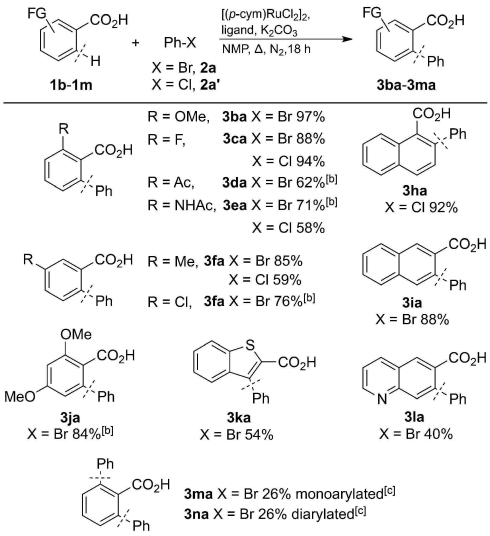


[a] Reaction conditions: Method A: **1a** (0.5 mmol), ArBr (0.5 mmol), $[(p\text{-cym})RuCl_2]_2$ (4 mol%), $PEt_3{\cdot}HBF_4$ (8 mol%), K_2CO_3 (1.1 equiv), NMP (3 mL), 100°C, 18 h, N_2 atmosphere. Method B: **1a** (0.5 mmol), ArCl (0.75 mmol), $[(p\text{-cym})RuCl_2]_2$ (4 mol%), DL-pipecolinic acid (8 mol%), K_2CO_3 (1.1 equiv), NMP (3 mL), 120°C, 18 h. Yields of the corresponding methyl esters after esterification with K_2CO_3 (2 equiv) and MeI (5 equiv) in NMP. [b] Isolated as the methyl ether. [c] ArBr (1.5 equiv). [d] Isolated as the free acid.

were tolerated in the *para* or *meta* position. *ortho* Substituents led to only moderate yields. It is noteworthy that under these conditions, aryl halides bearing functional groups that would be expected to be more efficient directing groups smoothly reacted with the *ortho* position of the carboxylates. This opens up welcome opportunities for polyfunctionalization. Products **3aa** and **3ab** demonstrate that comparable yields were achieved starting from aryl chlorides using method B (4 mol% $[(p\text{-cym})RuCl_2]_2$, 8 mol% DL-pipecolinic acid, 1.1 equiv K_2CO_3 in 3 mL NMP at 120 °C).

The scope with regard to the aromatic carboxylate was investigated with bromobenzene (**2a**) and chlorobenzene (**2a′**; Table 3). Benzoic acids bearing electron-donating or electron-withdrawing substituents, including methoxy, halo, and acyl groups, were smoothly coupled. Heterocyclic carboxylates were also successfully converted into the desired products. Unwanted double arylation could not be suppressed with unsubstituted or *para*-substituted benzoic acids. However, a substituent in the 3-position was sufficient to direct the arylation to the 6-position exclusively. This regioselectivity towards the less hindered *ortho* position was also observed with fused (hetero)aromatic quinoline 6-carboxylic acid (**1l**) and 2-naphthylcarboxylic acid (**1i**). A particularly remarkable example is the coupling of 2-acetamidobenzoic acid with **2a**. The new bond is selectively formed in the *ortho* position of the benzoic acid rather than in the *ortho* position of the amide

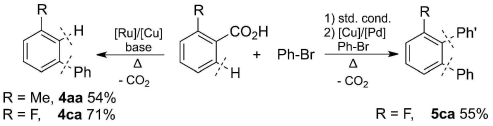
Table 3: Substrate scope of the direct arylation with various benzoic acids.[a]



[a] Reaction conditions: Method A: **1** (0.5 mmol), **2a** (0.75 mmol), $[(p\text{-cym})RuCl_2]_2$ (4 mol%), $PEt_3{\cdot}HBF_4$ (8 mol%), K_2CO_3 (1.1 equiv), NMP (3 mL), 100 °C, 18 h. Method B: **1** (0.5 mmol), **2a′** (0.75 mmol), $[(p\text{-cym})RuCl_2]_2$ (4 mol%), DL-pipecolinic acid (8 mol%), K_2CO_3 (1.1 equiv), NMP (3 mL), 120 °C, 18 h. Yields of the corresponding methyl esters after esterification with K_2CO_3 (2 equiv) and MeI (5 equiv) in NMP. [b] ArBr (1 equiv). [c] Yield determined by GC analysis.

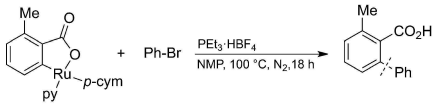
despite the C–H directing ability of the latter, which by far exceeds that of carboxylic acids in related C–H functionalizations. Four additional examples demonstrate that method B permits the coupling of aryl chlorides in comparable yields.

We next probed whether the biaryl synthesis could also be combined with concomitant protodecarboxylation.[23] The examples in Scheme 2 demonstrate that this process does not even require an additional reaction step. By simply adding a copper catalyst to the reaction medium and increasing the temperature to 190 °C, the corresponding biaryl products **4** were formed in good yields. The *ortho* arylation can also be combined with decarboxylative cross-couplings,[24] as demonstrated by the synthesis of terphenyl **5ca** in 55% non-optimized yield.



Scheme 2. *ortho* Arylations followed by decarboxylative reactions.

To shed light on the mechanism proposed in Scheme 1, we synthesized *ortho*-ruthenated toluate **6a**. The stoichiometric reaction of **6a** and $PEt_3{\cdot}HBF_4$ with bromobenzene (**2a**) yielded **3aa** in 57% yield (Scheme 3), which supports the intermediacy of an *ortho*-metalated species in the catalytic cycle. In the presence of only pyridine as the ligand, no product formation was observed, which confirmed the necessity for a suitable ligand (see the Supporting Information). In-depth mechanistic studies are underway to fully clarify the reaction pathway.



Scheme 3. Stoichiometric reaction of the *ortho*-ruthenated toluate **6a**.

In conclusion, we have shown that cost-effective ruthenium complexes are at least as effective and broadly applicable as state-of-the-art palladium systems for catalyzing the synthetically useful *ortho* arylation of benzoic acids. In combination with subsequent decarboxylative *ipso* substitutions, they promise to open up new perspectives for sustainable, regioselective arene (di)functionalization.

Experimental Section

An oven-dried 20 mL vessel was charged with $[Ru(p\text{-cym})Cl_2]_2$ (12.2 mg, 0.02 mmol, 4 mol%), triethylphosphonium tetrafluoroborate (8.3 mg, 0.04 mmol, 8 mol%, method A) or DL-pipecolinic acid (5.2 mg, 0.04 mmol, 8 mol%, method B), K_2CO_3 (76 mg, 0.55 mmol, 1.1 equiv), and benzoic acid **1** (0.50 mmol). After the vessel had been subjected to three alternating vacuum and nitrogen purge cycles, NMP (3 mL) and the aryl halide **2** (0.50 mmol, method A; 0.75 mmol, method B) were added via syringe. The resulting mixture was stirred at 100 °C for 18 h. After the reaction was complete, the mixture was

allowed to cool to room temperature. NMP (2 mL), K_2CO_3 (207 mg, 3 equiv), and MeI (156 μL, 5 equiv) were added, and the mixture was stirred at 60 °C for 2 h. The mixture was allowed to cool to room temperature, ethyl acetate (20 mL) was added, and the resulting mixture was washed with water, aqueous LiCl solution (20 %), and brine (20 mL each). The organic layer was dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient), yielding the corresponding biaryl.

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Keywords: aryl halides · benzoic acids · biaryls · C–H arylation · ruthenium

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Independently to this project, the groups of Weix, Ackermann and Larrosa reported almost simultaneously alternative but related protocols. This emphasizes how topical the research area in carboxylate-directed ruthenium-catalyzed C–H functionalizations is (**Table 3**).[327]

Table 3: Alternative protocols for the carboxylate-directed *ortho*-C–H arylation catalyzed by ruthenium.

group	Weix[331]	Ackermann[332]	Larrosa[333]
conditions	[(*p*–cym)$RuCl_2$]$_2$, PCy_3, K_2CO_3, NMP, 100 °C, 24 h	[(*p*–cym)Ru($MesCO_2$)$_2$], PCy_3, K_2CO_3, NMP, 120 °C, 16 h	[Ru(^{t}BuCN)$_6$](BF_4)$_2$], KOC(CF_3)$_3$, K_2CO_3, ^{t}BuCN, 140 °C, 16 h
aryl-source	Ar–I, Ar–Br, Ar–OTf	Ar–Br	Ar–I, Ar–Br, Ar–OTf

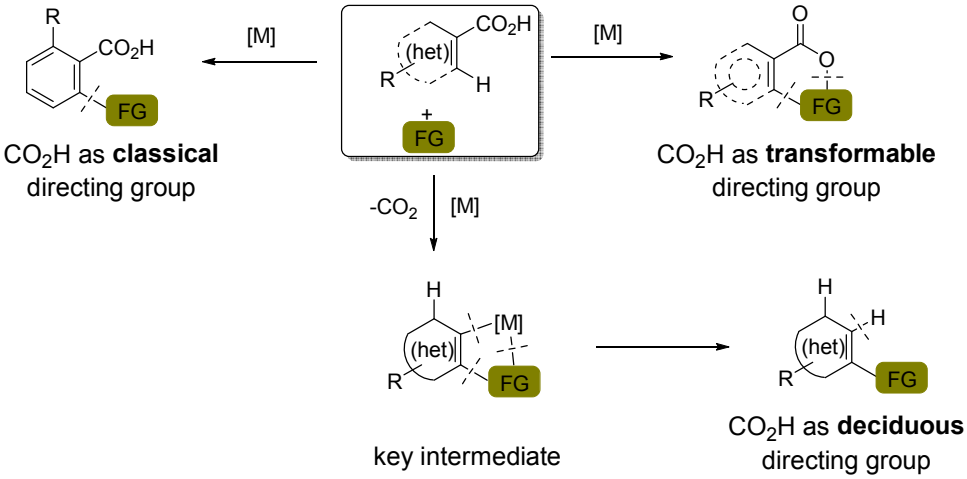
***Weix**: scope consists of 36 examples, up to 99% yield; **Ackermann**: scope consists of 30 examples, up to 93% yield; **Larrosa**: scope consists of 90 examples, up to 99% yield.*

The reaction conditions, scope, and yields reported by Weix and Ackermann are somewhat similar to the one reported in this work. Additionally, Weix's method can be applied to the arylation of heteroaromatic carboxylates. Ackermann's protocol is not restricted to *ortho*-arylations. Instead, implementing bromoalkenes or bromoalkynes leads to the formation of vinyl- as well as alkynyl arene carboxylic acids.[334] The group of Larrosa disclosed reaction conditions which rely on a cationic Ru(II)-species instead of adding electron-rich ligands. They presented an impressive scope of 90 isolated products and highlighted the robustness of his protocol by upscaling the reaction to 50 mmol, maintaining excellent yields even with very low 0.5 mol% catalyst loadings. It is important to mention that in contrast to our protocol, all these methods are, although important and versatile, inefficient for the coupling of aryl chlorides.

5.3. Regioselective C–H Hydroarylation of Internal Alkynes with Arenecarboxylates: Carboxylates as Deciduous Directing Groups

The ambitious objective of this project was the development of a catalytic carboxylate directed C–H functionalization, which fully exploits the benefits of aromatic carboxylic acids as starting materials in homogeneous catalysis. By marginal deviation of reaction conditions, the carboxylate should reveal its manifold nature serving as classical (**Scheme 36**, left), transformable (**Scheme 36**, right), and cleavable directing group (**Scheme 36**, bottom). Especially in the latter case, we aimed at an inherently selective pathway, which would

circumvent often observed yet unwanted unselective double functionalization. The carboxylate directing group is supposed to be discarded within the catalytic cycle during one functionalization event. Since the directing group is used only as long it is required to guide one single functionalization before being cast off to prevent a second C–H cleavage, this reaction mode can be figuratively compared to a deciduous tree in autumn, which sheds his leafs after they fulfilled their purpose. Hence, we define this reaction pathway as *deciduous*.

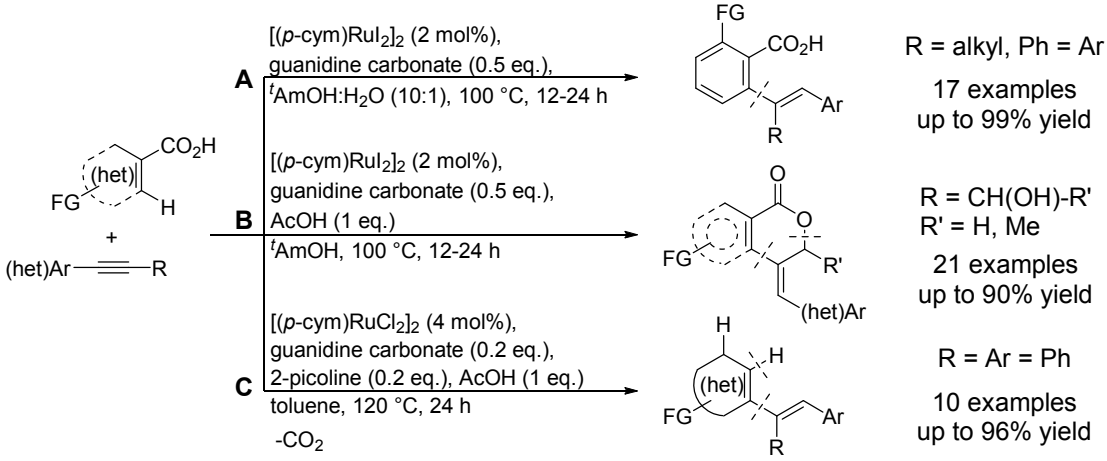


Scheme 36: Multipurpose directing ability of a carboxylic acid group.

As shown in section 3.3.2.2., alkynes proved to be efficient coupling partners in carboxylate directed oxidative C–C bond formations. These reactions occur *via* intermediary formed vinyl-metal species, which at this stage immediately undergo uncontrollable oxidative cyclization steps before a possible protonolysis can take place. In contrast, a redox neutral alkenylation *via* hydroarylation of alkynes obviates the presence of oxidants, hampering oxidative reaction channels, thus, keeping the reactive carboxylate group after the reaction untouched. Another challenge enters into force when the tendency of alkynes to react with the nucleophilic carboxylate to form enol esters, rather than with the C–H moiety, is enhanced by electron-deficient transition metal catalysts or ruthenium(II)-species. This innate reactivity emphasizes the arduous task associated with elaborating selective C–H hydroarylations of alkynes in the presence of a reactive carboxylate.

Scheme 37 shows the reaction conditions which were developed within this project. Screening experiments revealed that ruthenium is the only metal capable to catalyze this transformation and that the reaction outcome strongly depends on the nature and the amount of base. Interestingly, guanidine carbonate, a base which has never been used in analogous transformation, was found to be crucial to achieve desired high yields and high levels of

regioselectivity. This base is ideally administered substoichiometrically in order to avoid the absence of protons, thus, guaranteeing a prompt product forming protonolysis. However, the reaction outcome is mostly manipulated by the solvent system. In a *tert*-amyl alcohol/water mixture, the carboxylate acts as a classical directing group (**Scheme 37A**). The reaction is as expected not inherently monoselective. The second *ortho* position thus needs to be blocked in order to avoid double functionalization. The reaction shows high functional group tolerance. Symmetrical diaryl alkynes as well as unsymmetrically substituted alkyl,aryl alkynes are well-tolerated. The latter react with impressive regioselectivity for the alkyl branched product.

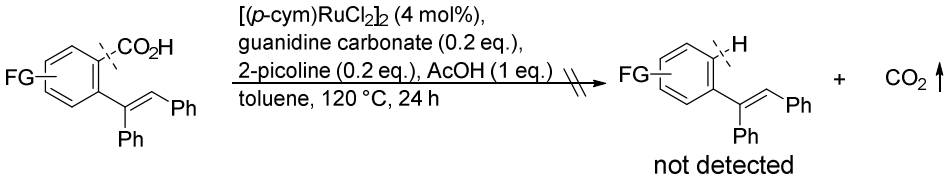


Scheme 37: Carboxylate directed C–H hydroarylation of benzoic acids with internal alkynes with the CO_2H moiety operating as **A** classical, **B** transformable, and **C** deciduous directing group.

Under more acidic conditions and with propargylic alcohols as coupling partner, benzoic acids as well as acrylic acids react to form *γ*-alkylidene-*δ*-lactones *via* a tandem *ortho*-C–H vinylation/esterification process (**Scheme 37B**). The carboxylate group acts as a transformable directing group, complementing the numerous oxidative C–H vinylation/lactonizations which usually lead to isocoumarins. Yields and functional group tolerance for this case are also very high. Moreover, the *in situ* esterification deactivates the directing ability of the carboxyl group so that double functionalization is completely omitted. In the less polar solvent toluene the reaction leads to the exclusive formation of the decarboxylated product (**Scheme 37C**). The reaction is limited to symmetrical diaryl alkynes. However, the key finding is that double-functionalized products were never observed under these conditions which led us to the assumption of a concerted C–H vinylation/decarboxylation instead of a sequential process. In our case, the C–CO_2H bond is truncated within the catalytic cycle, which makes a double functionalization impossible; a

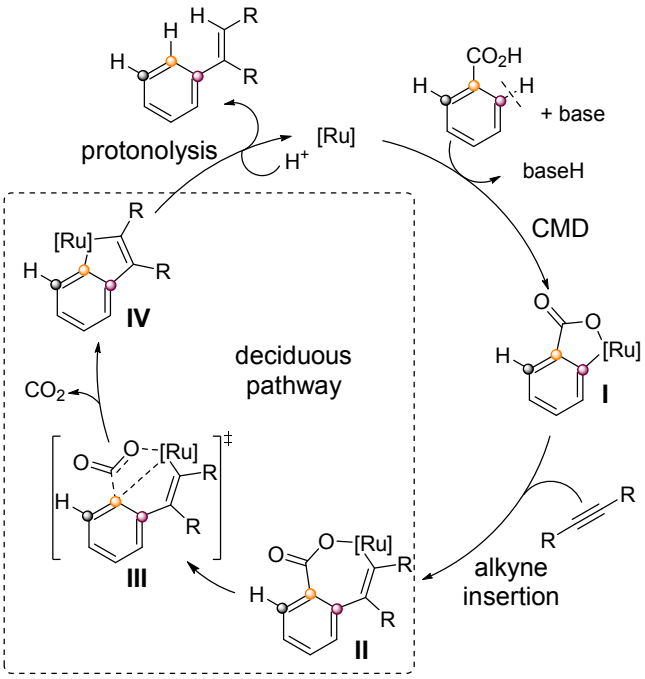
pathway that we define as *deciduous*. A *para*- or *ortho*-substituted benzoic acid thus leads exclusively to a *meta*-monofunctionalized arene, whereas a *meta*-substituted benzoic acid leads to a *para*-functionalized product. Hence, the formal *meta*- or *para*-functionalization of arenes, which are by far the most challenging positions to manipulate selectively *via* direct C–H activation methods or electrophilic substitutions, becomes accessible.[335]

The postulated deciduous pathway was further supported by a control experiment in which the products of the non-decarboxylative hydroarylation were submitted to the decarboxylative hydroarylation conditions (**Scheme 38**). In this case, the starting materials were recovered quantitatively.



Scheme 38: Protodecarboxylation control experiment under decarboxylative hydroarylation conditions.

Based on preliminary mechanistic investigations and previously reported related processes,[274,275,284] we proposed a tentative catalytic cycle for the deciduous reaction mode, which is depicted in **Scheme 39**. The first step consists of a carboxylate-directed C–H activation *via* a concerted metallation deprotonation (CMD) mechanism to form the ruthenacycle **I**. In the next step the alkyne inserts into the aryl-ruthenium bond, generating the seven-membered intermediate **II**. Intermediate **IV** is formed after a direct decarboxylation, preferentially in less polar solvent *via* transition state **III**. Protonolysis of the five-membered ruthenacycle **IV** regenerates the active catalyst species along with the mono-vinylated arene product.



Scheme 39: Proposed mechanism for the deciduous reaction mode.

In conclusion, this project highlights the multifaceted nature of a carboxylate opening up a versatile, waste-free synthesis of 2-vinylbenzoic acids or lactones from abundant precursors. Additionally, the discovery of the carboxylic acid moiety to act as a deciduous directing group is presented as an highly powerful reaction mode to guarantee regioselective mono-functionalizations. It bypasses the issues of a weak directing group and overrules innate regioselectivity which are unavoidably caused by intrinsic electronic properties.

Authors' contributions:

This work was performed in collaboration with Dr. L. Huang, Mr. G. Zhang and Mrs. V. Bragoni. Dr. L. Huang performed the initial screening and optimization. I re-optimized the reaction conditions for the non-decarboxylative hydroarylation as well as for the deciduous reaction mode. The reaction conditions for the tandem hydroarylation/esterification were optimized by Dr. L. Huang. Mr. G. Zhang and Mrs. V. Bragoni supported me during the final optimization process and processing analytical data. I performed all mechanistic experiments. The products were isolated equally by me and Dr. L. Huang. He wrote the first version of the manuscript and supporting information, which were revised by me. The final submission process, which includes further improvements of the manuscript, was performed by me and Prof. Dr. L. J. Gooßen.

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Regioselective C–H Hydroarylation of Internal Alkynes with Arenecarboxylates: Carboxylates as Deciduous Directing Groups

*Liangbin Huang, Agostino Biafora, Guodong Zhang, Valentina Bragoni, and Lukas J. Gooßen**

Dedicated to K. Peter C. Vollhardt on the occasion of his 70th birthday

Abstract: *In the presence of catalytic $[Ru(p\text{-}cym)I_2]_2$ and the base guanidine carbonate, benzoic acids react with internal alkynes to give the corresponding 2-vinylbenzoic acids. This alkyne hydroarylation is generally applicable to diversely substituted electron-rich and electron-poor benzoic and acrylic acids. Aryl(alkyl)acetylenes react regioselectively with formation of the alkyl-branched hydroarylation products, and propargylic alcohols are converted into γ-alkylidene-δ-lactones. The hydroarylation can also be conducted decarboxylatively with a different choice of catalyst and reaction conditions. This reaction variant, which does not proceed via intermediate formation of 2-vinylbenzoic acids, opens up a regioselective, waste-minimized synthetic entry to vinylarenes.*

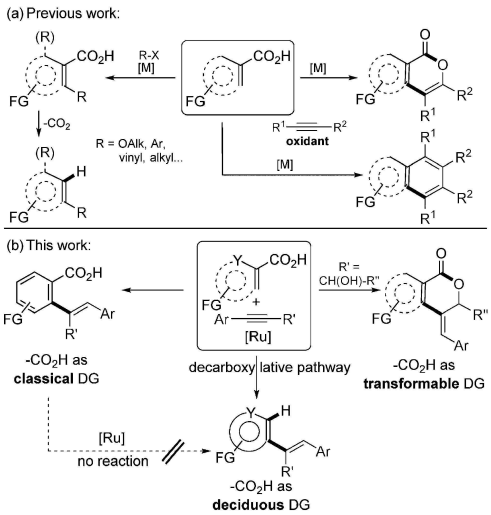
Given the prevalence of vinylarene moieties in functional materials, pharmaceuticals, and natural products,[1] efficient methods for the construction of this structural motif are constantly sought. Established synthetic approaches include Mizoroki–Heck[2] and Fujiwara–Moritani reactions,[3] as well as various catalytic cross-couplings of organometallic reagents with alkynes.[4]

C–H hydroarylations of alkynes are advantageous over these processes, because they require neither prefunctionalized substrates nor oxidants. Since the pioneering studies by Murai and co-workers,[5] various metals have been found to efficiently catalyze the hydroarylation of alkynes, for example Ru,[6] Rh,[7] Re,[8] Co,[9] and others.[10] However, these C–H functionalizations are highly regioselective only when directed by ketone, pyridine, amide, sulfoxide, or other strong directing groups, groups which need to be synthesized in additional reaction steps and are not easily removed.

Arguably, the most advantageous directing groups in *ortho*-functionalizations are carboxylates, because benzoic acids are widely available in great structural diversity and at low cost, and can subsequently be derivatized further, utilized as leaving groups in decarboxylative couplings,[11] or removed tracelessly by protodecarboxylation.[12] However, the weak coordinating ability of this group poses additional challenges in the development of regiospecific C–H-activating processes. In recent years, substantial advances in carboxylate-directed C–H activation have been made,[13] for example, by the groups of Yu,[14] Miura,[15] Ackermann,[16] and Larrosa,[12b,c] as well as our own group.[12d,17]

In this context, oxidative couplings of benzoic acids with alkynes to form isocoumarins, naphthalenes, and other cyclic structures have intensively been studied. These reactions involve carboxylate-directed C–H activation to give vinylmetal intermediates, which immediately undergo cyclization steps before either reductive elimination or protonolysis can occur (Scheme 1 a).[15,18] Moreover, in the presence of electron-deficient transition-metal catalysts or ruthenium(II), alkynes preferentially react with the nucleophilic carboxylate, to form enol esters, rather than with the C–H moiety.[19] This reactivity points to the challenges associated with developing selective C–H hydroarylations in the proximity of a reactive carboxylate.[20]

In continuation of our research on the use of carboxylic acids as substrates in transition-metal catalysis,[11,12d,17] we explored whether carboxylate groups could be utilized as directing groups in redox-neutral intermolecular hydroaryla-



Scheme 1. Carboxylate-directed C–H activation and coupling with alkynes. DG = directing group, FG = functional group.

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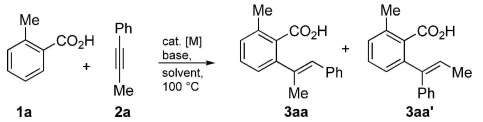
tions of alkynes (Scheme 1b). The desired process would have to be initiated by a carboxylate-directed *ortho*-C–H alkyne insertion step. The resulting vinyl–metal species would then need to be forced towards a reductive elimination step to yield alkenylbenzoic acids, despite the abundance of facile pathways leading to cyclized products.

To probe the feasibility of this concept, we investigated the reaction of 2-methylbenzoic acid (**1a**) with 1-phenyl-1-propyne (**2a**) in the presence of various metal catalysts (Table 1). Many complexes known for their ability to mediate

Table 1: Optimization of the directed hydroarylation conditions.[a]



1a **2a** **3aa** **3aa'**

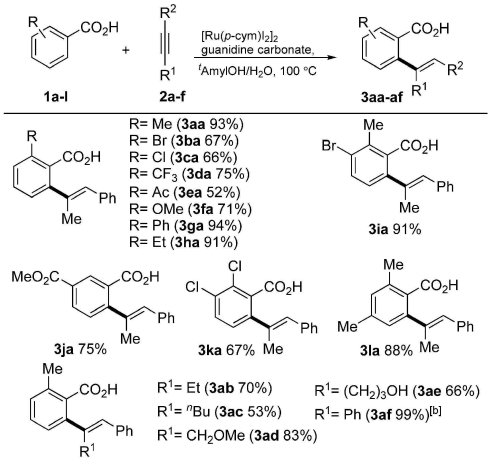
Entry	[M] (mol%)	Base	Yield [%] (**3aa**/**3aa'**)[b]
1	$[Ru(p\text{-cym})Cl_2]_2$ (4)	0.3 equiv K_2CO_3	43:5
2	$[Ru(p\text{-cym})I_2]_2$ (4)	0.3 equiv K_2CO_3	52:10
3	$[Ru(p\text{-cym})I_2]_2$ (2)	0.3 equiv K_2CO_3	60:6
4	$[Ru(p\text{-cym})I_2]_2$ (2)	0.1 equiv K_2CO_3	39:7
5	$[Ru(p\text{-cym})I_2]_2$ (2)	0.5 equiv K_2CO_3	46:trace
6	$[Ru(p\text{-cym})I_2]_2$ (2)	1.0 equiv K_2CO_3	n.d.
7	$[Ru(p\text{-cym})I_2]_2$ (2)	0.5 equiv Cs_2CO_3	53:14
8	$[Ru(p\text{-cym})I_2]_2$ (2)	0.5 equiv Li_2CO_3	44:9
9	$[Ru(p\text{-cym})I_2]_2$ (2)	0.5 equiv guanidine carbonate	68:7
10[c]	$[Ru(p\text{-cym})I_2]_2$ (2)	0.5 equiv guanidine carbonate	74:5
11[c,d]	$[Ru(p\text{-cym})I_2]_2$ (2)	0.5 equiv guanidine carbonate	73:6
12[c,e]	$[Ru(p\text{-cym})I_2]_2$ (2)	0.5 equiv guanidine carbonate	90 (93):5

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), [M] (4 mol%), base, 1,4-dioxane:H_2O (10:1, 1.1 mL), 100°C, 12 h. [b] Yields of corresponding methyl esters determined by GC after esterification with K_2CO_3 (2 equiv) and MeI (5 equiv) in MeCN using *n*-tetradecane as the internal standard. Yields of isolated products are given within parentheses. [c] ^{t}AmOH/H_2O = 10:1 as solvent. [d] 0.6 mmol **1a**. [e] 0.75 mmol **2a**. n.d. = not determined. cym = cymene.

C–H functionalizations, including $Pd(OAc)_2$, $[\{IrCp^*Cl_2\}_2]$, $[\{Ir(cod)_2Cl\}_2]$, and $[\{Rh(cod)_2Cl\}_2]$ were investigated, but none of them gave the hydroarylation product **3aa** in the desired selectivity (see the Supporting Information for details). However, the simple ruthenium complex $[Ru(p\text{-cym})Cl_2]_2$, usually an efficient hydroacyloxylation catalyst,[19] surprisingly furnished **3aa** in an encouraging 48% yield with a high 7:1 regioselectivity in favor of the methyl-branched stilbene derivative (entry 1). The iodine-bridged analogue $[Ru(p\text{-cym})I_2]_2$ proved to be an even more active and selective catalyst (entries 2 and 3). The process requires the presence of substoichiometric amounts of base, ideally 50 mol%, thus giving the best balance between conversion and selectivity. If stoichiometric amounts of base are present, the reaction is completely suppressed, thus indicating that protons are required in the overall process (entries 4–6). Carbonate bases, and guanidinium carbonate in particular, were found to be most effective (entries 7–9). The remarkable reactivity of the guanidinium base may result from the known ability of guanidine to form stable ruthenium(II) complexes.[21] A thorough solvent screening revealed that a 10:1 mixture of ^{t}AmOH and H_2O gives the highest yields and selectivities (entry 10; see the Supporting Information). Substrates **1a** and **2a** were best employed in a 1:1.5 ratio (entries 11 and 12).

The scope of the hydroarylation reaction with regard to the acid component was investigated using 1-phenyl-1-propyne (**2a**) as the coupling partner (Table 2). Benzoic acids

Table 2: Substrate scope of the directed hydroarylation.[a]

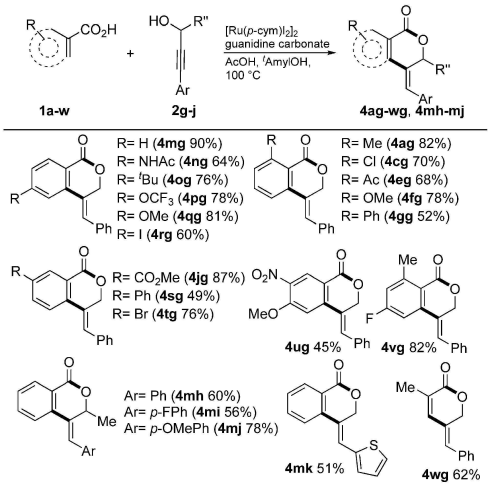


[a] Reaction conditions: **1a–l** (0.5 mmol), **2a–f** (0.75 mmol), $[Ru(p\text{-cym})I_2]_2$ (2 mol%), guanidine carbonate (0.5 equiv.), ^{t}AmOH/H_2O = 10:1 (1.1 mL), 100°C, 12–24 h. Yields of the corresponding methyl ester isolated after derivatization with MeI. [b] **2f** (0.5 mmol).

bearing various functional groups, including halides (**1b–c**), electron-withdrawing groups such as CF_3, Ac, CO_2Me (**1d–e,j**), or electron-donating moieties (**1a,f–g**) all gave good to moderate yields. Multisubstituted benzoic acids (**1i,k,l**)were also suitable substrates for this transformation. Next, several alkynes were evaluated as coupling partners in combination with toluic acid (**1a**). All gave reasonable yields, with best results being obtained with diphenylacetylene (**2f**). Unprotected hydroxy groups remained intact when at a distance from the C–C triple bond (**2e**).

With propargylic alcohols (**2g–k**) as substrates, the C–H hydroarylation was followed by intramolecular lactonization, so that γ-alkylidene-δ-lactones were formed in high yields (Table 3). This reaction nicely complements the oxidative C–H functionalizations/lactonizations, which lead to endocyclic C–C double bonds (Scheme 1). The broad scope spans from electron-rich to electron-deficient benzoic acids bearing a wealth of functional groups in the *para*-, *ortho*-, or *meta*-position (Table 3; **1m–v**). Various propargylic alcohols were smoothly converted into the corresponding lactones (**2h–k**). Not only benzoic acid, but also methacrylic acid (**1w**) was successfully converted. During the optimization of the

Table 3: Substrate scope of benzoic acids for hydroarylation and annulation.[a]

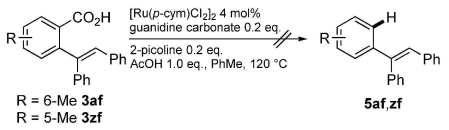


[a] Reaction conditions: **1a–w** (0.5 mmol), **2g–k** (0.75 mmol), [Ru(*p*-cym)I_2]$_2$ (2 mol%), guanidine carbonate (0.5 equiv), HOAc (1.0 equiv), ^{t}AmOH (1 mL), 100°C, 12–24 h.

reaction conditions, we had occasionally observed the formation of decarboxylation products.

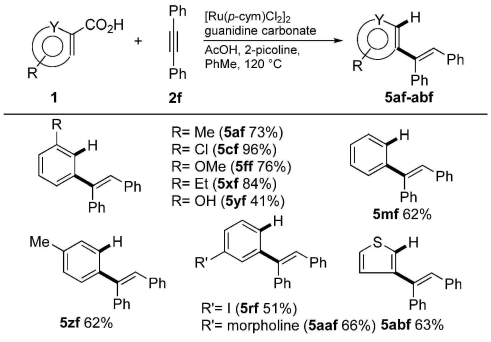
Intrigued by this observation, we optimized the catalyst and reaction conditions using the model reaction of **2f** with **1a** until the decarboxylative reaction pathway became predominant (see the Supporting Information). In the presence of [Ru(*p*-cym)Cl_2]$_2$ (4 mol%), guanidine carbonate (0.2 equiv), 2-picoline (0.2 equiv), HOAc (1.0 equiv), and in the nonpolar solvent toluene (2 mL), the decarboxylative coupling product **5af** was finally obtained in 73% yield at 120°C (Table 4). In this decarboxylative reaction variant, various functional groups are tolerated including halides, methoxy, and alkyl groups (Table 4). It also extends to heterocyclic substrates. The tolerance of chloro and even iodo groups demonstrates the orthogonality of the present transformation into traditional cross-coupling processes. However, this prototype protocol does not presently allow a high-yielding coupling of alkyl-substituted alkynes.

In a control experiment, we submitted the products **3af**,**zf** of the non-decarboxylative hydroarylation to the decarboxylative hydroarylation conditions (Scheme 2). These did not decarboxylate, which suggests that the decarboxylated prod-



Scheme 2. Protodecarboxylation experiment under standard reaction conditions.

Table 4: Scope with respect to benzoic acids for decarboxylative hydroarylation.[a]

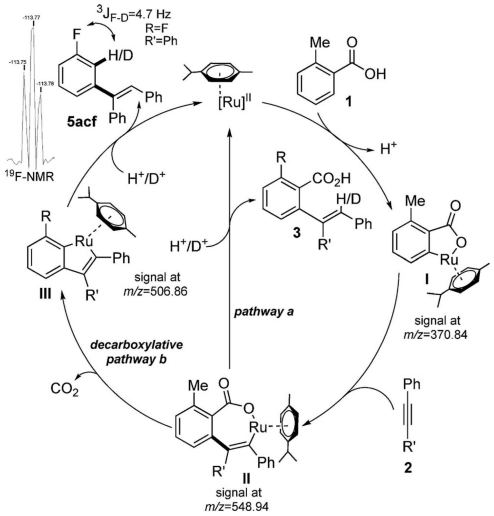


[a] Reaction conditions: **1a–ab** (0.5 mmol), **2f** (0.5 mmol), [Ru(*p*-cym)Cl_2]$_2$ (4 mol%), guanidine carbonate (0.2 equiv), 2-picoline (0.2 equiv), HOAc (1.0 equiv), toluene (2 mL), 120°C, 24 h.

ucts are not formed by a hydroarylation/protodecarboxylation sequence, but by an alternative mechanistic pathway. The carboxylate group may thus be considered to act as a deciduous directing group, remaining in place for as long as it is required to direct C–H functionalization, but being shed tracelessly within the catalytic cycle.[12] The key advantage of the concept of deciduous directing groups is that the unwanted formation of byproducts resulting from C–H functionalization on both sides of the directing group is impossible, because the directing group is removed in course of the first C–H functionalization, and is no longer in place to activate a second C–H bond.

Based on the above findings and mechanistic investigations for related processes,[18] a tentative catalytic cycle for the ruthenium-catalyzed C–H hydroarylation of alkynes can be outlined (Scheme 3). It starts with formation of the cyclometallated ruthenium complex **I**, which coordinates to the alkyne substrate. Migratory insertion affords the seven-membered alkenyl–ruthenium species **II**. In pathway a, which predominates in polar solvents, protonolysis occurs (or reductive elimination, if the proton resides at the ruthenium), thus releasing the hydroarylation product **3aa**. The alternative pathway b, leading to the decarboxylated product **5acf**, becomes more favorable at higher temperatures, when protonolysis is slower, that is, in less polar solvents, and when coordinating chloride ions are present. These factors contribute to facilitate extrusion of CO_2 from **II**. In-depth mechanistic studies are underway to fully clarify the reaction pathways of this intriguing transformation.

In conclusion, the carboxylate-directed C–H hydroarylation of internal alkynes with benzoic or acrylic acids catalyzed by the inexpensive, easy-to-handle [Ru(*p*-cym)I_2]$_2$ complex opens up a convenient and waste-free entry to a wide variety of 2-vinylbenzoic acids or aromatic δ-lactones from abundant precursors. In a less-polar solvent mixture and at higher temperatures, the carboxylate group is removed directly within the hydroarylation process. Beyond being removable, the carboxylates thus become deciduous directing groups,



Scheme 3. Proposed mechanism for the ruthenium-catalyzed (decarboxylative) C–H hydroarylation of alkynes. ESI-MS results provided for compounds where R = Me, R′ = Ph.

intrinsically preventing disubstitution in this directed C–H functionalization.

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Keywords: alkynes · C–H activation · decarboxylation · ruthenium · synthetic methods

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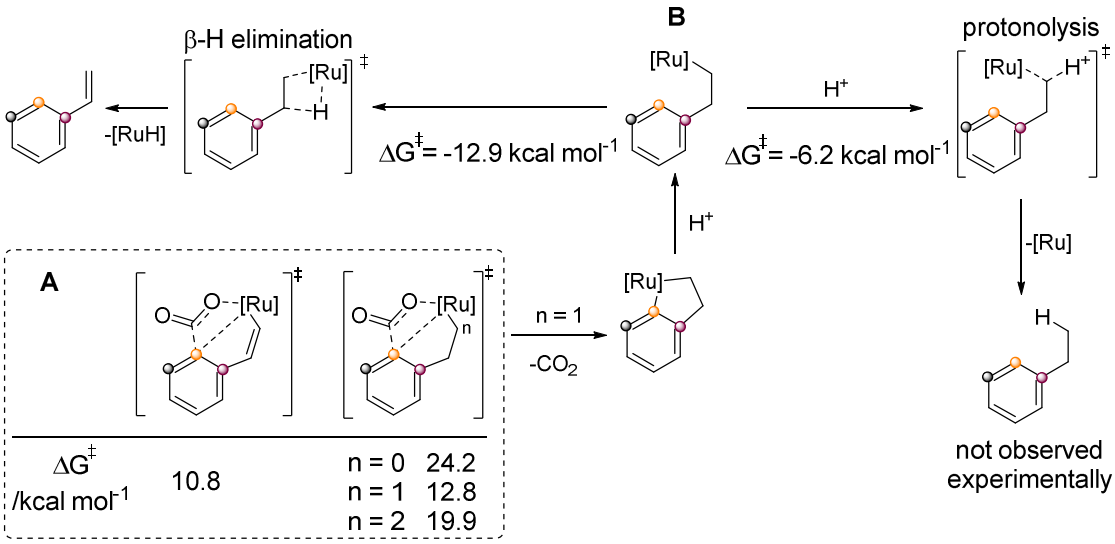
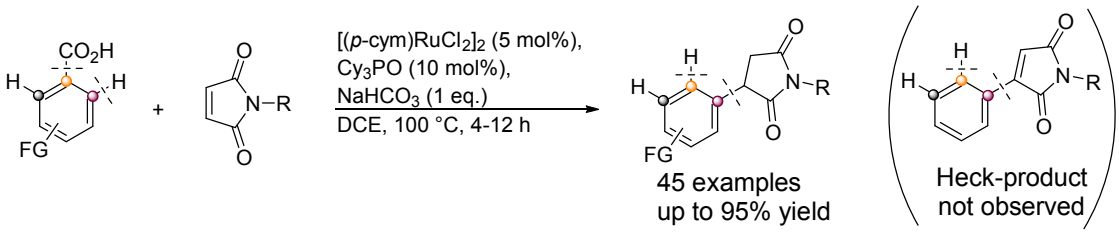
Independently to this work, the groups of Ackermann and Zhao together with Hartwig disclosed decarboxylative *ortho*-C–H hydroarylation processes leading to the same products as those arising from a deciduous reaction pathway.[337,338] The conditions reported by Ackermann *et al.* comprise a customized (*p*-cym)Ru($MesCO_2$)$_2$-catalyst in toluene at 100 °C and remarkably obviates any additional base. However, the benzoic acids chosen for the decarboxylative hydroarylation bear σ-electron withdrawing *ortho* substituents and have thus strong tendency to decarboxylate. Zhao and Hartwig report a catalyst system comprising a (*p*-cym)Ru(OAc)$_2$ catalyst in a sophisticated mixture of solvents (dioxane/mesitylene/*n*-heptane (2:2:1)). These conditions allow the decarboxylative hydroarylation of numerous *ortho*-, *meta*-, and *para*-substituted benzoic acids at already 80 °C. Additionally, implementing 20 mol% Cu(OAc)$_2$ unsymmetrically substituted alkyl,aryl alkynes were also reacted to the corresponding vinylarenes with rather poor regioselectivity for the alkyl branched product. In this case, the reaction is more likely to occur *via* a sequential hydroarylation/decarboxylation process mediated by the presence of copper. It is important to mention that none of the reported protocols, including our work, allow the hydroarylation of terminal alkynes. In the case of phenyl acetylene we observed that the starting materials are recovered entirely unreacted after the reaction.

Our initial preliminary mechanistic experiments and the hypothesis of a deciduous reaction mode were later confirmed by DFT-studies calculated by the group of Prof. Xin Hong.[339] Their investigations additionally showed that the deciduous pathway is considerably dependent on the ring size of intermediate **II** depicted in **Scheme 39**. The seven-membered ring seems to have the right geometry to allow a prompt decarboxylation directly from the intermediary metallacycle. The decarboxylation from a five- or eight-membered ring (n = 0 or n = 2, respectively) entails an energy barrier almost twice as high as the corresponding seven-membered metallacycle (**Scheme 40A**).



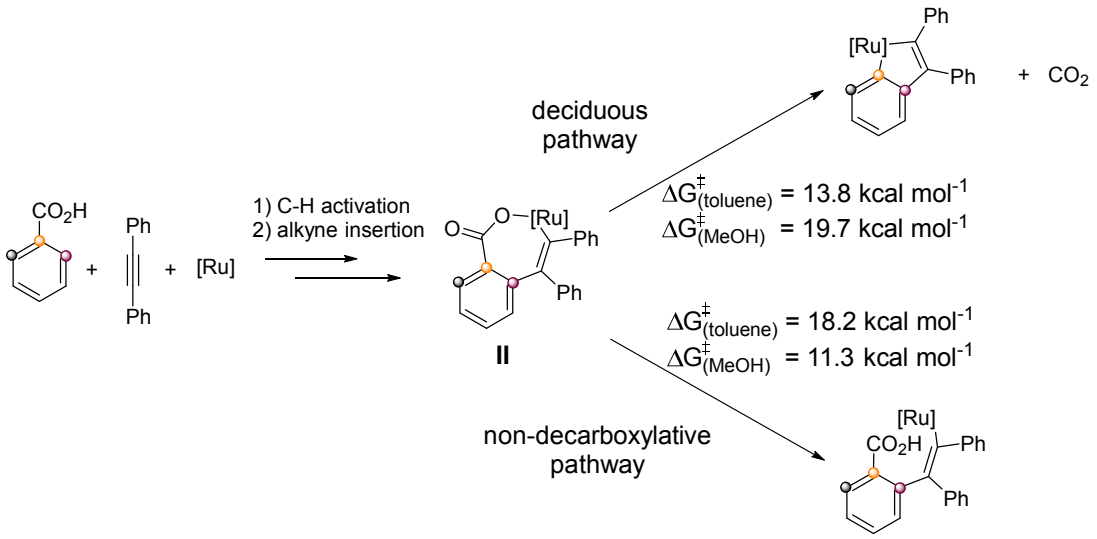
Scheme 40: Calculated Gibbs free energies for decarboxylation barriers in a deciduous reaction mode depending on the intermediate structure (**A**). Calculated energy barriers for competing protonolysis and β-H elimination pathways (**B**).

On the other hand, the vinyl functionality does not seem to play a detrimental role. The decarboxylation barrier of the saturated seven-membered metallacycle (n = 1), which would derive from an alkene insertion rather than alkyne insertion, is only 2 kcal mol^{-1} higher and should therefore be in theory also feasible. A successful reaction would be highly desirable because alkyl arenes are otherwise difficult to obtain. However, Xin Hong and coworkers have calculated, that after the decarboxylation a β-hydride elimination is preferred over protodemetallation, yielding again the corresponding vinylarenes (**Scheme 40B**). Interestingly, very recently the group of Baidya reported the decarboxylative hydroarylation of maleimides using carboxylate as deciduous directing group.[340] In this particular case, protodemetallation is preferred over β-hydride elimination leading to the alkylated arene instead of the Heck-product (**Scheme 41**). The authors do not comment on the reason for this selectivity. After the alkene insertion, the carbonyl group on the maleimide probably interacts with the ruthenium center hampering the conformation strictly required for successful β-hydride elimination.



Scheme 41: Ruthenium-catalyzed C–H hydroarylation of maleimides using carboxylates as deciduous directing groups.

The group of Xin Hong further calculated the solvent effect. We observed a strong impact on the reaction outcome depending on the nature of the solvent. In our case the polar protic solvent *tert*-amyl alcohol steers the reaction towards the non-decarboxylative pathway, whereas the aprotic and less polar solvent toluene favors the deciduous pathway. These trends were confirmed by the theoretical study (**Scheme 42**).

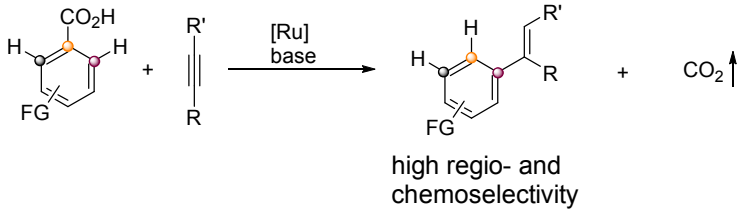


Scheme 42: Gibbs free energies calculated under the influence of the solvent.

In toluene, the energy barrier for the deciduous pathway is 13.8 kcal mol^{-1}. On the other hand, the energy barrier for the stepwise protonolysis in the same solvent is 4.4 kcal mol^{-1} higher in energy, showing that in toluene this competing pathway is improbable. Instead, in the polar protic solvent methanol the non-decarboxylative reaction is favored, showing an energy barrier of only 11.3 kcal mol^{-1}, which is 8.4 kcal mol^{-1} lower than the competing deciduous pathway.

5.4. Doubly Regioselective C–H Hydroarylation of Unsymmetrical Alkynes Using Carboxylates as Deciduous Directing Groups

In continuation with regioselective carboxylate-directed C–H functionalizations and our findings on the new reaction mode of the carboxylate moiety to act as a deciduous directing group, we aimed toward a more potent catalyst system, which would allow the decarboxylative C–H hydroarylation of all sorts of internal alkynes.

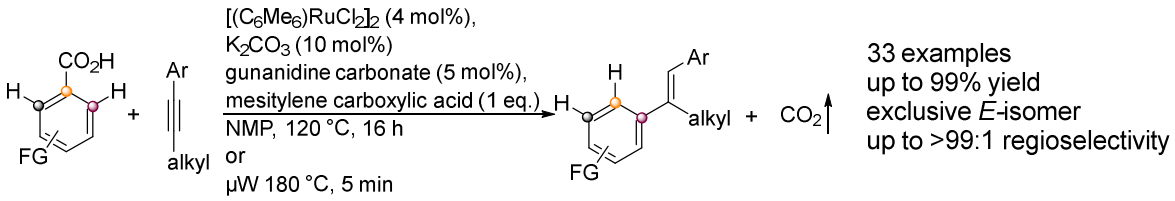


Scheme 43: Envisioned carboxylate directed decarboxylative C–H hydroarylation of unsymmetrical alkynes using carboxylates as deciduous directing groups.

Especially unsymmetrically substituted alkyl,aryl alkynes were found to be reluctantly reactive in previous reports and required the presence of copper promoting the decarboxylation in order to avoid double functionalization. That means that in this case the reaction occurs *via* a sequential vinylation/decarboxylation process rather than a deciduous reaction mode. We were therefore eager to find a catalyst system based on one single metal capable of activating the deciduous character of the carboxylate directing group.

Due to the numerous parameters that had to be taken into account, this reaction was particularly challenging to optimize. The major task was to avoid double functionalization by activating the deciduous pathway. Moreover, the reaction had to take place regioselectively in favor of the alkyl-branched formal *ortho*-vinylation and with high levels of *E*/*Z* stereoselectivity as well. The ruthenium-precursor [(hexamethylbenzene)$RuCl_2]_2$ was found to be more efficient in terms of conversion and selectivity instead of the *state-of-the-art* catalyst [(*p*-cym)$RuCl_2]_2$. The greater selectivity performance of this catalyst is probably due to the more bulky hexamethylbenzene ligand, which forces the alkyne insertion to occur in a specified trajectory. Moreover, the steric pressure induced by the ligand could ease the decarboxylation step by expelling the carboxyl group. To ensure a prompt protonolysis, the right proton source (mesitylene carboxylic acid) was particularly decisive. This additive is required to steer the reaction in favor of the deciduous pathway and diminishes competing

non-decarboxylative routes. Additionally, in order to achieve high conversions, the reaction medium needed to be buffered by a base system consisting of catalytic amounts of potassium carbonate and guanidine carbonate. Under conventional heating (120 °C) the reaction time is 16 h. However, the desired transformation can be conducted under microwave irradiation within 5 minutes only, which is particularly desirable for drug discovery. With both reaction conditions (**Scheme 44**) the corresponding vinyl-arenes were formed in high to quantitative yields, with exclusive formation of the *E*-isomer and with impressive regioselectivities in favor of the alkyl-branched product (up to 99:1).



Scheme 44: Doubly regioselective C–H hydroarylation of unsymmetrical alkynes using carboxylates as deciduous directing group.

To summarize, a second-generation catalyst elaborated within this project allows for the first time the doubly regioselective decarboxylative mono-hydroarylation of unsymmetrical alkynes. The protocol requires only low loadings of inexpensive and easy-to-handle $[(C_6Me_6)RuCl_2]_2$ and no additional decarboxylation catalyst. With the new system, the extrusion of CO_2 occurs along with the C–C bond formation even for alkyl aryl alkynes, so that double functionalization, a side reaction widely encountered in *ortho*-C–H activation, is fully suppressed. The new protocol is generally applicable to both electron-rich and -deficient (hetero-)arylcarboxylic acids bearing a broad range of substituents, in combination with diversely functionalized alkynes. In most cases, high yields and remarkable regioselectivities were achieved even for products that were inaccessible with the first-generation catalysts. The diaryl alkene products are key functionalities in functional materials, pharmaceuticals and natural products and the provided reaction variant under microwave irradiation offers the opportunity of a fast and cost-efficient drug discovery.

Authors' contributions:

This work was performed in collaboration with Dr. B. A. Khan, Dr. J. Bahri, and Mr. J. M. Hewer. I performed all screening experiments and optimized both reaction conditions. The products were isolated and characterized equally by me and Dr. B. A. Khan. Dr. J. Bahri performed initial microwave screening experiments. Dr. B. A. Khan wrote the first draft of

the manuscript and supporting information that were both revised by me. Mechanistic investigations and ESI-MS measurements in particular, were performed equally by Mr. J. M. Hewer and me. The final submission process, which includes further improvements of the manuscript, was performed by me and Prof. Dr. L. J. Gooßen.

The results of this project have been published in *Organic Letters*. The original publication has been adapted for this work and enclosed with permission of the publisher: "Reprinted (adapted) with permission from A. Biafora, B. A. Khan, J. Bahri, J. M. Hewer, L. J. Goossen, *Org. Lett.* **2017**, *19*, 1232–1235: „*Doubly Regioselective C−H Hydroarylation of Unsymmetrical Alkynes Using Carboxylates as Deciduous Directing Groups*".[342] Copyright 2017 American Chemical Society." An additional license is not provided by this journal and is not required.

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Doubly Regioselective C−H Hydroarylation of Unsymmetrical Alkynes Using Carboxylates as Deciduous Directing Groups

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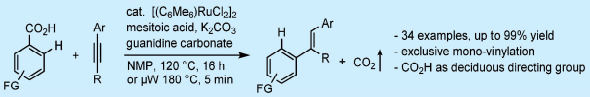
Supporting Information



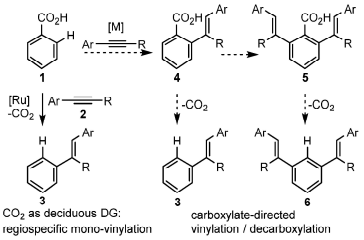
ABSTRACT: A catalyst system composed of $[(C_6Me_6)RuCl_2]_2$, potassium carbonate/guanidine carbonate, and mesitoic acid efficiently promotes the doubly regioselective C−H hydroarylation of unsymmetrical alkynes. The process involves carboxylate-directed *ortho*-C−H bond activation followed by regioselective addition to the alkyne C−C triple bond with concerted decarboxylation. This action of the carboxylate as a deciduous directing group ensures exclusive monovinylation with high selectivity for the (*E*)-1,2-diarylalkene.

Styrenes are prevalent structures often encountered in functional materials, pharmaceuticals, and natural and synthetic products.[1] Stoichiometric methods to access this structural motif, including Wittig[2] or Peterson olefinations[3] and insertions of alkynes into organometallic reagents,[4] are waste-intensive and require prefunctionalized substrates. Catalytic alternatives such as the Mizoroki−Heck reaction[5] and olefin metathesis[6] are more atom-economic but also require prefunctionalized arenes. C−H vinylations of the Fujiwara−Moritani type[7] have emerged as a powerful alternative but rely on stoichiometric oxidants.

C−H hydroarylations of alkynes compare favorably to the above concepts, especially when the regioselectivity is controlled effectively, e.g., by chelation assistance. Following early reports on ruthenium-catalyzed carbonyl-directed hydroarylations of alkynes,[8] several transition-metal catalysts, including precious[9−12] and first-row metals,[13,14] have been found to efficiently promote the insertion of alkynes into the C−H bond *ortho* to various directing groups. However, most of these directing groups, including phenol, ketone, pyridine, amide, and sulfoxide, require additional chemical steps for their synthesis, removal, or modification.

In this context, the use of carboxylates as directing groups is particularly desirable because they are easily accessible at low cost and in great structural diversity, can be transformed into a wealth of other compound classes, may serve as leaving groups in decarboxylative couplings, and are tracelessly removable by a subsequent protodecarboxylation step.[15,16] Over the years, extensive research has led to the discovery of carboxylate-directed substitutions of *ortho*-C−H atoms with (hetero)aryl, alkyl, acyl, allyl, alkoxy, olefin, amine, amide, and halogen groups.[17] The discovery that carboxylates can act as deciduous directing groups[18] that stay in place just long enough to direct one group into their *ortho*-position further improves the versatility of this group. A deciduous-type reaction pathway, in which the CO_2 is released concomitantly to C−C bond formation, intrinsically prevents unwanted double functionalization, a typical side reaction in *ortho*-C−H functionalizations (Scheme 1).[19]

Scheme 1. CO_2H as Deciduous vs Removable Directing Group (DG) in Catalytic Hydroarylations



The development of carboxylate-directed regiospecific C−H hydroarylations is challenging because of the weak coordinating ability of the carboxylate group and the known reactivity of alkynes to undergo carboxylate addition to the enol esters in the presence of Ru^{II}[20] and because carboxylate groups reduce the electron density at the arene ring, thereby lowering its reactivity.

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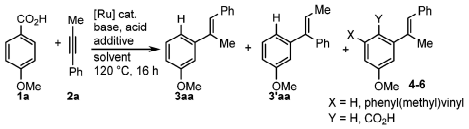
The Ackermann group, the group of Hartwig and Zhao, and our own group have independently developed Ru-catalyzed carboxylate-directed C−H hydroarylations of internal alkynes.[19a−c] All of these processes allow the decarboxylative hydroarylation of diarylalkynes in high yields. However, examples with alkylarylalkynes as coupling partners were provided only by Hartwig and Zhao, and these reactions did not proceed via a deciduous-type pathway. Selectivity for the monovinylated, decarboxylated product was achieved by using a 2-fold excess of the arenecarboxylate and a powerful copper protodecarboxylation catalyst. Satisfactory yields and selectivities were obtained merely for a few substrates.[19c]

We herein report a catalyst system that requires only low Ru loadings and no copper mediator to promote the regioselective decarboxylative monovinylation using unsymmetrical alkynes. In the search for an efficient protocol for the desired transformation, we used the reaction of *p*-methoxybenzoic acid **1a** and 1-phenyl-1-propyne **2a** as a model (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



#	[Ru]	base (mol %)	acid	additive (mol %)	yield (%)		
					3aa	3'aa	4-6
1[b]	**[Ru1]**	-	-	$Cu(OAc)_2$ (20)	59	5	n.d.[19c]
2[b]	"	-	-	-	13	2	8
3[c]	**[Ru2]**	$GuanCO_3$ (20)	AcOH	2-picoline (20)	25	n.d.	21
4[c]	**[Ru3]**	"	"	"	38	"	20
5	"	"	"	"	53	3	23
6	"	"	"	-	53	3	29
8	"	K_2CO_3 (20)	"	-	31	16	8
9	"	Cs_2CO_3 (20)	"	-	23	9	8
10	"	K_2CO_3 (10)	"	-	39	3	5
11	"	$GuanCO_3$ (5) + K_2CO_3 (10)	"	-	60	9	13
12	"	"	TMBA	-	71	2	n.d.
13[d]	"	$GuanCO_3$ (10)	"	-	76	9	n.d.

[a]Method A: **1a** (0.5 mmol), **2a** (0.75 mmol), [Ru] (4 mol %), base, acid (1 equiv), additive, NMP (1 mL), 120 °C, 16 h. [b]Method A: **1a** (1 mmol), **2a** (0.5 mmol), **[Ru1]** (10 mol %) in dioxane/mesitylene/*n*-heptane (2:2:1), 80 °C, 48 h. [c]Method A: **2a** (0.5 mmol) in PhMe. [d]Method B: **1a** (1 mmol), **2a** (0.5 mmol), [Ru] (4 mol %), guanidine carbonate (10 mol %), TMBA (0.5 equiv), NMP (2 mL), 180 °C μW, 5 min. Yields were determined by GC analysis after esterification with MeI/K_2CO_3 using *n*-tetradecane as internal standard. **[Ru1]** = (*p*-cym)Ru$(OAc)_2$, **[Ru2]** = $[(p\text{-cym})RuCl_2]_2$, **[Ru3]** = $[(C_6Me_6)RuCl_2]_2$. $GuanCO_3$ = guanidinium carbonate. TMBA = 2,4,6-trimethylbenzoic (mesitoic) acid.

When Hartwig and Zhao's conditions were used, i.e., treatment a 2-fold excess of **1a** with **2a** in the presence of **[Ru1]** and 20 mol % $Cu(OAc)_2$ in dioxane/mesitylene/*n*-heptane at 80 °C for 48 h,[19c] the desired styrene **3aa** was formed in 59% yield and a **3aa**/**3′aa** regioselectivity of 12:1 (Table 1, entry 1). Unsatisfactory results and formation of products **4**−**6** in notable amounts were observed without the copper mediator (entry 2). Our conditions previously optimized for diarylalkynes, namely **1a** (0.5 mmol), **2a** (1 equiv), $[(p\text{-cymene})RuCl_2]_2$ (4 mol %, **[Ru2]**), guanidine carbonate (20 mol %), AcOH (1 equiv), and 2-picoline (20 mol %) in toluene, provided **3aa** in 25% yield along with 21% of **4aa**−**6aa**, which are products arising from a competing nondeciduous directing mode of the carboxylate group (entry 3). Screening of various catalysts, additives, and solvents showed that the combination of a $[(C_6Me_6)RuCl_2]_2$ (**[Ru3]**) catalyst and the polar aprotic solvent NMP gave greater conversion and good regioselectivity (entry 4 and Table S1). Increasing the amount of **2a** to 1.5 equiv further improved the yield (entry 5). Interestingly, 2-picoline, which was an important component of our original conditions, did not affect the outcome here (entry 6). Higher yields were obtained when the acetic medium was buffered with 5 mol % of guanidine carbonate and 10 mol % of potassium carbonate (entries 8−11). Substituting acetic by mesitoic acid shifted the reaction completely toward the desired pathway, so that products **4**−**6** arising from competing pathways were no longer detected. Within 16 h under optimal conditions, i.e., **1a** (0.5 mmol), **2a** (0.75 mmol), $[(C_6Me_6)RuCl_2]_2$ (4 mol %), guanidine carbonate (5 mol %), K_2CO_3 (10 mol %), and mesitoic acid (1 equiv) in NMP (1 mL) at 120 °C, the monovinylated product **3aa** was obtained exclusively and with an impressive **3aa**/**3′aa** regioselectivity of 36:1 in favor of the less sterically hindered alkyl-branched product (entry 12, method A). The regiochemical preference is in agreement with findings by Fagnou, Miura, Rovis, Li, Ackermann, Larock, and others on mechanistically related oxidative annulation reactions.[21]

When a preformed *o*-vinylbenzoic acid (**4ba**) was subjected to the reaction conditions, no decarboxylation was observed (see the Supporting Information), which confirms that C−C bond formation and decarboxylation indeed occur concertedly. Further control experiments established that both base and acid additive are required (Table S1).

The only drawback of this protocol was the long reaction time. However, this can be shortened to only 5 min by employing microwave irradiation (method B) after small adjustments to the catalyst system (10 mol % of guanidine carbonate as the only base and with the amount of mesitoic acid reduced to 0.5 equiv).[22]

With two effective sets of conditions in hand, the scope and selectivity of the ruthenium-catalyzed decarboxylative C−H hydroarylation of **2a** with substituted benzoic acids **1** were evaluated (Scheme 2). The scope extends from electron-rich to electron-poor benzoic acids with various functional groups in the *ortho*, *meta*, or *para* positions, as well as heterocyclic carboxylates. Benzoic acids bearing *ortho* substituents generally gave excellent yields (**3ba**−**ka**). *Para*-substituted benzoic acids afforded monofunctionalized products (**3aa**,**la**−**oa**) exclusively and in good yields. *p*-Toluic acid (**1m**) afforded 30% of non-decarboxylated product **4ma** along with **3ma**, which presumably result from a competing nondeciduous pathway. Extending the reaction time to 48 h did not shift the product distribution further toward **3ma** (see the SI). This clearly indicates that the decarboxylated product results from a concerted C−C bond formation/decarboxylation process, and that once the non-decarboxylated product is released, it does not re-enter the catalytic cycle. The reactivity of *meta*-substituted acids was lower (**3pa**,**qa**). Deactivating substituents such as nitro groups reduced the yields (**3wa**). With 2-allyl benzoate, the side-chain double bond isomerized into conjugation under the reaction conditions (**3da**). The efficiency of the microwave method was generally

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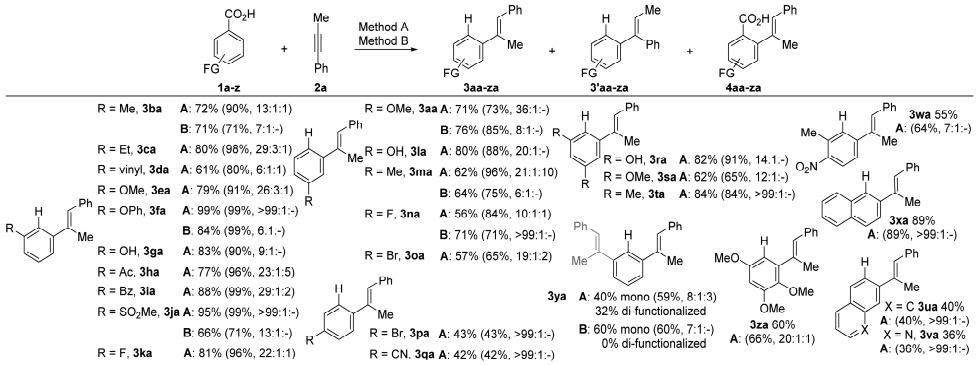
Scheme 2. Scope with Respect to the Benzoic Acids[a]

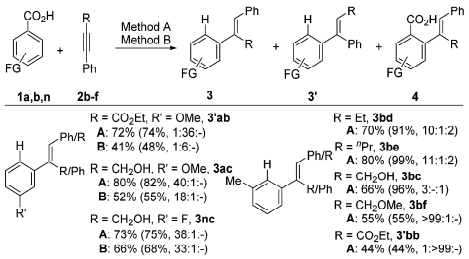


[a]Isolated yields. GC yields and product ratios of **3**:**3′**:**4**, in parentheses, after esterification using *n*-tetradecane as internal standard.

comparable, although the higher reaction temperature somewhat affected the regioselectivity. Only for unsubstituted benzoic acid (**1y**) was nondecarboxylative hydroarylation a major side reaction under thermal conditions, leading to the formation of substantial amounts of disubstituted products. However, under microwave conditions, the carboxylate acted as a deciduous directing group again, and only monovinylated product **3ya** was observed.

We next investigated the alkyne substrate scope in combination with *p*-anisic (**1a**), *p*-fluorobenzoic (**1n**), and *o*-toluic acid (**1b**) (Scheme 3). For alkylarylalkynes **2b**−**f**, high

Scheme 3. Scope with Respect to the Alkynes[a]

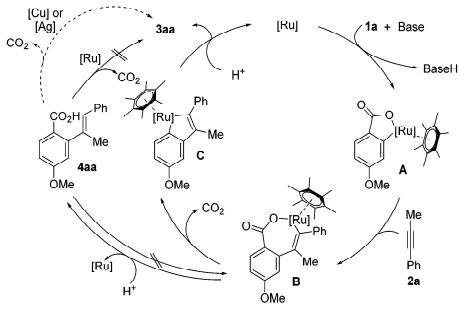


[a]Isolated yields. GC yields and product ratios of **3**:**3′**:**4**, in parentheses, after esterification using *n*-tetradecane as internal standard.

yields and excellent regioselectivities of the desired products were achieved. Electron-poor propiolates (**2b**) were successfully converted to β,β-diaryl acrylates, which are valuable synthons for further decarboxylative couplings.[18,23] Terminal alkynes did not react under the reaction conditions.

A plausible reaction pathway derived from mechanistic experiments (see the SI) is outlined in Scheme 4. Following C−H activation, the *ortho*-ruthenated complex **A** coordinates the alkyne substrate. Migratory insertion leads to the seven-membered ruthenacycle **B**. Possible next steps involve either decarboxylation to intermediate **C**, which is then protodemetalated to product **3aa**, or early protodemetalation of **B**, resulting in the nondecarboxylated compound **4aa**. Ruthenium is not

Scheme 4. Proposed Mechanism for the Ruthenium-Catalyzed Decarboxylative Hydroarylation



capable by itself of decarboxylating **4aa** under these conditions. CO_2 extrusion can occur only in the presence of copper or silver decarboxylation catalysts, as previously reported.[16]

In conclusion, an effective and broadly applicable C−H hydroarylation of unsymmetrical alkynes has been developed on the basis of the inexpensive and easy-to-handle catalyst $[(C_6Me_6)RuCl_2]_2$. The concerted C−C bond formation/CO_2 extrusion process ensures nearly exclusive formation of monovinylated products and obviates a subsequent protodecarboxylation step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00300.

Detailed screening tables, experimental procedures, analytical data for all the products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Due to the great response of the concept of carboxylates as deciduous directing group, we were asked to write an Account article in occasion of the special issue “Thieme Chemistry Journals Awardees – Where Are They Now?”. In here, we define the possible reaction modes of the carboxylate as directing group and specify in particular the concept of the deciduous reaction mode.

Authors’ contributions:

I wrote the first version of the manuscript. The final submission process, which includes further improvements of the manuscript, was performed by me and Prof. Dr. L. J. Gooßen.

The article has been published in *Synlett*. The original publication has been adapted for this work and enclosed with permission of the publisher: "Reprinted (adapted) with permission from A. Biafora, L. J. Goossen, *Synlett*. **2017**, *28*, A–F:„*Thieme Chemistry Journals Awardees – Where Are They Now? New Reaction Mode in Carboxylate-Directed C–H Functionalizations: Carboxylates as Deciduous Directing Groups*".[341] Copyright 2017 Georg Thieme Verlag Stuttgart • New York."

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A

Synlett A. Biafora et al. Account

Thieme Chemistry Journals Awardees – Where Are They Now? New Reaction Mode in Carboxylate-Directed C–H Functionalizations: Carboxylates as Deciduous Directing Groups

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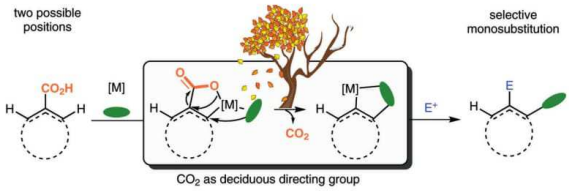

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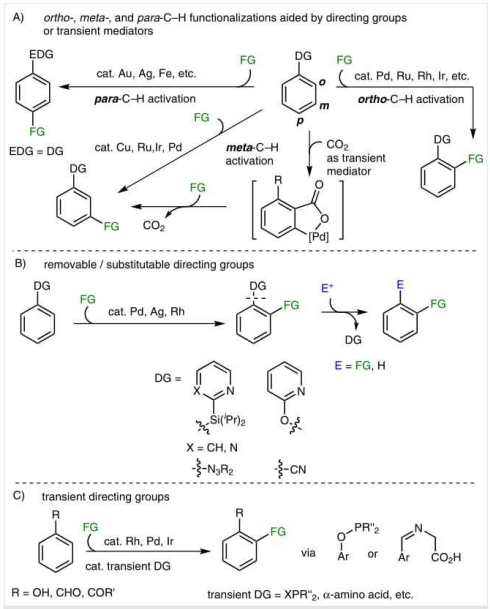
Abstract The widely available carboxylate groups have recently emerged as advantageous leaving groups for regioselective *ipso* substitutions and directing groups for *ortho*-C–H functionalizations in transition-metal catalysis. In the latter reactions, they can subsequently be transformed into a wealth of functionalities through decarboxylative *ipso* substitutions, or tracelessly removed through protodecarboxylation. The latest development in this field are reactions in which carboxylic acids function as deciduous directing groups, unlocking their unique potential for achieving regioselective monofunctionalization of a single *ortho*-C–H position. A deciduous directing group stays in place just long enough to direct an incoming reagent into a specific position and is then shed tracelessly as soon as the new C–C or C–heteroatom bond has formed. This inherently prevents unwanted double functionalization. This account discusses characteristics and synthetic opportunities of reactions with carboxylates as deciduous directing groups.

Key words C–H activation, deciduous directing groups, catalysis, benzoic acids, decarboxylation

1 Introduction

The development of methods for the regioselective functionalization of (hetero)arenes occupies a pivotal position in contemporary organic chemistry given the broad application of substituted aromatic compounds in functional materials, pharmaceuticals, and agrochemicals.[1] In this context, transition-metal-catalyzed functionalizations of aromatic C–H and C–C bonds are key technologies that enable the efficient and environmentally benign construction of new C–C and C–heteroatom bonds.[2] The regioselectivity of C–H functionalizations is usually governed by electronic and/or steric factors. However, these can be overridden by the action of directing groups, which guide the transition metals into specific positions at the aromatic ring. Substitution mostly occurs *ortho* to the coordinating group, but with particularly large directing groups, even *meta* and *para* positions have been functionalized selectively (Scheme 1, a).[3]



Scheme 1 Regiospecific arene functionalization controlled by directing groups (DG = directing group, EDG = electron-donating group, FG = functional group)

The key problems associated with the use of directing groups are that (1) they need several steps to be installed, (2) it is hard to avoid double functionalization of two similar *ortho* positions, and (3) only few can be tracelessly removed under mild conditions or used as anchor points for further *ipso* substitution. Scheme 1, b gives an overview over state-of-the-art directing groups, for which these key issues have partially been addressed. These include 2-(diisopropylsilyl)-pyridines and -pyrimidines by Gevorgyan, 2-pyridyloxy groups by Chatani, and substituted triazenes by Bräse and others.[4]

Recently, arene *ortho*-C–H functionalization was also achieved with transient directing groups, which are formed and removed in situ by reversible condensation of a functional group of the substrate with an added reagent (Scheme 1, c).[5]

Our work has focused on carboxylic acids as directing groups in *ortho*-C–H functionalization reactions. Their use has significant advantages.[6] For one, no additional synthetic steps are needed for their preparation, as they are cheap and readily available in great structural diversity. In addition, carboxylate groups can be tracelessly removed by liberation of innocuous CO_2. Moreover, they can be utilized as leaving groups in a rapidly growing number of decarboxylative coupling reactions, with formation e.g. of C–C, C–O, C–N, C–S, C–P, and C–halogen bonds.[7] Despite the challenges encountered with C–H functionalizations based on carboxylates as directing groups (weak coordinating ability, weak σ-donor tendency, and intrinsic reactive character), our group and those of Yu, Miura, Ackermann, Daugulis, and others have succeeded in developing an array of synthetically valuable transformations.[8]

Particularly noteworthy are transformations in which the carboxylate group can tracelessly be removed after a C–H functionalization step (Scheme 2).[9] The groups of Larrosa, Li, Chang, and Su presented *ortho*-C–H arylations with arenes and heteroarenes, as well as amidation and sulfonamidation reactions, each of which was combined with a subsequent protodecarboxylation.[10] However, since the decarboxylation proceeds in an extra reaction step, unavoidable side products arise from double C–H functionalization. The second *ortho* position therefore needs to be protected, diminishing the synthetic utility of these transformations. To date, only a handful of examples exist in which *ortho* functionalizations have been combined with decarboxylative couplings rather than protodecarboxylations, all of them reported by our group.[8m,11]

Biographical Sketches

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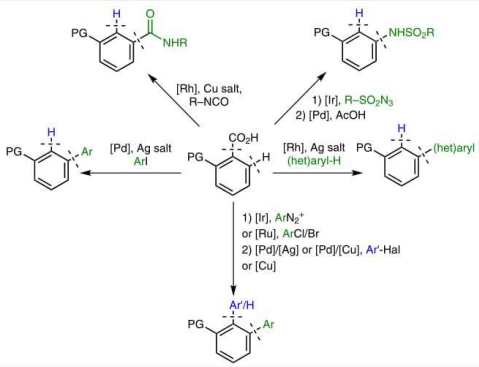
Lukas Gooßen studied chemistry at the universities of Bielefeld and Michigan, and wrote his Master's thesis in the group of K. P. C. Vollhardt at UC Berkeley. He was awarded a Ph.D. from the TU Munich in 1997 for research on N-heterocyclic carbene complexes supervised by W. A. Herrmann, and pursued postdoctoral research with K. B. Sharpless. He began his professional career as an industrial chemist at Bayer AG in 1999, and then moved back to academia to the group of M. T. Reetz, MPI for Coal Research, for his habilitation. He held academic positions at RWTH Aachen and TU Kaiserslautern before being appointed Evonik Chair of Organic Chemistry at the Ruhr University Bochum in 2016. His research interests include the development of catalytic reaction concepts for C–C and C–heteroatom bond formation designed to reduce the production of waste salts and effluents with a focus on decarboxylative couplings, fluoroalkylation reactions, and valorizations of renewables. He received the Thieme literature prize (2002), the Jochen-Block award of the DECHEMA (2003), the Carl-Duisberg Award of the GDCh (2007), the Novartis Young Investigator Award (2007), and the AstraZeneca Award in Organic Chemistry (2008).

Agostino Biafora was born in 1986 in Crotone, Italy. He studied chemistry at the Technische Universität Kaiserslautern (Germany) where he obtained his diploma degree of chemistry in the group of Prof. F. W. Patureau working on transition-metal-catalyzed cross-dehydrogenative C–N bond formations. In April 2014 he started his PhD in the group of Prof. L. J. Gooßen to work on carboxylate-directed C–H functionalizations.

c



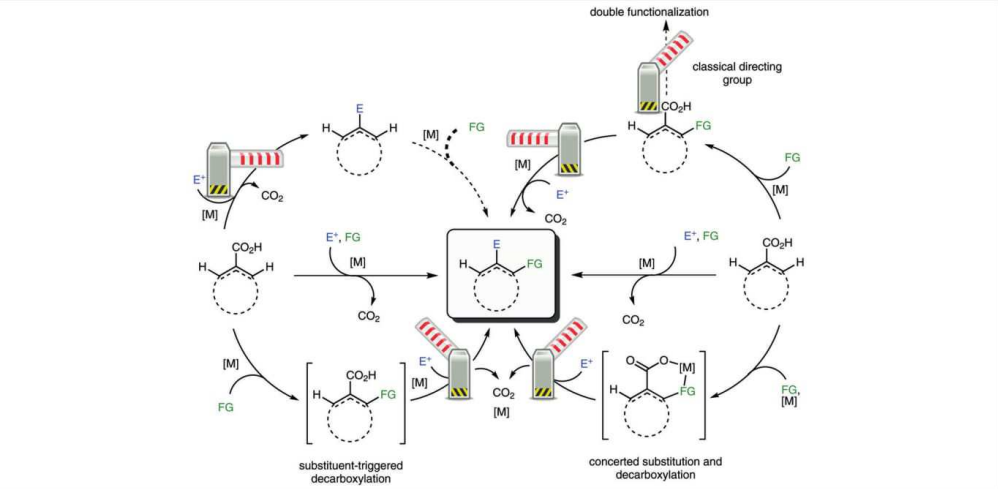
Scheme 2 Carboxylate-directed *ortho* and *ipso* substitutions with traceless removal of the carboxylate (PG = protecting group)

Carboxylate groups have also been shown to act as transient directing groups in the synthesis of *meta*-substituted phenols.[12] The reaction proceeds through sequential Kolbe *ortho*-C–H carboxylation, followed by carboxylate-directed *ortho*-C–H functionalization, and thermal decarboxylation.

2 The Concept of Deciduous Directing Groups

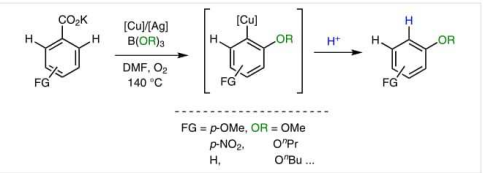
In the attractive and dynamic field of carboxylate-directed transformations, our vision was to fully exploit the benefits of the broad availability and traceless removability of COOH directing groups by seeking an inherently selective mechanistic pathway leading to a single product. Two principal strategies were considered. (1) Installing a σ-electron-withdrawing *ortho* substituent by C–H functionalization activates the carboxylate group towards decarboxylation. DFT and mechanistic studies have shown that the activation energy for the decarboxylation step is reduced by up to 10 kcal/mol by introducing nitro, alkoxy, or fluoro groups. Bulky *ortho* substituents also facilitate the decarboxylation step.[13] Therefore, a newly introduced functional group in the *ortho* position may trigger decarboxylation of a substrate under conditions where the starting benzoate was perfectly stable (Scheme 3, left). (2) CO_2 extrusion takes place exclusively in an intermediate metallacycle formed within the catalytic cycle (Scheme 3, right). In either case, the carboxylate directing group is discarded immediately after C–H functionalization takes place, preventing substitution at the second available position. We refer to reaction mode 2 as deciduous, because the directing group may be compared to the leaf of a tree that is shed in autumn after it has fulfilled its purpose.

Our carboxylate-directed Ag/Cu-catalyzed C–H alkoxylation is one early example for a substituent-triggered decarboxylation.[14] Protodecarboxylation of the benzoate sub-



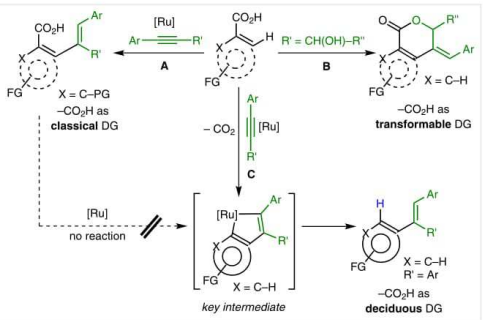
Scheme 3 Left: decarboxylation occurs only after insertion of a functional group: substituent-triggered decarboxylation. Right: decarboxylation occurs only within the catalytic cycle: decarboxylation via intermediate metallacycle (E⁺ = electrophile, including protons)

strate is negligible under the reaction conditions. Once the electron-rich alkoxide group is introduced in the *ortho* position, it destabilizes the C–COOH bond to an extent that no further substitution of the second *ortho*-C–H bond occurs, and the aryl monoether is the only detectable product (Scheme 4). This proves the viability of substituent-triggered decarboxylations (reaction mode 1) for achieving selective monosubstitution. However, the arylcopper intermediates have not yet successfully been trapped with electrophiles other than protons.



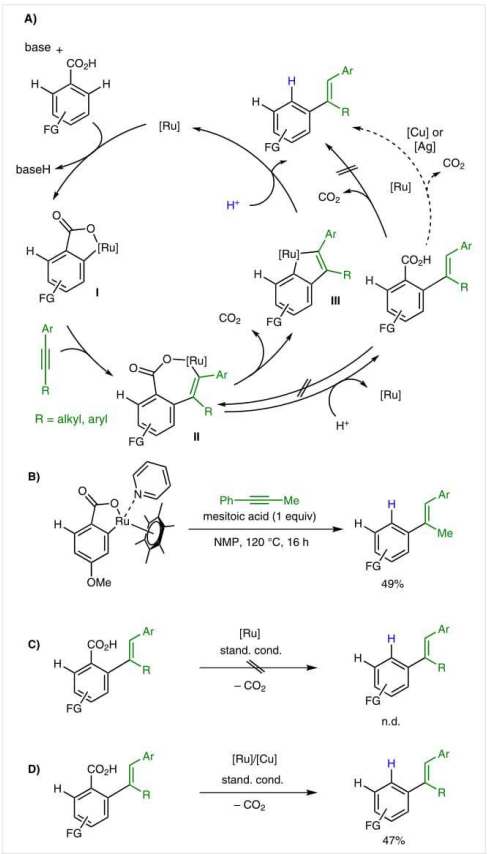
Scheme 4 Synthesis of aryl ethers from benzoates by C–H alkoxylation with concomitant substituent-triggered protodecarboxylation

Carboxylate-directed redox-neutral intermolecular hydroarylations of internal alkynes are a particularly versatile reaction type because of the variety of possible products (Scheme 5),[15] which bear the potential for further derivatization at the carboxylate or alkenyl groups. In the pathway **A**, the carboxylate group serves as a classical directing group, and the reaction possesses no inherent monoselectivity. To obtain a single *ortho*-vinyl arene product, the second *ortho* position needs to be blocked or made sterically inaccessible. In pathway **B**, COOH is used as a transformable directing group: *ortho*-C–H vinylation with a propargylic alcohol, followed by in situ esterification, leads to a lactone product. Pathway **C** entails a concerted vinylation and decarboxylation. The C–COOH bond is broken only within the intermediate metallacycle and is no longer in place to activate a second C–H bond, resulting in an inherently monoselective transformation. The carboxylate group may thus be



Scheme 5 COOH as classical, transformable, and deciduous directing group for the regioselective synthesis of vinylarenes

considered a deciduous directing group, which is removed after it has fulfilled its assigned task. To date, the 5-membered ruthenacycle intermediate has been trapped only by protons.



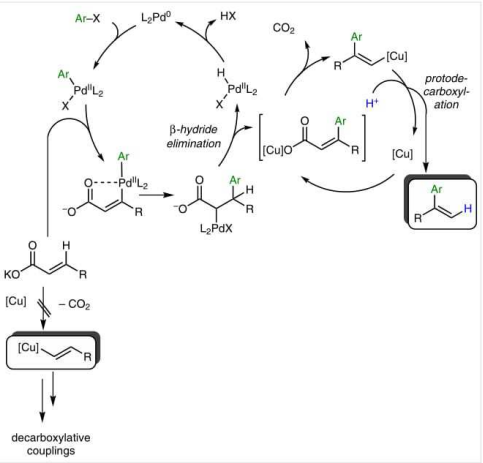
Scheme 6 (**A**) Proposed mechanism for the decarboxylative hydroarylation. (**B**) A presynthesized ruthenacycle leads to product formation, supporting the presence of such intermediates during the reaction. (**C**) Ruthenium alone does not decarboxylate the *ortho*-vinyl benzoic acid. (**D**) CO_2 extrusion from the nondecarboxylated vinyl arene product requires [Cu] as a dedicated decarboxylation catalyst.

The initial reaction conditions applied only to diaryl alkynes, but were later extended to alkyl aryl alkynes.[16] Alkyl-branched monosubstitution products were obtained with excellent yields and selectivities. The reaction is mediated by ruthenium, and is completed after 16 hours under conventional heating or within 5 minutes under microwave irradiation. Mechanistic experiments outlined in Scheme 6

showed that the decarboxylation occurs immediately after C–C bond formation, confirming the deciduous reaction mode.

Coincidentally, the groups of Ackermann and Hartwig/Zhao almost simultaneously discovered decarboxylative *ortho* hydroarylation processes leading to the same products.[17] Hartwig and Zhao propose a consecutive hydroarylation/protodecarboxylation pathway, which we ruled out for our catalyst system based on experiment C in Scheme 6. Ackermann observed decarboxylative hydroarylation exclusively, which may be a result of his choice of substrates that all have a strong tendency to decarboxylate.

Applied to Heck reactions, the concept of deciduous directing groups showed additional benefits: Instead of the linear alkenes typically obtained when starting from aryl halides and terminal alkenes, the strategy presented in Scheme 7 led to a de facto inversion of the regioselectivity in favor of the branched products (Scheme 7).[18] The process starts with cinnamic acid substrates. Palladation occurs selectively in the β position of the cinnamate due to electronic factors, so that the new C–C bond is also formed at the β carbon. This arylation activates the cinnamate towards decarboxylation, preventing further arylation and leading to branched, monoaryl alkene products.



Scheme 7 Selective formation of branched aryl alkenes from cinnamates using the carboxylate as a deciduous directing group

3 Summary and Perspectives

The flexibility of carboxylic acids in catalytic cross-coupling reactions is remarkable. They are able to undergo diverse catalytic *ipso* substitutions and *ortho*-C–H functionalizations with release of environmentally innocuous CO_2, and the potential follow-up reactions of this functionality are abundant. Consequently, stepwise multifunctionalizations of arenes may be built around carboxylate substrates. They may be employed as classical, transformable, or deciduous *ortho*-directing groups in C–H functionalization.

The concept of deciduous directing groups is a particularly powerful tool for the expedient, regioselective monofunctionalization of arenes. This is possible because the carboxylate group is shed simultaneously with the formation of a new bond, which prevents any further C–H activation. The full synthetic potential of using carboxylates as deciduous directing groups would be unleashed by future methods combining the decarboxylation with concerted *ipso* functionalizations with substituents other than protons.

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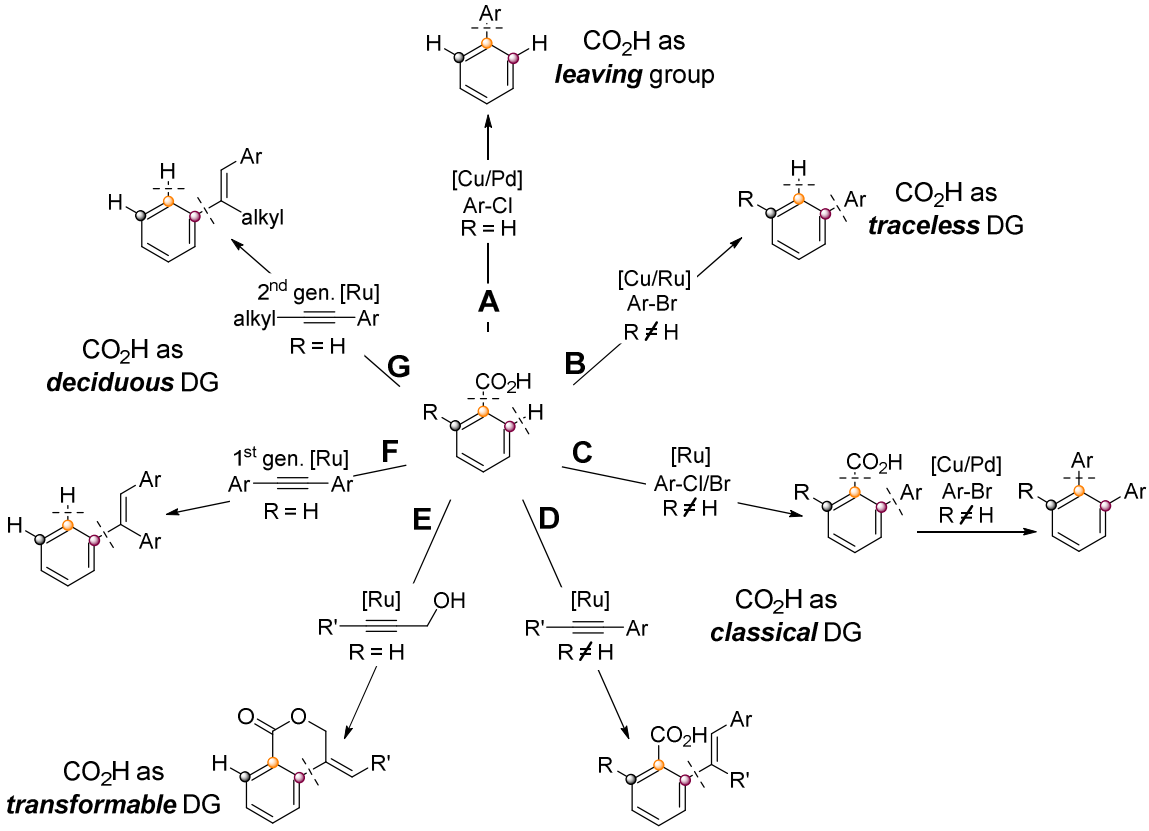
6. Conclusion and outlook

This work demonstrates new sustainable methods for the regioselective functionalization of aromatic carboxylic acids for the straightforward synthesis of chemically relevant scaffolds.

Decarboxylative cross-couplings and C–H activation were the two concepts applied to reveal the full synthetic potential of benzoic acid derivatives as starting materials in homogeneous catalysis. Both aspects were merged into the novel concept of deciduous directing groups, improving significantly the expediency of the carboxyl group as a synthetic target. The tremendous catalytic performance of the developed methods certifies that decarboxylative cross-couplings and carboxylate directed C–H functionalizations can fully compete with traditional cross-coupling reactions, and that aromatic carboxylic acids can be regarded as a worthwhile and beneficial alternative to preformed organometallic starting materials. **Scheme 45** summarizes all methods for the diversification of aromatic carboxylic acids that were developed within this doctoral work.



Scheme 45: Overview on the cross-coupling reactions of benzoic acid derivatives developed within this work.

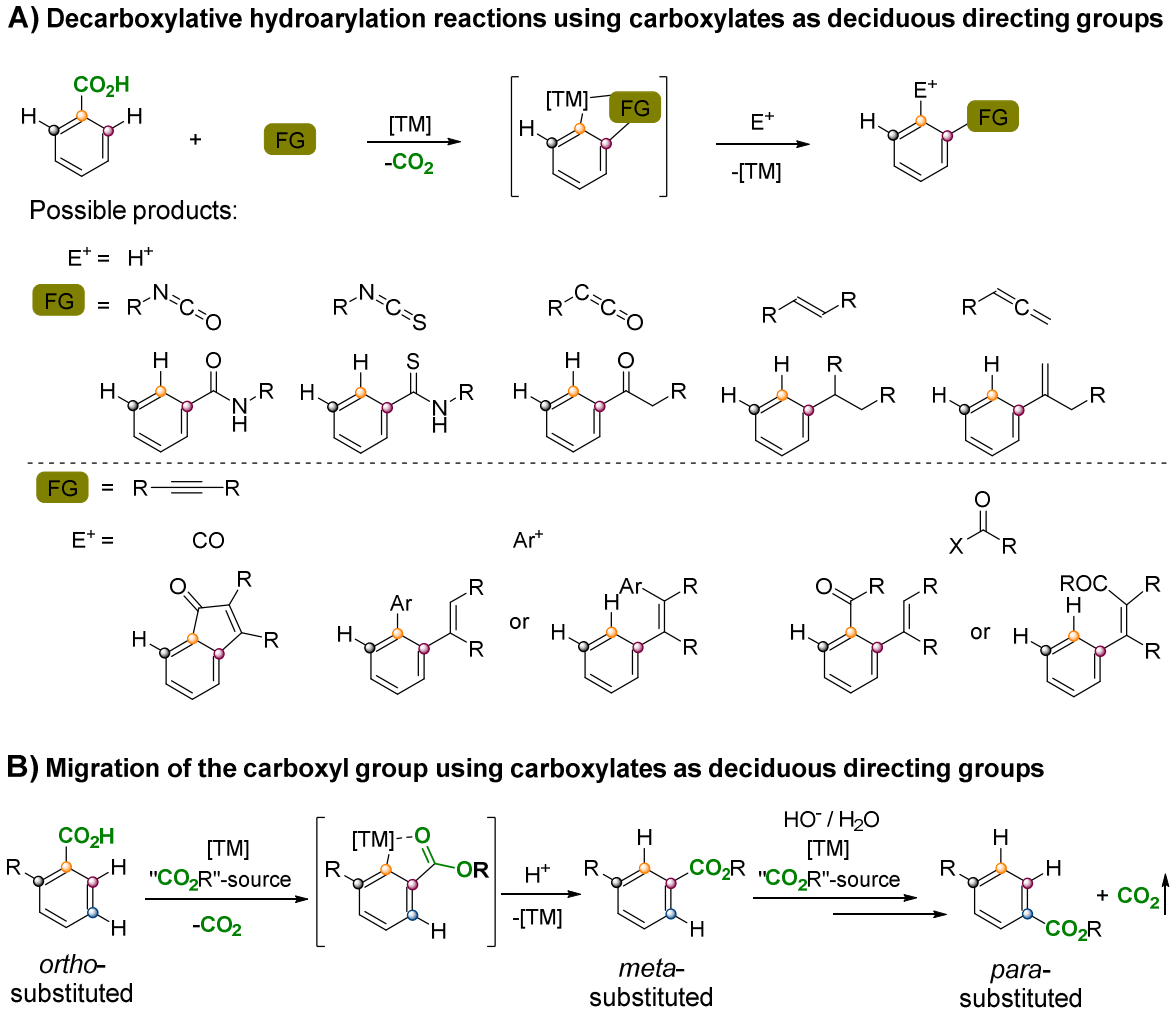
Based on theoretical insights on the bimetallic decarboxylative cross-coupling catalysis, we developed a new generation of Cu/Pd-catalyst with enhanced catalytic performance (**Scheme 45A**). This system allows for the first time the decarboxylative biaryl synthesis starting from aryl chlorides and benzoates without activating *ortho* substituents. As postulated at an early stage, this reaction is the experimental proof that decarboxylative cross-couplings are not intrinsically limited. Further studies should aim at reducing the admittedly high reaction temperature, which is still required for this process. One very promising strategy could involve the implementation of P,N-ligands capable of aiding the reputedly energetically disfavored transmetallation-step by bridging and pre-organizing the two catalysts involved.

In a second project, an inexpensive ruthenium-catalyst was used for the *ortho*-arylation under retention of the carboxylic acid moiety (**Scheme 45C**). Aryl bromides were used as coupling partners when the Ru-precursor is aided by a small electron-rich phosphine ligand. More remarkably, with DL-pipecolinic acid as ligand the more challenging aryl chlorides were also efficiently coupled. Within the same project a Cu/Ru bimetallic catalyst system was found to shift the decarboxylative arylation from the *ipso* to the *ortho* position by using the carboxyl group as a traceless directing group and complementing the Cu/Pd catalyst system developed in the first project (**Scheme 45B**). Additionally, in a sequential *ortho*-arylation / *ipso*-arylation process, we demonstrated for the first time that merging C–H activation and decarboxylative couplings can be an expedient approach for the regioselective synthesis of multi-decorated arenes.

In a third project, under redox neutral conditions, internal alkynes were used as coupling partners for the *ortho*-vinylation *via* C–H hydroarylation. In this case the carboxyl group revealed even more reaction modes. As a classical directing group, the carboxylate moiety was used to trigger the efficient *ortho*-vinylation yielding the 2-vinyl benzoic acids with high functional group tolerance and regioselectivities (**Scheme 45D**). Despite the importance of this protocol, the scope is restricted to *ortho*-substituted benzoic acids in order to avoid double functionalization. However, when the carboxy group is used as a transformable directing group in a tandem *ortho*-vinylation/esterification process, the directing ability is immediately deactivated after the reaction yielding the γ-alkylidene-δ-lactones exclusively (**Scheme 45E**). Another and within this doctoral work newly developed reaction concept is the deciduous reaction mode of the carboxyl moiety (**Scheme 45F**). The *ortho*-vinylation and decarboxylation occur in one step leading to an inherently monoselective pathway. Double functionalization is impossible because the directing group is shed within the catalytic cycle

after it fulfilled its purpose and is then no longer there to trigger a second C–H activation event. The first generation catalyst system was restricted to diphenylacetylene only. Finally, the second generation catalyst system, which was developed within the fourth project of this doctoral work, was applicable for the coupling of unsymmetrically substituted internal alkynes, yielding the corresponding vinylarenes in high yields and impressive regio- and stereoselectivities, optionally within just five minutes reaction times (**Scheme 45G**).

The newly discovered deciduous reaction mode of the carboxyl group has tremendous synthetic potential. It is capable of overriding electronic effects of an already existing substitution pattern on the arene, formally guiding a coupling partner regiospecifically in a position which is usually inaccessible by conventional electrophilic substitutions of simple arenes. This new concept can be viewed as the gateway to advanced synthetic transformations, extending and diversifying the portfolio of carboxylate directed C−H functionalizations.



Scheme 46: Potential future applications of the deciduous reaction mode.

Scheme 46 displays potential transformations enabled by the deciduous reaction mode. Part **A** shows that pursuing the strategy of hydroarylation reactions is worthwhile to install numerous coupling partners, including iso(thio)cyanates, allenes, ketenes, and simple alkenes regioselectively into the former *ortho*-position of a benzoic acid. It is a straightforward approach to synthesize (thio)amides, ketones, as well as alkylated and alkenylated aromates. Moreover, a possible electrophile introduced in the catalytic cycle at the decisive moment could allow the inherently regioselective multi-functionalization of benzoic acids in one single process. Unfortunately, we were not able to trap the intermediary metallacycle by any coupling partners other than just protons, to date. Such a reaction would be complementary to the Catellani reaction, but would obviate the addition of transient mediators such as norbornene. Part **B** in **Scheme 46** shows that with the deciduous reaction mode the carboxyl group itself can migrate along the aromatic skeleton formally transforming an *ortho*-substituted benzoic acid into a *meta*- or *para*-substituted one. More abundant *meta*-substituted benzoic acids can be transformed this way into *para*-substituted benzoic acids which are not easily accessible *via* conventional electrophilic substitutions. Further studies should aim exactly at these improvements in order to fully establish carboxylic acids not only as surrogates for organometallic reagents but as a more potent and versatile starting material for the synthesis of complex and otherwise inaccessible yet important building blocks.

7. Experimental Section

7.1. General annotations

7.1.1. Chemicals and solvents

Commercially available chemicals and solvents with a purity of ≥95% were used directly or otherwise first purified by standard techniques.[343] Air and moisture sensitive compounds were handled and stored under nitrogen or argon atmosphere using standard Schlenk techniques. Liquid substances including reaction media were saturated with argon to exclude atmospheric oxygen. Toluene, 1,4–dioxane and mesitylene were dried over sodium/benzophenone. NMP and DMF were dried *via* azeotrope distillation with toluene. All solvents were stored over molecular sieves (3 Å), which were heated before in a microwave oven (2x2 min, 600 W) and cooled under vacuum (10^{-3} mbar) to room temperature. The benzoates were dried under vacuum (10^{-3} mbar) at room temperature for 1 h before using. All other organic salts were dried overnight under vacuum (10^{-3} mbar) at 60 °C. Inorganic salts were dried overnight under vacuum (10^{-3} mbar) at 160 °C.

7.1.2. Parallel reaction set-up

If not stated otherwise, a set of 10 parallel reactions were carried out in oven-dried 20 mL headspace-vials for gas chromatography. All solid compounds were weighted under air, the reaction vessel were equipped with a 20 mm Teflon-coated stirring bar and closed with a vacuum-tight aluminum crimp-cap with Teflon-coated butyl rubber septa. Parallel vacuum/nitrogen flushing cycles of the reaction vessels (3 times) were carried out using a vacuum distributor, which was connected to the Schlenk line. Each distributor had 10 vacuum-tight Teflon-tubing equipped with adapter for mounting Luer-Lock syringe needles. Extremely air and moisture sensitive compounds were weighted in the glovebox with nitrogen as inert gas. Liquid reaction components were injected *via* syringe through the Teflon-coated butyl rubber septum. The vials were placed in cylindrical holes (7 cm deep with a diameter of 2.27 cm), which were drilled in a cylindrical aluminum block (height 8 cm, diameter 15 cm) with one additional hole for the temperature sensor.

After the reaction, the aluminum block was allowed to cool down to room temperature. The reaction vessels were carefully vented through the septum with a hollow needle. A suitable internal standard was added to the reaction mixture and diluted with a suitable organic solvent and water after which the reaction vial was shaken and the cap carefully opened. The reaction was either analyzed directly *via* ^{1}H– or ^{19}F–NMR or *via* gas chromatography by filtering 1.5 mL of the organic phase in a 2 mL GC-vial through a glass pipette containing a pad of 0.3 mL anhydrous magnesium sulfate.

7.1.3. Analytical methods

Mass spectra were recorded on a *Varian GC-MS Saturn 2100 T* or on an *Agilent GC-MS 5973N System*. Ionization was performed *via* electron impact ionization (EI). High resolution mass analyses were performed with a *Waters GTC Premier*.

Thin layer chromatography was performed using silica gel TLC-plates Polygram SIL G/UV254 from *Macherey-Nagel*. The Substances were detected either by quenching at 254 nm or by fluorescence at 366 nm.

Separation of substance mixtures were performed *via* column chromatography with a Combi Flash Companion-Chromatography-System from *Isco-Systems*. Readily packed *RediSep* and *Grace Reveleris* silica gel cartridges or *Telos* cartridges with basic aluminum oxide (0.063–0.200 mm, activity level I) were used as stationary phase.

Gas chromatographic analyses were performed on a *Hewlett Packard* 6890 equipped with HP–5-columns with 5% phenyl-methyl-siloxane (30 m × 320 µm × 1.0 µm) from *Agilent*, *Macherey-Nagel* and *Perkin Elmer*. Injector temperature was set at 220 °C and the detector temperature was set at 330 °C. The standard measurement started with 2 min at 60 °C, followed by a linear temperature increase up to 300 °C with a rate of 30 °C/min after which the oven temperature was kept at 300 °C for additional 3 min.

Mass spectra were recorded on a *Varian GC-MS Saturn 2100 T* or on an *Agilent GC-MS 5973N System*. Ionization was performed *via* electron impact ionization (EI). High resolution mass analyses were performed with a *Waters GTC Premier*.

Infrared spectroscopy was performed on a *Perkin Elmer Spectrum 100 FT-IR* spectrometer with *Universal ATR Sampling Accessory*.

ESI-MS data were generated *via* electrospray ionization (ESI) from an acetonitrile solution with a concentration of approximately 0.1 mm and, if required, acidified with 5 µL of formic

acid. The solutions were infused continuously into the ESI chamber with a syringe pump at a flow rate of 2 µL/min. We used nitrogen as nebulizer gas at a pressure of 7 to 8 psi and as a drying gas with a temperature of 200 °C and a flow rate of 1 to 2 L/min. The electrospray needle was held at 4.5 kV. The mass spectra were recorded using a Paul-type ion trap mass spectrometer (*AmaZon ETD, Bruker Daltonics*). The ion source was operated in the positive and negative electrospray ionization mode. The scan speed was 32500 m/z per second with a resolution of 0.3 FWHM, the scan range was at least from 50 to 1500 m/z. The Instrument was controlled by *BrukerTrapControl 7.2* software, data analysis was done with *BrukerDataAnalysis 4.2* software.

NMR spectra were recorded on a *Bruker AMX 400* system using chloroform–*d*, methanol–d_4 and dimethylsulfoxide–d_6 as solvents, with proton, carbon, fluor and phosphor resonances at 400 MHz, 101 MHz, 376 MHz and 162 MHz, respectively. Some measurements were performed on a *Bruker FT-NMR DPX 200* und *Avance 600* and are marked as such. Processing the raw-data was done with ACD-*Labs 12* software. The multiplicity of the signals is abbreviated with s = singlet, d = doublet, dd = doublet of a doublet, dt = doublet of a triplet, t = triplet, etc. All coupling constants are given in Hertz.

Elemental analyses were performed on a *Hanau Elemental Analyzer vario Micro cube*. All melting points were determined with a *Mettler* FP61.

7.2. Catalytic Decarboxylative Cross-Coupling of Aryl Chlorides and Benzoates without Activating *ortho* Substituents

7.2.1. General Methods

Chemicals and solvents were either purchased (puriss p.A.) from commercial supplier or purified by standard techniques.[343] All reactions, if not stated otherwise, were performed in oven-dried glassware under a nitrogen atmosphere containing a Teflon-coated stirring bar and dry septum. Reaction media were saturated with argon to exclude atmospheric oxygen. All reactions were monitored by GC using *n*-tetradecane as internal standard. Response factors of the products with regard to *n*-tetradecane were obtained experimentally by analyzing known quantities of the substances. The palladium catalysts $(MeCN)_4Pd(OTf)_2$, $(MeCN)_2Pd(OTs)_2$, $(MeCN)_4Pd(OMs)_2$ and ligand 4,7-dimethoxyl-1,10-phenanthroline were prepared according to the literature procedures and identified by comparison of their spectra with those of

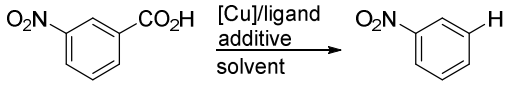
authentic samples.[344][345] The aromatic carboxylates were prepared from the corresponding aromatic carboxylic acids following the procedures below and were directly used.

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.

7.2.2. Catalyst development

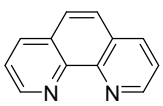
7.2.2.1. Protodecarboxylation experiments

Table 4: Evaluation of the protodecarboxylation catalyst for carboxylates without activating *ortho* substituents.

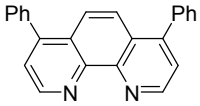


#	[Cu]	ligand	additive	solvent	T/°C	Yield/%
1	Cu_2O	phen	-	NMP/quin=3/1	190	99
2	"	"	KCl	"	"	14
3	"	"	KOTf	"	"	99
4	"	Ph_2phen	"	"	"	50
5	"	"	LiCl	"	"	-
6	"	"	NaCl	"	"	16
7	"	"	CsCl	"	"	30
8	"	"	$MgCl_2$	"	"	-
9	"	"	$CaCl_2$	"	"	trace
10	"	"	$^nBu_4NCl$	"	"	trace
11	"	"	KCl	quin	"	99
12	"	Me_4phen	"	"	"	99
13	"	"	$^nBu_4NCl$	"	"	trace
14	"	"	KCl	"	170	50
15	Ag_2CO_3	-	"	"	190	-

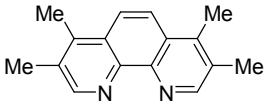
Reaction conditions: 3-nitro-benzoic acid (0.5 mmol), Cu_2O (5 mol %), ligand (10 mol %), additive (0.5 mmol), 3 mL of solvent, 190 °C, 16 h. quin = quinoline; NMP = N-methyl-2-pyrrolidone. Yields determined by GC analysis using n-tetradecane as the internal standard.



Phen



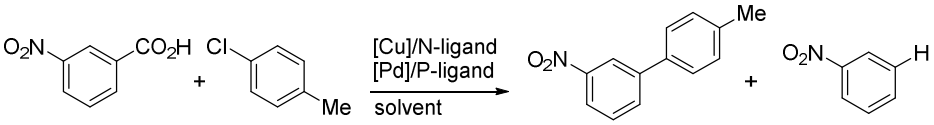
Ph_2phen



Me_4phen

7.2.2.2. Cross-coupling experiments

Table 5: Evaluation of the bimetallic catalyst system for the cross-coupling reaction.

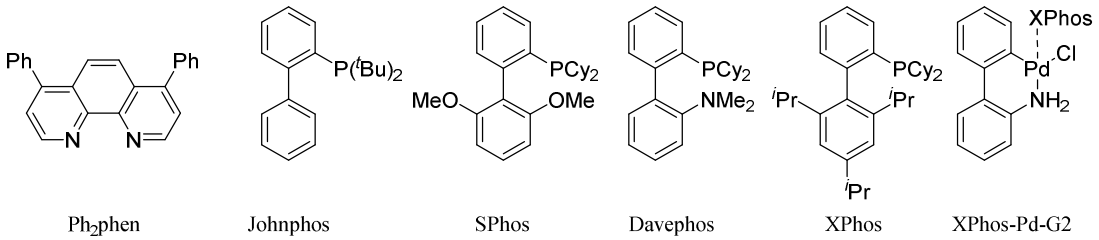


7.2.2.-1 **7.2.2.-2** **7.2.2.-3** **7.2.2.-4**

#	[Cu]	N-ligand	[Pd]	P-ligand	solvent	Yield/%	
						7.2.2.-3	**7.2.2.-4**
1	Cu_2O	Me_4Phen	$PdBr_2$	JohnPhos	quin	15	70
2	"	Phen	"	"	"	4	60
3	"	Ph_2Phen	"	"	"	5	72
4	"	$(MeO)_2$Phen	"	"	"	-	18
5	"	Me_4Phen	"	"	quin/NMP (1:1)	16	40
6	CuBr	"	"	"	"	12	42
7	CuCl	"	"	"	"	14	38
8	CuI	"	"	"	"	19	30
9	"	"	"	$^tBu_4P\cdot HBF_4$	"	17	28
10	"	"	"	PCy_3	"	8	28
11	"	"	"	SPhos	"	14	34
12	"	"	"	DavePhos	"	17	25
13	"	"	"	XPhos	"	36	23
14	"	"	PdI_2	"	"	37	24
15	"	"	$Pd(OAc)_2$	"	"	42	40
16	"	"	$Pd_2(dba)_3$	"	"	7	25
17	"	"	$Pd(allyl)_2Cl_2$	"	"	29	32
18	"	"	XPhos–Pd–G2	"	"	12	27
19	"	"	$(MeCN)_4Pd(OTf)_2$	"	"	58	50
20[a]	"	"	"	"	"	67	38
21[a][b]	"	"	"	"	"	38	36
22[a][c]	"	"	"	"	"	30	33

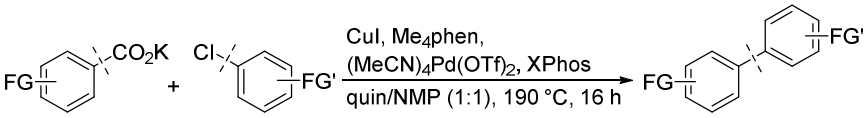
23[a][d]	"	"	"	"	"	-	6
24[a][e]	"	"	"	"	"	-	trace
25[a]	"	"	-	-	"	-	25
26[b]	-	-	$(MeCN)_4Pd(OTf)_2$	XPhos	"	-	trace
27[b]	-	-	-	-	"	-	-

Reaction conditions: ***7.2.2.-1*** *(0.6 mmol),* ***7.2.2.-2*** *(0.5 mmol), Cu-source (10 mol%), N-ligand (10 mol%), Pd-source (2 mol%), P-ligand (5 mol%), 3 mL of solvent, 19 °C, 16 h. Yields determined by GC analysis using n-tetradecane as the internal standard. NMP = N–methyl–2–pyrrolidone; quin = quinoline. [a] 5 mL of solvent. [b] 180 °C. [c] 170 °C. [d] 150 °C. [e] 100 °C.*



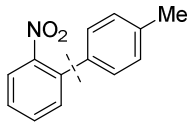
Ph_2phen Johnphos SPhos Davephos XPhos XPhos-Pd-G2

7.2.3. Synthesis of the biaryls via decarboxylative cross-coupling



Standard procedure: An oven-dried, nitrogen-flushed 20 mL crimp cap vessel was charged with the potassium carboxylate (0.60 mmol, 1.2 equiv.), $(MeCN)_4Pd(OTf)_2$ (5.7 mg, 0.01 mmol, 2.0 mol%), XPhos (12.3 mg, 0.025 mmol, 5.0 mol%), copper(I) iodide (9.7 mg, 0.05 mmol, 10.0 mol %), 3,4,7,8–tetramethyl–1,10–phenanthroline (11.9 mg, 0.05 mmol, 10.0 mol%), and aryl chloride (0.5 mmol). A degassed mixture of NMP (2.5 mL) and quinoline (2.5 mL) was added *via* syringe. The resulting solution was then stirred at 190 °C for 16 h. After the reaction was complete, the mixture was cooled to room temperature, diluted with 1 N HCl and extracted with ethyl acetate (3 x 50 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/cyclohexane gradient) yielding the corresponding biaryl.

7.2.3.1. Synthesis of 4'–methyl–2–nitrobiphenyl

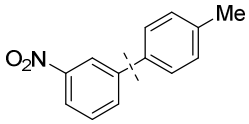


[CAS: 70680-21-6]

The title compound was prepared following general method from potassium 2–nitrobenzoate (154 mg, 0.75 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, compound was obtained by column chromatography as a yellow liquid (85 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, J = 8.0, 1.1 Hz, 1H), 7.61 (td, J = 7.5, 1.2 Hz, 1H), 7.49–7.44 (m, 2H), 7.27–7.22 (m, 4H), 7.00 (d, J = 8.5 Hz, 1H), 2.41 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 149.38 (s), 138.15 (s), 136.26 (s), 134.36 (s), 132.16 (s), 131.90 (s), 129.43 (s, 2C), 127.88 (s), 127.72 (s, 2C), 124.00 (s), 21.22 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3027, 2922, 1614, 1522, 1475, 1353, 748 cm^{-1}; **MS** (EI, 70 eV) m/z (%): 213 (75) [M^+], 196 (60), 185 (100), 168 (86), 152 (50), 115 (44); **HRMS** (EI-TOF) calcd for $C_{13}H_{11}NO_2$: 213.0790; found: 213.0787.

7.2.3.2. Synthesis of 4'–methyl–3–nitrobiphenyl



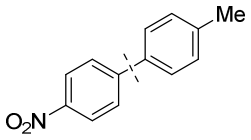
[CAS: 53812-68-3]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (65 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (t, J = 1.7 Hz, 1H), 8.18 (dd, J = 8.2, 2.0 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 2.44 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.69 (s), 142.75 (s), 138.53 (s), 135.72 (s), 132.77 (s), 129.84 (s, 2C), 129.60 (s), 126.93 (s, 2C), 121.67 (d, J = 3.6 Hz, 2C), 21.13 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3029, 2922, 1528, 1511, 1345, 1294, 804, 738 cm^{-1}; **MS** (EI,

70 eV) m/z (%): 213 (100) [M^+], 167 (16), 152 (19), 139 (3), 115 (4); **HRMS** (EI-TOF) calcd for $C_{13}H_{11}NO_2$: 213.0790; found: 213.0786; **m.p.**: 76–77 °C.

7.2.3.3. Synthesis of 4–methyl–4'–nitrobiphenyl

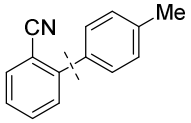


[CAS: 2143-88-6]

The title compound was prepared following general method from potassium 4–nitrobenzoate (135 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (55 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (dt, J = 12.0, 4.0 Hz, 2H), 7.73 (dt, J = 8.0, 4.0 Hz, 2H), 7.54 (dt, J = 8.0, 4.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 2.44 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 147.56 (s), 139.07 (s), 135.83 (s), 129.87 (s, 2C), 127.47 (s, 2C), 127.21 (s, 2C), 124.09 (s, 2C), 121.34 (s), 21.21 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3080, 2921, 1594, 1509, 1484, 1337, 1325, 821 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 213 (100) [M^+], 183 (38), 165 (12), 155 (16), 115 (5); **HRMS** (EI-TOF) calcd for $C_{13}H_{11}NO_2$: 213.0790; found: 213.0787; **m.p.**: 139–140 °C.

7.2.3.4. Synthesis of 4'–methylbiphenyl–2–carbonitrile



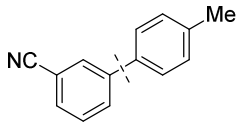
[CAS: 2143-88-6]

The title compound was prepared following general method from potassium 2–cyanobenzoate (139 mg, 0.75 mmol) and 4-chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (74 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (dd, J = 7.8, 1.0 Hz, 1H), 7.64 (td, J = 7.6, 1.3 Hz, 1H), 7.52 (dd, J = 7.8, 0.7 Hz, 1H), 7.48-7.46 (m, 2H), 7.43 (td, J = 7.6, 1.2 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 2.43 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 145.57 (s), 138.67 (s),

135.30 (s), 133.67 (s), 132.67 (s), 129.95 (s), 129.41 (s, 2C), 128.59 (s, 2C), 127.22 (s), 118.77 (s), 111.28 (s), 21.18 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3059, 3022, 2916, 2225, 1595, 1517, 1478, 1441, 1184, 761 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 193 (100) [M^+], 165 (31), 113 (3), 91 (4); **HRMS** (EI-TOF) calcd for $C_{14}H_{11}N$: 193.0891; found: 193.0888; **m.p.**: 81–82 °C.

7.2.3.5. Synthesis of 4'–methylbiphenyl–3–carbonitrile

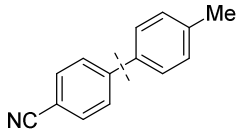


[CAS: 133909-96-3]

The title compound was prepared following general method from potassium 3–cyanobenzoate (111 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a white solid (68 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (t, *J* = 1.8 Hz, 1H), 7.81 (dt, *J* = 7.9, 1.4 Hz, 1H), 7.62 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.42 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.34 (s), 138.38 (s), 135.96 (s), 131.26 (s, 2C), 130.47 (s), 130.38 (s), 129.82 (s), 129.52 (s), 126.88 (s, 2C), 118.94 (s), 112.86 (s), 21.14 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3033, 2919, 2228, 1515, 1474, 1386, 1263, 794 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 193 (100) [M^+], 178 (10), 165 (17), 140 (4), 91 (7), 75 (5); **HRMS** (EI-TOF) calcd for $C_{14}H_{11}N$: 193.0891; found: 193.0889; **m.p.**: 63–64 °C.

7.2.3.6. Synthesis of 4'–methylbiphenyl–4–carbonitrile

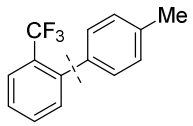


[CAS: 50670-50-3]

The title compound was prepared following general method from potassium 4–cyanobenzoate (111 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a white solid (53 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (q, *J* = 8.0 Hz, 4H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.62–5.60 (m, 1H), 2.43 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 145.57 (s), 138.73 (s), 136.23 (s), 132.54 (s, 2C), 129.81 (s, 2C), 127.44 (s, 2C), 127.03 (s, 2C), 119.03 (s), 110.49 (s), 21.47 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3026, 2918, 2224, 1644, 1603, 1494, 1396, 808 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 193 (100) [M^+], 178 (8), 165 (19), 91 (6), 75 (5), 63 (8); **HRMS** (EI-TOF) calcd for $C_{14}H_{11}N$: 193.0891; found: 193.0885; **m.p.**: 101–102 °C.

7.2.3.7. Synthesis of 4–methyl–2'–(trifluoromethyl)biphenyl

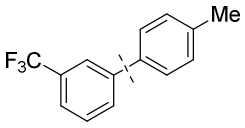


[CAS: 145486-55-1]

The title compound was prepared following general method from potassium 2–trifluoromethylbenzoate (171 mg, 0.75 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a colorless liquid (59 mg, 50%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.6 Hz, 4H), 7.60-7.42 (m, 2H), 7.34 (dd, *J* = 7.5, 0.6 Hz, 1H), 7.24 (s, 4H), 2.43 ppm (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 141.46 (q, *J* = 1.8 Hz, 1C), 137.30 (s), 136.96 (s), 132.14 (s, 2C), 131.23 (s), 128.80 (d, *J* = 1.5 Hz, 1C), 128.44 (s, 2C), 127.11 (s), 126.89 (d, *J* = 2.6 Hz, 1C), 126.01 (q, *J* = 5.2 Hz, 1C), 120.06 (d, *J* = 142.6 Hz, 1C), 21.20 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –56.83 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3030, 2924, 1488, 1448, 1313, 1167, 1125, 1109, 1070, 1035, 767 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 236 (100) [M^+], 215 (8), 196 (7), 167 (14), 91 (4); **HRMS** (EI-TOF) calcd for $C_{14}H_{11}F_3$: 236.0813; found: 236.0818.

7.2.3.8. Synthesis of 4–methyl–3'–(trifluoromethyl)biphenyl



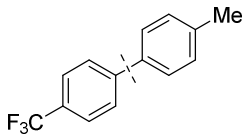
[CAS: 97067-19-1]

The title compound was prepared following general method from potassium 3–trifluoromethylbenzoate (137 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL,

0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a white solid (58 mg, 50%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.83 (s, 1H), 7.79–7.74 (m, 1H), 7.61–9.49 (m, 4H), 7.29 (d, J = 8.2 Hz, 2H), 2.42 ppm (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 141.92 (s), 137.94 (s), 136.87 (s), 131.10 (d, J = 32.1 Hz, 1C), 130.20 (s), 129.70 (s, 2C), 129.16 (s, 2C), 127.00 (s, 2C), 123.87 (d, J = 232.7 Hz, 1C), 123.70 (q, J = 4.1 Hz, 1C), 21.11 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –62.57 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3029, 2925, 1333, 1261, 1163, 1124. 1074, 796 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 236 (100) [M^+], 167 (27), 152 (3), 91 (4), 69 (7); **HRMS** (EI-TOF) calcd for $C_{14}H_{11}F_3$: 236.0813; found: 236.0816; **m.p.**: 35–36 °C.

7.2.3.9. Synthesis of 4–methyl–4'–(trifluoromethyl)biphenyl

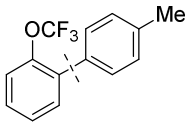


[CAS: 97067-18-0]

The title compound was prepared following general method from potassium 4–trifluoromethylbenzoate (137 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a white solid (90 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 4H), 7.51 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 2.42 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.63 (s), 138.14 (s), 136.85 (s), 129.69 (s, 2C), 129.02 (q, J = 32.7 Hz, 1C), 127.15 (s, 2C), 127.08 (s, 2C), 125.64 (q, J = 3.6, 2C), 124.34 (s), 21.13 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –62.33 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2960, 2925, 1606, 1323, 1166, 1120, 1111, 1071, 809 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 236 (100) [M^+], 217 (4), 167 (39), 91 (4), 69 (5); **HRMS** (EI-TOF) calcd for $C_{14}H_{11}F_3$: 236.0813; found: 236.0809; **m.p.**: 130–131 °C.

7.2.3.10. Synthesis of 4'–methyl–2–(trifluoromethoxy)biphenyl

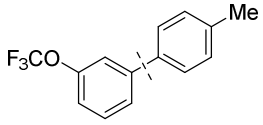


[CAS: 1809242-81-6]

The title compound was prepared following general method from potassium 2–trifluoromethoxybenzoate (147 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a colorless liquid (101 mg, 80%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.66 (dd, J = 7.9, 0.9 Hz, 1H), 7.60–7.42 (m, 2H), 7.34(d, J = 7.8 Hz, 1H), 7.24 (s, 4H), 2.43 ppm (s, 3H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 148.26 (d, J = 1.8 Hz, 1C), 137.43 (s), 135.28 (s), 133.91 (s), 131.51 (s), 129.07 (s, 2C), 128.99 (s, 2C), 128.33 (s), 126.97 (s), 123.02 (s), 121.24 (d, J = 1.5 Hz, 1C), 21.19 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –57.03 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3030, 2925, 2861, 1485, 1248, 1218, 1198, 1164, 817 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 252 (100) [M^+], 183 (4), 167 (14), 69 (9); **HRMS** (EI-TOF) calcd for $C_{14}H_{11}F_3O$: 252.0762; found: 252.0746.

7.2.3.11. Synthesis of 4'–methyl–3–(trifluoromethoxy)biphenyl



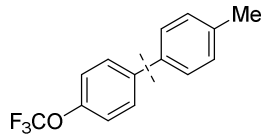
[CAS: 1809242-82-7]

The title compound was prepared following general method from potassium 3–trifluoromethoxybenzoate (147 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a white solid (77 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53-7.43 (m, 5H), 7.28 (d, J = 8.0 Hz, 2H), 7.19 (dt, J = 8.1, 1.0 Hz, 1H), 2.42 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 149.67 (s), 143.26 (s), 137.90 (s), 136.77 (s), 129.98 (s), 129.65 (s, 2C), 126.95 (s, 2C), 125.25 (s), 121.80 (s), 119.50 (s), 119.22 (s), 21.11 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –57.66 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2925, 2867, 1606, 1588, 1474, 1262, 1203, 1150, 787 cm^{-1}; **MS** (EI, 70 eV) *m/z*

(%): 252 (100) [M^+], 167 (3), 152 (2), 69 (3); **HRMS** (EI-TOF) calcd for $C_{14}H_{11}F_3O$: 252.0762; found: 252.0756; **m.p.**: 39–40 °C.

7.2.3.12. Synthesis of 4–methyl–4'–(trifluoromethoxy)biphenyl

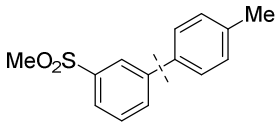


[CAS: 1546954-83-9]

The title compound was prepared following general method from potassium 4–trifluoromethoxylbenzoate (147 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a white solid (63 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.57(m, 2H), 7.47 (d, J = 8.0Hz, 2H), 7.29–7.26 (m, 4H), 2.42 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 148.42 (d, J = 1.5 Hz, 1C), 139.90 (s), 137.51 (s), 136.95 (s), 129.59 (s, 2C), 128.21 (s, 2C), 126.92 (s, 2C), 121.19 (s, 2C), 120.52 (d, J = 127.5 Hz, 1C), 21.08 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –57.81 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3033, 2925, 1738, 1609, 1493, 1207, 1152, 806 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 252 (100) [M^+], 183 (11), 167 (19), 155 (9), 115 (3), 69 (4); **HRMS** (EI-TOF) calcd for $C_{14}H_{11}F_3O$: 252.0762; found: 252.0762; **m.p.**: 98–99 °C.

7.2.3.13. Synthesis of 4–methyl–3'–(methylsulfonyl)biphenyl



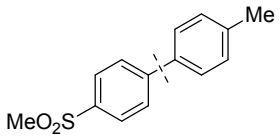
[CAS: 1809242-83-8]

The title compound was prepared following general method from potassium 3–methylsulfonylbenzoate (143 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a white solid (74 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (t, J = 1.8 Hz, 1H), 7.90 (dt, J = 7.7, 1.4 Hz, 1H), 7.87 (dt, J = 7.8, 1.3 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.55–7.52 (m, 2H), 7.30 (d, J = 8.0 Hz, 2H), 3.11 (s, 3H), 2.43 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.66 (s), 141.08 (s),

138.39 (s), 136.07 (s), 131.99 (s), 129.81 (s, 2C), 129.78 (s), 126.99 (s, 2C), 125.59 (s, 2C), 44.55 (s), 21.14 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3008, 2926, 1469. 1321, 1297, 1146, 958, 775 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 246 (100) [M^+], 167 (27), 152 (12), 44 (9); **HRMS** (EI-TOF) calcd for $C_{14}H_{14}O_2S$: 246.0715; found: 246.0714; **m.p.**: 118–119 °C.

7.2.3.14. Synthesis of 4–methyl–4'–(methylsulfonyl)biphenyl

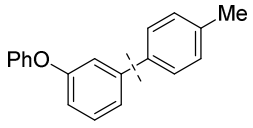


[CAS: 893738-58-4]

The title compound was prepared following general method from potassium 4–methylsulfonylbenzoate (143 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a white solid (108 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 2H), 7.76 (m, 2H), 7.74–7.72 (m, 2H), 7.31 (d, *J* = 7.8 Hz,2H), 3.10 (s, 3H), 2.43 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 146.63 (s), 138.77 (s), 138.71 (s), 136.18 (s), 129.81 (s, 2C), 127.87 (s, 2C), 127.69 (s, 2C), 127.20 (s, 2C), 44.63 (s), 21.17 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3010, 2927, 1317, 1297, 1148, 1093, 954, 807 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 246 (100) [M^+], 230 (30), 183 (36), 167 (22), 152 (12), 63 (8); **HRMS** (EI-TOF) calcd for $C_{14}H_{14}O_2S$: 246.0715; found: 246.0714; **m.p.**: 197–198 °C.

7.2.3.15. Synthesis of 4'–methyl–3–phenoxybiphenyl



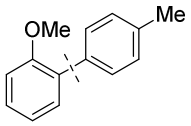
[CAS: 1809242-84-9]

The title compound was prepared following general method from potassium 3–phenoxybenzoate (151mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a colorless liquid (65 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.0 Hz, 2H), 7.41–7.32 (m, 4H), 7.26–7.23(m, 3H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.08–7.06 (m, 2H), 6.98 (ddd, *J* = 16.0, 8.0, 1.1 Hz, 1H),

2.40 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 157.60 (s), 157.22 (s), 143.02 (s), 137.60 (s), 137.41 (s), 129.96 (s), 129.76 (s, 2C), 129.49 (s, 2C), 126.93 (s, 2C), 123.24 (s), 121.86 (s), 118.89 (s, 2C), 117.43 (s), 117.34 (s), 21.09 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3027, 2920, 1582, 1567, 1488, 1478, 1219, 903 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 260 (100) [M^+], 232 (8), 217 (7), 165 (5), 152 (7), 77 (7); **HRMS** (EI-TOF) calcd for $C_{19}H_{16}O$: 260.1201; found: 260.1199.

7.2.3.16. Synthesis of 2–methoxy–4'–methylbiphenyl

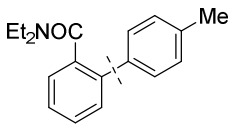


[CAS: 92495-53-9]

The title compound was prepared following general method from potassium 2–methoxybenzoate (143 mg, 0.75 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (79 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.0 Hz, 2H), 7.34–7.30 (m, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.04 (td, *J* = 7.5, 1.2 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 3.82 (s, 3H), 2.41 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.47 (s), 136.58 (s), 135.55 (s), 130.77 (s), 130.66 (s), 129.37 (s, 2C), 128.72 (s, 2C), 128.34 (s), 120.76 (s), 111.11 (s), 55.50 (s), 21.19 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3014, 2964, 2920, 1907, 1596, 1484, 1455, 1228, 1020, 757 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 198 (100) [M^+], 183 (15), 155 (24); **HRMS** (EI-TOF) calcd for $C_{14}H_{14}O$: 198.1045; found: 198.1044.; **m.p.**: 81–82 °C.

7.2.3.17. Synthesis of N,N–diethyl–4'–methylbiphenyl–2–carboxamide

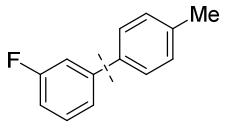


[CAS: 937166-55-7]

The title compound was prepared following general method from potassium 2–(diethylcarbamoyl)benzoate (195 mg, 0.75 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow liquid (114 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.42 (m, 1H), 7.39-7.36 (m, 5H), 7.19 (d, *J* = 7.9 Hz, 2H), 3.78–3.72 (m, 1H), 3.07–3.01 (m, 1H), 3.00–2.94 (m, 1H), 2.70–2.64 (m, 1H), 2.38 (s, 3H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.75 ppm (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.66 (s), 138.31 (s), 137.26 (s), 136.89 (s), 136.26 (s), 129.36 (s), 128.96 (s), 128.86 (s), 128.67 (s), 127.26 (s), 126.96 (s), 42.22 (s), 38.31 (s), 21.14 (s), 13.38 (s), 11.99 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2920, 2932, 2871, 1623, 1456, 1425, 1288, 1220, 1089, 757 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 266 (100) [M^+], 195 (89), 165 (25), 152 (21), 72 (10); **HRMS** (EI-TOF) calcd for $C_{18}H_{21}NO$: 267.1623; found: 267.1614.

7.2.3.18. Synthesis of 3–fluoro–4'–methylbiphenyl

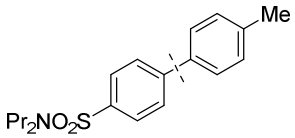


[CAS: 72093-42-6]

The title compound was prepared following general method from potassium 3–fluorobenzoate (109 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a white solid (45 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.0 Hz, 2H), 7.42–7.35 (m, 2H), 7.30–7.26 (m, 3H), 7.07–6.99 (m, 1H), 2.42 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 164.20 (d, *J* = 245.7 Hz, 1C), 143.44 (d, *J* = 8.1 Hz, 1C), 137.71 (s), 137.07 (d, *J* = 1.5 Hz, 1C), 130.12 (d, *J* = 8.8 Hz, 1C), 129.58 (s, 2C), 126.92 (s, 2C), 122.53 (d, *J* = 2.9 Hz, 1C), 113.84 (d, *J* = 6.0 Hz, 1C), 113.66 (d, *J* = 6.0 Hz, 1C), 21.11 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –113.27 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3032, 2919, 1611, 1588, 1567, 1485, 1473, 1183, 1160, 875 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 186 (100) [M^+], 171 (9), 165 (31), 133 (6), 91 (8), 74 (6); **HRMS** (EI-TOF) calcd for $C_{13}H_{11}F$: 186.0845; found: 186.0842; **m.p.**: 40–41 °C.

7.2.3.19. Synthesis of 4'–methyl–N,N–dipropylbiphenyl–4–sulfonamide

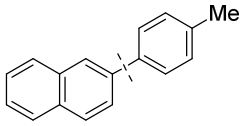


[CAS: 1809242-85-0]

The title compound was prepared following general method from potassium 4–(*N*,*N*–dipropylsulfamoyl)benzoate (194 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a white solid (147 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.13–3.10 (m, 4H), 2.43 (s, 3H), 1.64–1.54 (m, 4H), 0.90 ppm (t, *J* = 8.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.98 (s), 138.38 (s), 138.35 (s), 136.46 (s), 129.73 (s, 2C), 127.53 (s, 2C), 127.27 (s, 2C), 127.09 (s, 2C), 50.11 (s, 2C), 22.10 (s, 2C), 21.16 (s), 11.21 ppm (s, 2C); **IR** (ATR): $\tilde{\nu}$ = 2965, 2873, 1468, 1332, 1324, 1151, 1092, 992, 807 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 331 (100) [M^+], 302 (100), 231 (74), 183 (8), 167 (14), 152 (5); **HRMS** (EI-TOF) calcd for $C_{19}H_{25}NO_2S$: 331.1606; found: 331.1610; **m.p.**: 116–117 °C

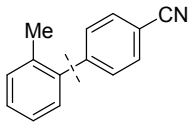
7.2.3.20. Synthesis of 2–p–tolylnaphthalene



[CAS: 59115-49-0]

The title compound was prepared following general method from potassium 2–naphthoate (126 mg, 0.6 mmol) and 4–chlorotoluene (64 mg, 60 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). The yield (17%) was determined by GC analysis using *n*-tetradecane as the internal standard.

7.2.3.21. Synthesis of 2'–methylbiphenyl–4–carbonitrile

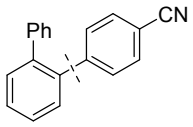


[CAS: 189828-30-6]

The title compound was prepared following general method from potassium 2–methylbenzoate (131 mg, 0.75 mmol) and 4–chlorbenzonitrile (70 mg, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (18 mg, 18%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.71 (m, 2H), 7.46–7.43 (m, 2H), 7.33–7.26 (m, 3H), 7.20 (d, J = 7.3 Hz, 1H), 2.26 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 146.77 (s), 139.97 (s), 135.02 (s), 131.95 (s, 2C), 130.64 (s), 129.98 (s, 2C), 129.40 (s), 128.27 (s), 126.08 (s), 118.95 (s), 110.69 (s), 20.30 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3062, 2924, 2853, 2227, 1608, 1482, 842, 759 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 193 (100) [M^+], 178 (11), 165 (22), 74 (6), 50 (10); **HRMS** (EI-TOF) calcd for $C_{14}H_{11}N$: 193.0891; found: 193.0890; **m.p.**: 64–65 °C.

7.2.3.22. Synthesis of 2'–phenylbiphenyl –4–carbonitrile



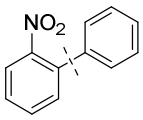
[CAS: 1071036-11-7]

The title compound was prepared following general method from potassium biphenyl–2–carboxylate (177 mg, 0.75 mmol) and 4–chlorbenzonitrile (70 mg, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (41 mg, 32%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.40 (m, 6H), 7.26–7.24 (m, 5H), 7.12–7.08 ppm (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 146.45 (s), 140,65 (s), 140.60 (s), 138.60 (s), 131.69 (s, 2C), 130.85 (s), 130.53 (s, 2C), 130.23 (s), 129.79 (s, 2C), 128.56 (s), 128.16 (s, 2C), 127.75 (s), 126.95 (s), 118.95 (s), 110.22 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3063, 2923, 2225, 1927, 1604, 1473, 1447, 830, 744 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 255 (100) [M^+], 240 (11), 227 (5),

215 (4), 113 (7), 50 (8); **HRMS** (EI-TOF) calcd for $C_{19}H_{13}N$: 255.1048; found: 255.1047; **m.p.**: 118–119 °C.

7.2.3.23. Synthesis of 3–nitrobiphenyl

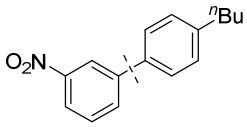


[CAS: 2113-58-8]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and chlorobenzene (57 mg, 52 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a white solid (63 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (t, J = 2.0 Hz, 1H), 8.22 (ddd, J = 8.0, 1.6, 1.0 Hz, 1H), 7.93 (ddd, J = 8.0, 1.6, 1.0 Hz, 1H), 7.66–7.61 (m, 3H), 7.54–7.49 (m, 2H), 7.47–7.43 ppm (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.70 (s), 142.86 (s), 138.66 (s), 133.03 (s), 129.69 (s), 129.15 (s, 2C), 128.52 (s), 127.15 (s, 2C), 122.02 (s), 121.95 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3084, 2923, 1738, 1531, 1522, 1500, 1347, 1293, 730 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 199 (100) [M^+], 152 (28), 141 (8), 115 (5), 76 (6); **HRMS** (EI-TOF) calcd for $C_{12}H_9NO_2$: 199.0633; found: 199.0630; **m.p.**: 57–58 °C.

7.2.3.24. Synthesis of 4'–butyl–3–nitrobiphenyl



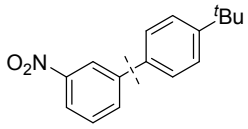
[CAS: 1809242-86-1]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 1–butyl–4–chlorobenzene (86 mg, 86 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a colorless liquid (73 mg, 57%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.46 (t, J = 1.9 Hz, 1H), 8.18 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H), 7.92 (dt, J = 7.7, 1.3 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.57–7.55 (m, 2H), 7.32 (d, J = 8.2 Hz, 2H), 2.69 (t, J = 8.0 Hz, 2H), 1.69–1.62 (m, 2H), 1.45–1.36(m, 2H), 0.96 ppm (t, J =

7.3 Hz, 3H). **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 148.71 (s), 143.58 (s), 142.84 (s), 135.95 (s), 132.82 (s), 129.61 (s), 129.22 (s, 2C), 126.98 (s, 2C), 121.72 (s), 121.70 (s), 35.28 (s), 33.55 (s), 22.36 (s), 13.94 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2956, 2928, 2858, 1529, 1515, 1346, 1101, 801 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 255 (73) [M^+], 212 (100), 165 (10), 152 (3), 89 (2); **HRMS** (EI-TOF) calcd for $C_{16}H_{17}NO_2$: 255.1259; found: 255.1263.

7.2.3.25. Synthesis of 4'–tert–butyl–3–nitrobiphenyl

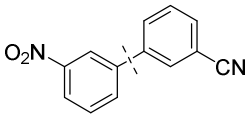


[CAS: 1809242-87-2]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 1–*tert*–butyl–4–chlorobenzene (86 mg, 86 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a colorless liquid (84 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (t, *J* = 1.9 Hz, 1H), 8.19 (ddd, *J* = 8.2, 2.2, 0.9 Hz, 1H), 7.92 (ddd, *J* = 8.0, 1.6, 1.0 Hz, 1H), 7.63-7.57 (m, 3H), 7.54–7.52 (m, 2H), 1.39 ppm (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.76 (s), 148.70 (s), 142.69 (s), 135.72 (s), 132.83 (s), 129.62 (s), 126.79 (s, 2C), 126.12 (s, 2C), 121.74 (s, 2C), 34.65 (s), 31.27 ppm (s, 3C); **IR** (ATR): $\tilde{\nu}$ = 2962, 2867, 1739, 1528, 1515, 1347, 834 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 255 (4) [M^+], 240 (100), 212 (15), 194 (3), 165 (3), 152 (3), 57 (2); **HRMS** (EI-TOF) calcd for $C_{16}H_{17}NO_2$: 255.1259; found: 255.1262.

7.2.3.26. Synthesis of 3'–nitrobiphenyl–3–carbonitrile

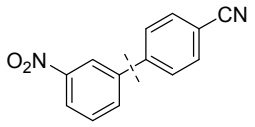


[CAS: 192699-67-5]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 3–chlorobenzonitrile (70 mg, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (67 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (t, J = 2.0 Hz, 1H), 8.30 (dd, J = 8.2, 1.4 Hz, 1H), 7.92-9.90 (m, 2H), 7.88 (d, J = 7.9 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.65 ppm (t, J = 8.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.78 (s), 140.47 (s), 139.92 (s), 132.95 (s), 131.91 (s), 131.48 (s), 130.69 (s), 130.21 (s), 130.08 (s), 123.12 (s), 121.98 (s), 118.28 (s), 113.48 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3067, 2922, 2226, 1520, 1491, 1346, 1266, 892 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 224 (100) [M^+], 178 (29), 166 (11), 151 (18), 75 (7); **HRMS** (EI-TOF) calcd for $C_{13}H_8N_2O_2$: 224.0586; found: 224.0584; **m.p.**: 176–177 °C.

7.2.3.27. Synthesis of 3'–nitrobiphenyl–4–carbonitrile

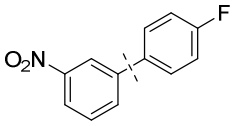


[CAS: 39117-72-1]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 4–chlorobenzonitrile (69.5 mg, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (77 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (t, J = 1.9 Hz, 1H), 8.30 (dd, J = 8.2, 1.3 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.83-7.81 (m, 2H), 7.76–7.74 (m, 2H), 7.70 ppm (t, J = 8.0 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.81 (s), 142.98 (s), 140.80 (s), 133.05 (s), 132.95 (s, 2C), 130.20 (s), 127.88 (s, 2C), 123.33 (s), 122.14 (s), 118.38 (s), 112.38 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3083, 2924, 2225, 1607, 1519, 1506, 1350, 1293, 804 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 224 (100) [M^+], 178 (32), 166 (9), 151 (20), 75 (6); **HRMS** (EI-TOF) calcd for $C_{13}H_8N_2O_2$: 224.0586; found: 224.0581; **m.p.**: 164–165 °C.

7.2.3.28. Synthesis of 4'–fluoro–3–nitrobiphenyl



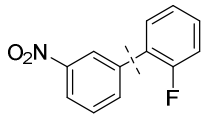
[CAS: 10540-32-6]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 1–chloro–4–fluorobenzene (67 mg, 54 µL,

0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (73 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (t, J = 1.9 Hz, 1H), 8.22 (ddd, J = 8.0, 2.0, 0.9 Hz, 1H), 7.89–7,87 (m, 1H), 7.64–7.59 (m, 3H), 7.23–7.17 ppm (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.33 (s), 161.86 (s), 148.70 (s), 141.84 (s), 134.81 (s), 132.86 (s), 129.79 (s), 128.88 (d, J = 8.2 Hz, 1C), 122.04 (s), 121.80 (s), 116.28 (s), 116.04 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –133.42 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3087, 1606, 1528, 1508, 1476, 1346, 1228, 1165, 831 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 217 (100) [M^+], 170 (29), 159 (15), 151 (3), 74 (4); **HRMS** (EI-TOF) calcd for $C_{12}H_8FNO_2$: 217.0539; found: 217.0544; **m.p.**: 66–67 °C.

7.2.3.29. Synthesis of 2–fluoro–3'–nitrobiphenyl

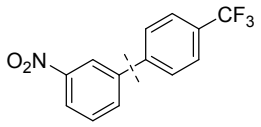


[CAS: 80254-88-2]

The title compound was prepared following general method from potassium 3-nitrobenzoate (124 mg, 0.6 mmol) and 1-chloro-2-fluorobenzene (66 mg, 53 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (56 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (t, J = 2.5 Hz, 1H), 8.25 (ddd, J = 8.3, 2.3, 1.0 Hz, 1H), 7.91 (dq, J = 7.7, 1.4 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.49 (td, J = 7.7, 1.8 Hz, 1H), 7.45–7.39 (m, 1H), 7.29 (td, J = 7.5, 1.3 Hz, 1H), 7.22 ppm (ddd, J = 10.7, 8.2, 1.1 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 160.85 (s), 158.38 (s), 148.37 (s), 137.39 (s), 135.04 (d, J = 3.7 Hz, 1C), 130.48 (d, J = 2.9 Hz, 1C), 130.34 (d, J = 8.1 Hz, 1C), 129.37 (s), 126.60 (d, J = 13.2 Hz, 1C), 124.31 (dd, J = 89.5. 3.7 Hz, 1C), 122.49 (s), 116.40 ppm (d, J = 22.7 Hz, 1C); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –117.91 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3091, 2922, 2851, 1961, 1525, 1496, 1469, 1347, 1204, 741 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 217 (100) [M^+], 170 (41), 159 (11), 151 (6), 133 (5), 85 (3); **HRMS** (EI-TOF) calcd for $C_{12}H_8FNO_2$: 217.0539; found: 217.0540; **m.p.**: 62–63 °C.

7.2.3.30. Synthesis of 3–nitro–4'–(trifluoromethyl)biphenyl

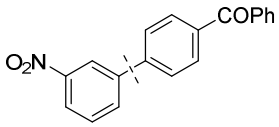


[CAS: 1138479-19-2]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 4–chlorobenzotrifluoride (92 mg, 68 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (80 mg, 60%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.48 (t, J = 1.9 Hz, 1H), 8.28 (ddd, J = 8.0, 1.6, 0.9 Hz, 1H), 7.94 (dt, J = 7.7, 1.3 Hz, 1H), 7.79-7.74 (m, 4H), 7.68 ppm (t, J = 8.0 Hz, 1H); **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 148.78 (s), 142.13 (s), 141.37 (s), 133.14 (s), 130.79 (s), 130.47 (s), 130.04 (s), 127.56 (s), 126.14 (q, J = 3.6 Hz, 1C), 125.33 (s), 122.93 (s), 122.62 (s), 122.15 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –62.60 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3081, 2923, 1618, 1531, 1514, 1346, 1322, 1159, 1110, 1068, 807 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 267 (100) [M^+], 248 (9), 221 (3), 209 (9), 201 (21), 152 (18), 75 (3); **HRMS** (EI-TOF) calcd for $C_{13}H_8F_3NO_2$: 267.0507; found: 267.0499; **m.p.**: 59–60 °C.

7.2.3.31. Synthesis of (3'–nitrobiphenyl–4–yl)–(phenyl)–methanone



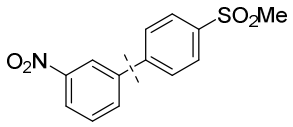
[CAS: 63242-13-7]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 4–chlorobenzophenone (109 mg, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (102 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (t, J = 2.0 Hz, 1H), 8.28 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 7.99 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.97–7.94 (m, 2H), 7.87-7.84 (m, 2H), 7.78–7.85 (m, 2H), 7.69 (t, J = 8.0 Hz, 1H), 7.66–7.62 (m, 1H), 7.56-7.51 ppm (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 196.02 (s), 148.77 (s), 142.40 (s), 141.65 (s), 137.42 (s), 137.34 (s), 133.15 (s), 132.66 (s), 130.91 (s, 2C), 130.01 (s, 2C), 129.99 (s), 128.40 (s, 2C), 127.08 (s,

2C), 122.84 (s), 122.13 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3088, 3066, 1651, 1603, 1522, 1511, 1347, 1279, 695 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 303 (100) [M^+], 286 (13), 226 (65), 152 (8), 105 (31), 77 (30); **HRMS** (EI-TOF) calcd for $C_{19}H_{13}NO_3$: 303.0895; found: 303.0901; **m.p.**: 139–140 °C.

7.2.3.32. Synthesis of 4'–(methylsulfonyl)–3–nitrobiphenyl

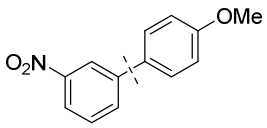


[CAS: 1809242-88-3]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 4–chlorophenylmethylsulfone (97 mg, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (69 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (t, *J* = 1.9 Hz, 1H), 8.32 (ddd, *J* = 8.2, 2.1, 0.9 Hz, 1H), 8.11–8.08 (m, 2H), 7.96 (ddd, *J* = 7.8, 1.5, 1.1 Hz, 1H), 7.86–7.82 (m, 2H), 7.71 (t, *J* = 8.0 Hz, 1H), 3.13 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 148.83 (s), 144.05 (s), 140.79 (s), 140.49 (s), 133.24 (s), 130.21 (s), 128.34 (s, 2C), 128.19 (s, 2C), 123.39 (s), 122.30 (s), 44.57 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3083, 3016, 2930, 1927, 1597, 1525, 1342, 1306, 1291, 1144, 1087, 967 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 277 (100) [M^+], 262 (43), 214 (72), 198 (36), 152 (31), 43 (38); **HRMS** (EI-TOF) calcd for $C_{13}H_{11}NO_4S$: 277.0409; found: 277.0408; **m.p.**: 118–119 °C.

7.2.3.33. Synthesis of 4'–methoxy–3–nitrobiphenyl

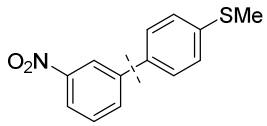


[CAS: 53059-31-7]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 4–chloroanisole (73 mg, 63 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (45 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (t, J = 1.9, Hz, 1H), 8.16 (ddd, J = 8.0, 1.6, 1.0 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.61–7.57 (m, 3H), 7.05–7.02 (m, 2H), 3.89 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.04 (s), 148.72 (s), 142.46 (s), 132.51 (s), 131.06 (s), 129.62 (s), 128.27 (s, 2C), 121.39 (s), 121.36 (s), 114.58 (s, 2C), 55.41 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3085, 2964, 2838, 1607, 1527, 1509, 1475, 1346, 1247, 1022, 804 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 229 (100) [M^+], 183 (20), 168 (17), 139 (14), 128 (17), 74 (5); **HRMS** (EI-TOF) calcd for $C_{13}H_{11}NO_3$: 229.0739; found: 229.0742; **m.p.**: 75–76 °C.

7.2.3.34. Synthesis of methyl–(3'–nitrobiphenyl–4–yl)–sulfane

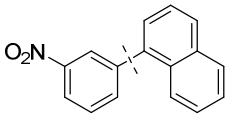


[CAS: 1355247-56-1]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 4–chlorothioanisole (81 mg, 66 µL, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (51 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (t, J = 1.9 Hz, 1H), 8.19 (ddd, J = 8.0, 1.6, 1.0 Hz, 1H), 7.90 (ddd, J = 8.0, 1.6, 1.1 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.59–7.55 (m, 2H), 7.39–7.36 (m, 2H), 2.55 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.70 (s), 142.12 (s), 139.58 (s), 135.06 (s), 132.58 (s), 129.71 (s), 127.36 (s, 2C), 126.72 (s, 2C), 121.84 (s), 121.48 (s), 15.49 ppm (s). **IR** (ATR): $\tilde{\nu}$ = 3074, 2922, 2852, 1594, 1525, 1497, 1344, 1102, 739 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 245 (100) [M^+], 199 (18), 187 (3), 152 (32), 139 (5), 63 (3); **HRMS** (EI-TOF) calcd for $C_{13}H_{11}NO_2S$: 245.0511; found: 245.0513; **m.p.**: 95–96 °C.

7.2.3.35. Synthesis of 1–(3–nitrophenyl)naphthalene



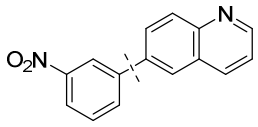
[CAS: 94064-81-0]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 1–chloronaphthalene (83 mg, 70 µL, 0.5 mmol) in a

mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow liquid (53 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39 (t, *J* = 1.9 Hz, 1H), 8.32 (ddd, *J* = 8.0, 1.6, 1.0 Hz, 1H),7.95 (dd, *J* = 7.9, 4.6 Hz, 2H), 7.85 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.59–7.44 ppm (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.29 (s), 142.39 (s), 137.47 (s), 136.14 (s), 133.76 (s), 131.05 (s), 129.22 (s), 128.79 (s), 128.55 (s), 127.23 (s), 126.71 (s), 126.17 (s), 125.32 (s), 125.02 (s), 124.85 (s), 122.25 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3060, 2922, 1737, 1524, 1508, 1345, 799 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 249 (100) [M^+], 232 (14), 202 (42), 101 (6), 88 (3), 50 (4); **HRMS** (EI-TOF) calcd for $C_{16}H_{11}NO_2$: 249.0790; found: 249.0789.

7.2.3.36. Synthesis of 6–(3–nitrophenyl)quinoline



[CAS: 1809242-89-4]

The title compound was prepared following general method from potassium 3–nitrobenzoate (124 mg, 0.6 mmol) and 6–chloroquinoline (83 mg, 0.5 mmol) in a mixture of NMP (2.5 mL) and quinoline (2.5 mL). After the reaction, the title compound was obtained by column chromatography as a yellow solid (90 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.61 (t, *J* = 1.9 Hz, 1H), 8.29–8.24 (m, 3H), 8.09 (d, *J* = 2.0 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 8.01 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.50 ppm (dd, *J* = 8.3, 4.2 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.16 (s), 148.83 (s), 148.03 (s), 142.02 (s), 136.71 (s), 136.36 (s), 133.29 (s), 130.59 (s), 129.96 (s), 128.52 (s), 128.40 (s), 126.18 (s), 122.48 (s), 122.27 (s), 121.92 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3028, 2970, 1740, 1523, 1500, 1342, 1291, 838 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 250 (100) [M^+], 204 (18), 176 (6), 150 (2), 88 (4), 75 (3); **HRMS** (EI-TOF) calcd for $C_{15}H_{10}N_2O_2$: 250.0742; found: 250.0747; **m.p.**: 169–170 °C.

7.3. *ortho*-C–H Arylation of Benzoic Acids with Aryl Bromides and Chlorides Catalyzed by Ruthenium

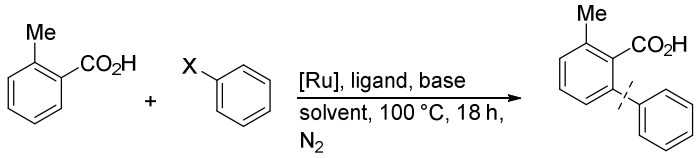
7.3.1. General Methods

Chemicals and solvents were either purchased (puriss p.A.) from commercial supplier or purified by standard techniques.[343] All reactions, if not stated otherwise, were performed in oven-dried glassware under a nitrogen atmosphere containing a Teflon-coated stirrer bar and dry septum. All reactions were monitored by GC using tetradecane as an internal standard. Response factors of the products with regard to *n*-tetradecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP–5 capillary column (Phenyl methyl siloxane, 30 m × 320 × 0.25, 100/2.3-30-300/3, 2 min at 60 °C, heating rate 30 °C/min, 3 or 10 min at 300 °C). Column chromatography was performed using a Combi Flash Companion-Chromatography-System (*Isco-Systems*) and *Reveleris* packed columns (12 g). NMR spectra were recorded on *Bruker Avance 400* at ambient temperature using $CDCl_3$ as solvent, with proton, carbon, and fluorine resonances at 400, 101, and 376 MHz respectively.

7.3.2. Catalyst development

7.3.2.1. Cross-coupling experiments

Table 6: Screening experiments for the *ortho*-arylation of *o*-tolyl benzoic acid with iodobenzene and bromobenzene.



7.3.2.1.-1 **7.3.2.1.-2** **7.3.2.1.-3**

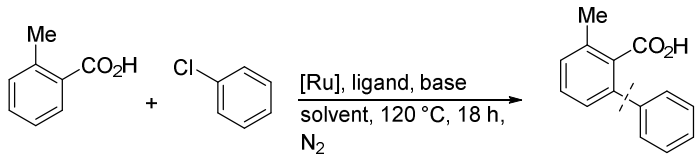
#	[Ru] /mol%	PhX/eq.	base /eq.	ligand /mol%	solvent/mL	Y[a]/%
1	$[Ru(MeCN)_6(OTf)_2]$ /4	PhI/1	K_2CO_3 /1	-	PhMe/3	-
2	"	"	"	-	Dioxane/3	trace
3	"	"	"	-	^{t}AmylOH/3	5
4	"	"	"	-	C_2H_5CN/3	trace

5	"	"	"	-	H_2O/3	-
6	"	"	"	-	NMP/3	12
7	[(*p*–cym)Ru Cl_2]$_2$ /4	"	"	-	"	25
8	(COD)$RuCl_2$ /8	"	"	-	"	8
9	[(C_6H_6)$RuCl_2$]$_2$ /4	"	"	-	"	16
10	[(*p*–cym)RuI_2]$_2$ /4	"	"	-	"	15
11	$RuCl_3$ x $3H_2O$ /8	"	"	-	"	20
12	(COD)RuCp*Cl /8	"	"	-	"	trace
13	Ru(metallyl)(COD) /8	"	"	-	"	12
14	$RuCl_2(PPh_3)_3$ /8	"	"	-	"	trace
15	(NBD)$RuCl_2$ /8	"	"	-	"	16
16	[(C_6Me_6)$RuCl_2$]$_2$ /4	"	"	-	"	trace
17	[(*p*–cym)$RuCl_2$]$_2$ /4	PhI/4	"	-	"	34
18	Ru(metallyl)(COD) /8	"	"	-	"	18
19	(NBD)$RuCl_2$ /8	"	"	-	"	24
20	[$Ru(MeCN)_6(OTf)_2$] /4	"	"	-	"	33
21	[(C_6H_6)$RuCl_2$]$_2$ /4	"	"	-	"	35
22	[(*p*–cym)$RuCl_2$]$_2$ /4	PhBr/4	GuanCO_3 /0.5	-	"	trace
23	"	"	GuanCO_3 /1	-	"	5
24	"	"	K_2CO_3 /1.1	-	"	13
25	"	"	"	PPh_3 /8	"	35
26	"	"	"	P^tBu_3 /8	"	trace
27	"	"	"	$P(Ad)_2Ph$ /8	"	-
28	"	"	"	$P(Mes)_3$ /8	"	trace
29	"	"	"	PCy_3 /8	"	76
30	"	"	"	Xphos /8	"	-
31	"	"	"	XantPhos /8	"	-
32	"	"	"	P(*o*–Tol)$_3$ /8		trace
33	"	PhBr/2	"	PCy_3 /8	"	73
34	"	PhBr/1	"	"	"	20
35	"	"	"	PEt_2Ph /8	"	65

36	"	"	"	$POct_3$ /8	"	78
37	"	"	"	PMe_3 /8	"	3
38	"	"	"	P^iPr_3 /8	"	43
39	"	"	"	$PMe_3 \cdot HBF_4$ /8	"	73
40	"	"	"	$PEt_3 \cdot HBF_4$ /8	"	93
41	"	"	Cs_2CO_3 /1.1	"	"	84
42	"	"	$CaCO_3$ /1.1	"	"	-
43	"	"	Na_2CO_3 /1.1	"	"	84
44	"	"	$GuanCO_3$ /1.1	"	"	-
45	"	"	Li_2CO_3 /1.1	"	"	13
46	"	"	NH_4CO_3 /1.1	"	"	-
47	"	"	K_2CO_3 /1	"	"	89
48	"	"	K_2CO_3 /0.8	"	"	85
49	"	"	K_2CO_3 /0.5	"	"	60
50	"	"	K_2CO_3 /1.1	"	NMP/3+1eq. H_2O	89
51	"	"	"	"	NMP/3+0.1eq. H_2O	89
52[c]	"	"	"	"	NMP/3	-
53	"	"	"	"	DMSO/3	25
54	"	"	"	"	DMF/3	trace
55	"	"	"	"	^{t}AmylOH/3	trace
56	"	"	"	"	Dioxane/3	trace
57	"	"	"	"	PhMe/3	trace
58	$[Cp^*IrCl_2]_2$ /4	"	"	"	NMP/3	-
59	$Pd(OAc)_2$ /8	"	"	"	"	-

Reaction conditions: ***7.3.2.1.-1*** *(0.5 mmol),* ***7.3.2.1.-2****, [M], ligand, base, solvent, 100 °C, 18 h under N_2-atmosphere. [a] Yields of corresponding methyl esters determined by GC after esterification with K_2CO_3 (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard; [c] under air atmosphere.*

Table 7: Screening experiments for the *ortho*-arylation of *o*-tolyl benzoic acid with chlorobenzene.



7.3.2.1.-1 **7.3.2.1.-2** **7.3.2.1.-3**

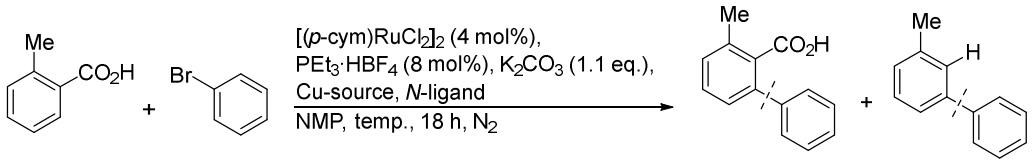
#	[Ru] /mol%	base /eq.	ligand /mol%	PhCl/eq.	Y[a]/%
1	[(*p*–cym)$RuCl_2$]$_2$ /4	K_2CO_3 /1.1	-	4	7
2	"	"	PPh_3 /8	"	trace
3	"	"	XPhos /8	"	trace
4	"	"	PCy_3 /8	"	trace
5	"	"	$P(Ad)_2CH_2Ph$ /8	"	trace
6	"	"	P^iPr_3 /8	"	trace
7	"	"	$P^tBu_3{\cdot}HBF_4$ /8	"	trace
8	"	"	$PEt_3{\cdot}HBF_4$ /8	"	12
9[b]	"	"	"	"	75
10	"	"	DL–Phe–OH /8	"	16
11	"	"	*N*–Cbz–L–Phe–OH /8	"	11
12	"	"	*N*–Boc–L–Phe–OH /8	"	17
13	"	"	*N*–Cbz–L–Asn–OH /8	"	trace
14	"	"	L–Pro–OH /8	"	47
15	"	"	DL–Val–OH /8	"	24
16	"	"	*N*–Boc–L–Asn–OH /8	"	trace
17	"	"	*N*–Bz–DL–Pro–OH /8	"	15
18	"	"	*N*–Cbz–DL–Val–OH /8	"	18
19	"	"	L–Ile–OH /8	"	26
20	"	"	L–Pyroglutamic acid /8	"	trace
21	"	"	*N*–Boc–L–Pro–OH /8	"	18
22	"	"	L–Ala–OH /8	"	11
23	"	"	DMPU /8	"	6

24	"	"	*N*–Cbz–L–Ile–OH /8	"	18
25	"	"	DL–pipecolinic acid /8	"	80
26	"	"	"	3	72
27	"	"	"	2	57
28	"	"	"	1.5	48
29	"	"	"	1	32
30[c]	"	"	"	"	23
31[d]	"	"	"	"	12
32[e]	"	"	"	"	80

Reaction conditions: ***7.3.2.1.-1*** *(0.5 mmol),* ***7.3.2.1.-2*** *(2 mmol), [(p–cym)RuCl$_2$]$_2$ (4 mol%), K$_2$CO$_3$ (1.1 eq.), NMP (3 mL), 120 °C, 18 h. [a] Yields of corresponding methyl esters determined by GC after esterification with K$_2$CO$_3$ (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard; [b] 48 h; [c] 1.5 eq.* ***7.3.2.1.-2****; [d] 2 eq.* ***7.3.2.1.-2****; [e] 140 °C.*

7.3.2.2. Protodecarboxylation experiments

Table 8: Screening experiments for the protodecarboxylation of **7.3.2.1.-1**. *In situ* and sequential one-pot procedure.



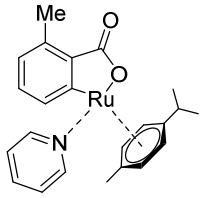
7.3.2.2.-1 **7.3.2.2.-2** **7.3.2.2.-3** **7.3.2.2.-4**

#	[M] /mol%	T/°C	N-ligand/mol%	t/h	Y[a]/%	
					7.3.2.2.-3	**7.3.2.2.-4**
1	Cu$_2$O /10	100 → 170	-	18 + 12	76	9
2	"	170	-	18	70	10
3	"	180	-	"	41	46
4	Cu$_2$O /20	"	-	"	37	51
5	Cu$_2$O /50	"	-	"	40	44
6	Cu$_2$O /10	"	1,10–phen/20	"	trace	-
7[b]	"	100 → 180	"	18 + 12	77	9
8[c]	"	"	"	"	87	trace
9[c]	"	"	DL–pipecolinic acid/20	"	88	trace
10[c]	"	"	Pyridine/20	"	67	20

11	CuBr /20	180	-	18	49	32
12	Ag_2O /10	"	-	"	45	33
13[d]	"	100 → 180	-	18 + 12	69	4
14	"	160	-	18	68	11
15[e]	Cu_2O /10	180	-	"	71	11
16[f]	"	100 → 180	-	18 + 12	87	4
17	"	190	-	18	19 (23)	61 (54)
18[g]	"	"	-	"	10 (13)	63 (71)

Reaction conditions: ***7.3.2.2.-1*** *(0.5 mmol),* ***7.3.2.2.-2*** *(0.5 mmol), [(p-cym)RuCl$_2$]$_2$ (4 mol%), PEt$_3$·HBF$_4$ (8 mol%), K$_2$CO$_3$ (1.1 eq.), 100 °C for 18 h followed by T for 12 h or T for 18 h, 3 mL NMP. [a] GC yields after esterification with K$_2$CO$_3$ (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard, isolated yields in parenthesis; [b] Cu$_2$O and 1,10–phen were added after 18 h; [c] N-ligand was added after 18 h; [d] Ag$_2$O and was added after 18 h; [e] 1 eq. H$_2$O was added; [f] Cu$_2$O was added after 18 h; [g] with 2–fluorobenzoic acid.*

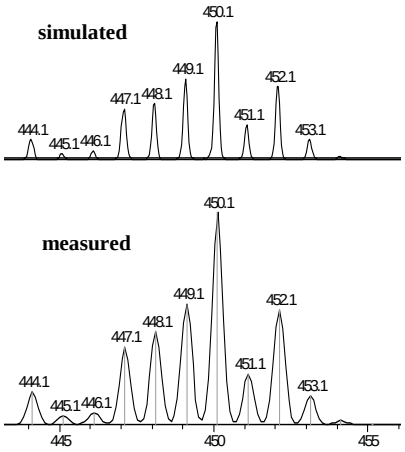
7.3.3. Synthesis of [Ru(2–Me–benzoato^2–C^6,O^1)(p–cymene)(pyridine)]



[CAS: 2036084-13-4]

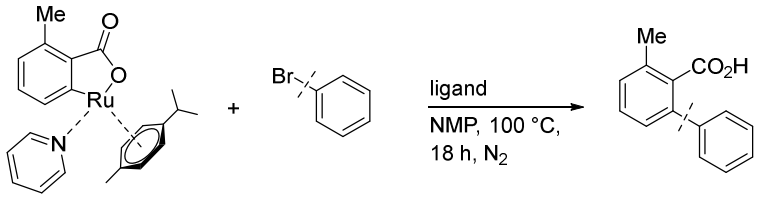
The title compound was synthesized following the literature reported procedure,[284] starting from potassium 2–methyl benzoate (261 mg, 1.5 mmol), [Ru(*p*-cym)Cl$_2$]$_2$ (312 mg, 0.5 mmol), pyridine (79 mg, 8.1 µL, 1 mmol) and trimethylamine (715 mg, 983 µL, 7 mmol). The title compound was isolated as a red wax (82 mg, 37%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54–8.60 (m, 2H), 7.86–7.91 (m, 1H), 7.46 (tt, *J* = 7.7, 1.5 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.99–7.04 (m, 2H), 6.73 (dd, *J* = 6.9, 0.6 Hz, 1H), 5.52 (dd, *J* = 5.8, 1.0 Hz, 1H), 5.45 (dd, *J* = 6.0, 0.8 Hz, 1H), 5.22 (dd, *J* = 5.9, 1.1 Hz, 1H), 4.79 (dd, *J* = 5.8, 1.0 Hz, 1H), 2.46 (s, 3H), 2.36 (quin, *J* = 6.9 Hz, 2H), 1.70 (s, 1H), 0.99 ppm (dd, *J* = 6.8, 1.5 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 181.3 (s), 177.5 (s), 153.6 (s), 140.0 (s), 136.6 (s), 135.5 (s), 134.5 (s), 129.6 (s), 126.6 (s), 124.3 (s), 101.8 (s), 97.9 (s), 87.9 (s), 87.2 (s), 84.3 (s), 80.2 (s), 30.7 (s), 22.6 (s), 22.2 (s), 19.9 (s), 17.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3050, 2965, 2926, 2872, 1600, 1468, 1443, 1213, 1091, 1008, 907, 759, 692 cm^{-1}; **HRMS** (ESI): *m/z* = calcd. for $C_{23}H_{25}O_2NRu+H^+$: 450.1007; found 450.1001.



7.3.3.1. Mechanistic control experiment

Table 9: Stoichiometric reaction of preformed ruthenacycle **7.3.3.1.-1** with bromobenzene.

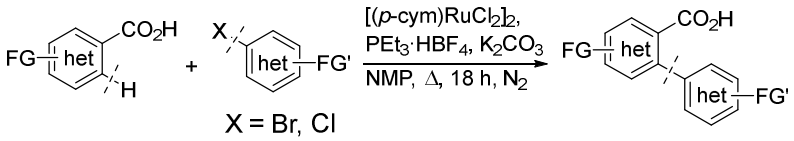


7.3.3.1.-1 **7.3.3.1.-2** **7.3.3.1.-3**

#	ligand /mol%	Y[a]/%
1	$PEt_3 \cdot HBF_4$ (100)	57
2	-	0

Reaction conditions: ***7.3.3.1.-1*** *(0.1 mmol),* ***7.3.3.1.-2*** *(0.1 mmol), 100 °C for 18 h, 3 mL NMP. [a] GC yields after esterification with K_2CO_3 (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard.*

7.3.4. Synthesis of the corresponding 1,1'–biphenyl–2–carboxylic acids via ortho-C–H arylation

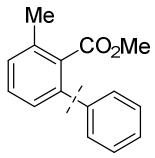


Standard procedure A – coupling of aryl bromides: An oven-dried 20 mL vessel was charged with $[(p\text{–cym})RuCl_2]_2$ (12.2 mg, 0.02 mmol, 4 mol%), triethylphosphonium tetrafluoroborate (8.3 mg, 0.04 mmol, 8 mol%), K_2CO_3 (76 mg, 0.55 mmol, 1.1 eq.), and the benzoic acid (0.50 mmol). After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, NMP (3 mL) and the aryl bromide (0.50 mmol) were added *via* syringe. The resulting mixture was stirred at 100 °C for 18 h. After the reaction was complete,

the mixture was allowed to cool to room temperature. NMP (2 mL), K_2CO_3 (207 mg, 3 eq.) and MeI (156 µL, 5 eq.) were added and the mixture was stirred at 60 °C for 2 h. The mixture was allowed to cool to room temperature, ethyl acetate (20 mL) was added and the resulting mixture was washed with water, aqueous LiCl solution (20%) and brine (20 mL each). The organic layer was dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient) yielding the corresponding biaryl.

Standard procedure B – coupling of aryl chlorides: An oven-dried 20 mL vessel was charged with $[Ru(p\text{–cym})Cl_2]_2$ (12.2 mg, 0.02 mmol, 4 mol%), DL-pipecolinic acid (5.17 mg, 0.04 mmol, 8 mol%), K_2CO_3 (76 mg, 0.55 mmol, 1.1 eq.), and the corresponding carboxylic acid (0.50 mmol, 1 eq.). After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, NMP (3 mL) and the corresponding aryl chloride (2.00 mmol, 4 eq.) were added *via* syringe. The resulting mixture was stirred at 120 °C for 18 h. After the reaction was completed, the mixture was allowed to cool to room temperature. NMP (2 mL), K_2CO_3 (207 mg, 3 eq.) and MeI (156 µL, 5 eq.) were added and the mixture was stirred at 60 °C for 2 h. The mixture was allowed to cool to room temperature, ethyl acetate (20 mL) was added and the resulting mixture was washed with water, aqueous LiCl solution (20%) and brine (20 mL each). The organic layer was dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient) yielding the corresponding biaryl.

7.3.4.1. Synthesis of methyl–3–methylbiphenyl–2–carboxylate



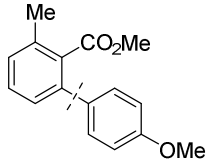
[CAS: 941320-77-0]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and bromobenzene (79.3 mg, 53.2 µL, 0.50 mmol). The title compound was isolated as colorless oil (105 mg, 93%).

The title compound was prepared following the general method B from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and chlorobenzene (227 mg, 205 µL, 2.00 mmol). The title compound was isolated as colorless oil (85 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.45 (m, 6H), 7.24 (d, *J* = 7.5 Hz, 2H), 3.60 (s, 3H), 2.42 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.3 (s), 140.9 (s), 140.2 (s), 135.5 (s), 133.2 (s), 129.5 (s), 129.1 (s), 128.3 (s), 128.2 (s), 127.4 (s), 127.3 (s), 51.9 (s), 19.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3062, 2950, 1726, 1463, 1436, 1267, 1122, 1066 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 226 (100) [M^+], 195 (90), 165 (22). The analytical data matched those reported in the literature.[262]

7.3.4.2. Synthesis of methyl–4'–methoxy–3–methylbiphenyl–2–carboxylate



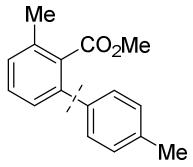
[CAS: 1097018-19-3]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 4–bromoanisole (93.5 mg, 62.8 µL, 0.50 mmol). The title compound was isolated as colorless solid (105 mg, 82%).

The title compound was prepared following the general method B from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 4–chloroanisole (291 mg, 251 µL, 2.00 mmol). The title compound was isolated as colorless solid (92 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.28–7.37 (m, 3H), 7.17–7.23 (m, 2H), 6.91–6.97 (m, 2H), 3.85 (s, 3H), 3.64 (s, 3H), 2.40 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): *δ* = 170.5 (s), 159.0 (s), 139.6 (s), 135.3 (s), 133.3 (s), 133.1 (s), 129.3 (s), 129.3 (s), 128.7 (s), 127.2 (s), 113.7 (s), 55.2 (s), 51.9 (s), 19.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2946, 2839, 1726, 1609, 1512, 1440, 1247, 1183 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):256 (100) [M^+], 225 (62), 209 (15), 181 (9), 153 (8); **HRMS** (EI-TOF) calcd. for $C_{16}H_{16}O_3$: 256.1099; found: 256.1091; **m.p.**: 69–70 °C. The analytical data matched those reported in the literature.[262]

7.3.4.3. Synthesis of methyl–3,4'–dimethylbiphenyl–2–carboxylate

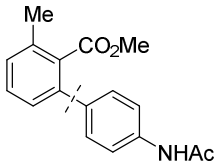


[CAS: 1097018-21-7]

The title compound was prepared following the general method B from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 4–chlorotoluene (258 mg, 241 µL, 2.00 mmol). The title compound was isolated as colorless oil (66 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.38 (m, 1H), 7.25–7.29 (m, 2H), 7.18–7.24 (m, 4H), 3.63 (s, 3H), 2.40 (s, 3H), 2.39 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.5 (s), 140.0 (s), 137.9 (s), 137.0 (s), 135.3 (s), 133.1 (s), 129.4 (s), 129.0 (s), 128.9 (s), 128.0 (s), 127.2 (s), 51.8 (s), 21.2 (s), 19.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2949, 1725, 1265, 1122, 1088, 1067, 783 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 240 (100) [M^+], 209 (55), 165 (17). The analytical data matched those reported in the literature.[262]

7.3.4.4. Synthesis of methyl–4'–(acetylamino)–3–methylbiphenyl–2–carboxylate

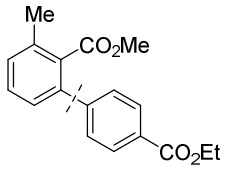


[CAS: 1809272-64-7]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and *N*–(4–bromophenyl)–acetamide (109 mg, 0.50 mmol). The title compound was isolated as colorless solid (131 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (m, *J* = 8.5 Hz, 2H), 7.29–7.40 (m, 4H), 7.18–7.24 (m, 2H), 3.64 (s, 3H), 2.40 (s, 3H), 2.17 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.5 (s), 168.3 (s), 139.4 (s), 137.3 (s), 136.7 (s), 135.4 (s), 133.1 (s), 129.5 (s), 129.0 (s), 128.8 (s), 127.2 (s), 120.0 (s), 119.4 (s), 51.9 (s), 24.6 (s), 19.7 ppm (s); IR (ATR): $\tilde{\nu}$ = 3322, 3275, 1679, 1532, 1456, 1320, 1288, 1257 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 283 (100) [M^+], 252 (11), 241 (43), 235 (12), 209 (50); **m.p.**: 189–190 °C. The analytical data matched those reported in the literature.[262]

7.3.4.5. Synthesis of 4'–ethyl–2–methyl–3–methylbiphenyl–2,4'–dicarboxylate

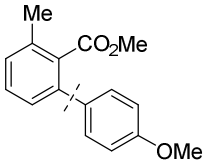


[CAS: 2040483-22-3]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and ethyl 4–bromobenzoate (116 mg, 82.6 µL, 0.50 mmol). The title compound was isolated as colorless oil (124 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 2H), 7.42–7.46 (m, 2H), 7.36–7.41 (m, 1H), 7.21–7.29 (m, 2H), 4.41 (q, J = 7.0 Hz, 2H), 3.59 (s, 3H), 2.42 (s, 3H), 1.42 ppm (t, J = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9 (s), 166.4 (s), 145.5 (s), 139.2 (s), 135.8 (s), 133.0 (s), 129.8 (s), 129.6 (s, 2C) 129.4 (s), 128.2 (s), 127.1 (s), 61.0 (s), 51.9 (s), 19.7 (s), 14.3 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2982, 2951, 1714, 1461, 1438, 1269, 1180, 1103 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):298 (100) [M^{+}], 266 (14), 253 (41), 239 (11), 195 (29), 165 (11); **HRMS** (EI–TOF) calcd. for $C_{18}H_{18}O_4$: 298.1205; found: 298.1203.

7.3.4.6. Synthesis of methyl–4'–methoxy–3–methylbiphenyl–2–carboxylate

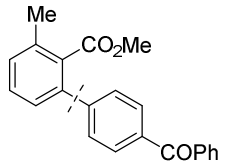


[CAS: 1097018-19-3]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 4–bromophenol (87.4 mg, 0. 5 mmol). The title compound was isolated as the methyl ether after treatment with MeI and K_2CO_3 in NMP. yellow oil (67 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.37 (m, 2H), 7.17–7.23 (m, 2H), 6.92–6.96 (m, 2H), 3.85 (s, 2H), 3.64 (s, 2H), 2.40 ppm (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.5 (s), 159.0 (s), 139.6 (s), 135.3 (s), 133.3 (s), 133.1 (s), 129.3 (s), 129.3 (s), 128.7 (s), 127.2 (s), 113.7 (s), 55.2 (s), 51.8 (s), 19.6 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2946, 2839, 1726, 1609, 1512, 1440, 1247, 1183 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):256 (100) [M^{+}], 225 (62), 209 (15), 181 (9), 153 (8); **m.p.**: 69–70 °C. The analytical data matched those reported in the literature.[262]

7.3.4.7. Synthesis of methyl–4'–benzoyl–3–methylbiphenyl–2–carboxylate

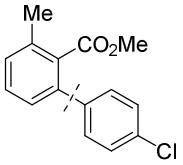


[CAS: 2051922-37-1]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and (4-bromophenyl)–(phenyl)–methanone (135 mg, 0.50 mmol). The title compound was isolated as colorless solid (134 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.90 (m, 3H), 7.58–7.65 (m, 1H), 7.47–7.55 (m, 3H), 7.41 (t, J = 7.7 Hz, 1H), 7.24–7.31 (m, 3H), 3.63 (s, 3H), 2.43 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 196.4 (s), 170.0 (s), 145.2 (s), 139.1 (s), 137.6 (s), 136.4 (s), 135.9 (s), 133.0 (s), 132.5 (s), 130.3 (s), 130.0 (s), 129.9 (s), 129.7 (s), 128.4 (s), 128.2 (s), 127.2 (s), 52.0 (s), 19.8 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3066, 2949, 1721, 1655, 1599, 1400, 1315, 1124 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 330 (100) [M^+], 315 (54), 299 (22), 253 (66), 195 (8), 165 (13), 105 (60); **HRMS** (EI–TOF) calcd. for $C_{22}H_{18}O_3$: 330.1256; found: 330.1259; **m.p.**: 83–84 °C.

7.3.4.8. Synthesis of methyl–4'–chloro–3–methylbiphenyl–2–carboxylate

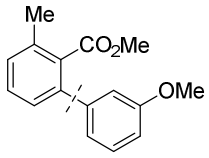


[CAS: 1809272-61-4]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 4–chloro bromobenzene (95.7 mg, 58µL, 0.50 mmol). The title compound was isolated as colorless oil (80 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.40 (m, 3H), 7.28–7.33 (m, 2H), 7.22–7.26 (m, 1H), 7.16–7.21 (m, 1H), 3.63 (s, 3H), 2.41 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.0 (s), 139.3 (s), 138.8 (s), 135.6 (s), 133.5 (s), 133.1 (s), 129.5 (s), 129.5 (s), 129.4 (s), 128.5 (s), 127.1 (s), 51.9 (s), 19.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2948, 1725, 1494, 1459, 1395, 1265, 1121, 835 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):260 (88) [M^+], 229 (100), 193 (22), 165 (20). The analytical data matched those reported in the literature.[262]

7.3.4.9. Synthesis of methyl–3'–methoxy–3–methylbiphenyl–2–carboxylate

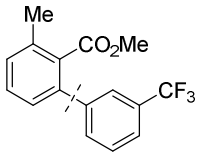


[CAS: 2040483-23-4]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 3–bromo anisole (95.4 mg, 64.5 µL, 0.50 mmol). The title compound was isolated as colorless solid (111 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (t, J = 7.8 Hz, 1H), 7.28 - 7.33 (m, 1H), 7.21–7.26 (m, 2H), 6.87–6.99 (m, 3H), 3.83 (s, 3H), 3.63 (s, 3H), 2.41 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.3 (s), 159.4 (s), 142.2 (s), 139.9 (s), 135.4 (s), 133.1 (s), 129.4 (s), 129.3 (s), 129.2 (s), 127.1 (s), 120.6 (s), 113.5 (s), 113.3 (s), 55.2 (s), 51.9 (s), 19.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2948, 2835, 1725, 1576, 1466, 1433, 1267, 1228 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):256 (94) [M^+], 224 (100), 182 (12), 153 (9); **HRMS** (EI–TOF) calcd. for $C_{16}H_{16}O_3$: 256.1099; found: 256.1082.

7.3.4.10. Synthesis of methyl–3–methyl–3'–(trifluoromethyl)biphenyl–2–carboxylate

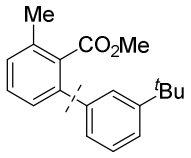


[CAS: 2022197-28-8]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 1–bromo–3–(trifluoromethyl)–benzene (114 mg, 70.6 µL, 0.50 mmol). The title compound was isolated as colorless oil (105 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.67 (m, 2H), 7.49–7.58 (m, 2H), 7.40 (t, J = 7.7 Hz, 1H), 7.26–7.30 (m, 1H), 7.21–7.25 (m, 1H), 3.62 (s, 3H), 2.42 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9 (s), 141.7 (s), 138.6 (s), 135.9 (s), 133.2 (s), 131.6 (s), 131.6 (s), 130.7 (q), 129.9 (s), 129.7 (s), 128.8 (s), 127.1 (s), 125.1 (q), 124.1 (q), 123.8 (q), 51.9 (s), 19.8 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –62.59 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2953, 1728, 1433, 1335, 1263, 1164, 1120, 1067 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):294 (68) [M^+], 263 (100), 215 (8), 165 (13); **HRMS** (EI–TOF) calcd. for $C_{16}H_{13}F_3O_2$: 294.0868; found: 294.0870.

7.3.4.11. Synthesis of methyl–3'–tert–butyl–3–methylbiphenyl–2–carboxylate

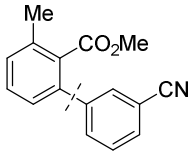


[CAS: 2051922-36-0]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 1–bromo–3–*tert*–butylbenzene (107 mg, 85.2 µL, 0.50 mmol). The title compound was isolated as colorless oil (111 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.46 (m, 4H), 7.17–7.28 (m, 3H), 3.60 (s, 3H), 2.42 (s, 3H), 1.35 ppm (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.4 (s), 151.1 (s), 140.6 (s), 140.5 (s), 135.4 (s), 133.2 (s), 129.4 (s), 128.9 (s), 128.1 (s), 127.2 (s), 125.4 (s), 125.3 (s), 124.2 (s), 51.8 (s), 34.7 (s), 31.4 (s), 19.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2952, 2867, 1727, 1589, 1463, 1436, 1365, 1117 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):282 (67) [M^+], 235 (100), 207 (16), 193 (42); **HRMS** (EI–TOF) calcd. for: $C_{19}H_{22}O_2$: 282.1620; found: 282.1624.

7.3.4.12. Synthesis of methyl–3'–cyano–3–methylbiphenyl–2–carboxylate

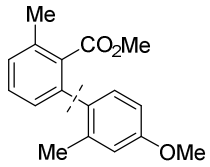


[CAS: 2051922-35-9]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 3–cyanobromobenzene (91.0 mg, 0.50 mmol). The title compound was isolated as colorless oil (65 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.68 (m, 2H), 7.57–7.62 (m, 1H), 7.48–7.54 (m, 1H), 7.37–7.43 (m, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 3.63 (s, 3H), 2.42 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.6 (s), 142.2 (s), 137.8 (s), 136.0 (s), 133.0 (s), 132.7 (s), 131.7 (s), 131.0 (s), 130.2 (s), 129.7 (s), 129.1 (s), 127.0 (s), 118.6 (s), 112.5 (s), 52.0 (s), 19.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2949, 2231, 1726, 1591, 1460, 1436, 1120, 1068 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):251 (64) [M^+], 220 (100), 190 (9), 165 (9); **HRMS** (EI–TOF) calcd. for $C_{16}H_{13}NO_2$: 251.0946; found: 251.0950.

7.3.4.13. Synthesis of 4'–methoxy–2',3–dimethylbiphenyl–2–carboxylate

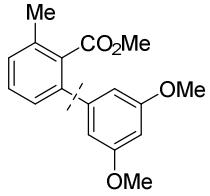


[CAS: 2051922-34-8]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 1–bromo–4–methoxy–2–methylbenzene (104 mg, 114 µL, 0.50 mmol). The title compound was isolated as yellow oil (54.0 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 7.3 Hz, 1H), 7.01–7.08 (m, 2H), 6.79 (d, J = 2.5 Hz, 1H), 6.72 (dd, J = 8.3, 2.8 Hz, 1H), 3.83 (s, 3H), 3.52 (s, 3H), 2.40 (s, 3H), 2.12 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9 (s), 158.8 (s), 139.6 (s), 137.5 (s), 135.0 (s), 134.2 (s), 132.6 (s), 130.2 (s), 128.9 (s), 128.7 (s), 127.6 (s), 115.2 (s), 110.3 (s), 55.1 (s), 51.6 (s), 20.4 (s), 19.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2948, 2835, 1728, 1608 , 1573, 1461, 1266, 1237 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 270 (100) [M^{+}], 238 (55), 223 (10), 195 (25), 152 (6); **HRMS** (EI–TOF) calcd. for $C_{17}H_{18}O_3$: 270.1256; found: 270.1257.

7.3.4.14. Synthesis of 3',5'–dimethoxy–3–methylbiphenyl–2–carboxylate

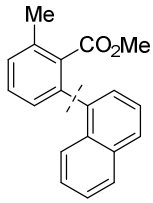


[CAS: 1261980-73-7]

The title compound was prepared following the general method B from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 5–chloro–1,3–dimethoxybenzene (356 mg, 2.00 mmol). The title compound was isolated as colorless oil (97 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (t, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 2H), 6.60 (d, J = 2.3 Hz, 2H), 6.48 (t, J = 2.3 Hz, 1H), 3.78 (s, 6H), 2.46 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 174.9 (s), 160.6 (s), 142.5 (s), 139.9 (s), 135.3 (s), 132.1 (s), 129.7 (s), 129.3 (s), 127.2 (s), 106.4 (s), 100.1 (s), 55.3 (s), 19.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2962, 2937, 2838, 1695, 1584, 1456, 1421, 1204, 1153, 1063, 907, 727, 695 cm^{-1}. The analytical data matched those reported in the literature.[265]

7.3.4.15. Synthesis of methyl–3–phenylnaphthalene–2–carboxylate

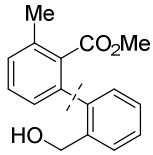


[CAS: 2051922-33-7]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 1–bromonaphthalene (158 mg, 106 µL, 0.75 mmol). The title compound was isolated as colorless oil (117 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.92 (m, 2H), 7.63–7.69 (m, 1H), 7.46–7.52 (m, 2H), 7.39–7.45 (m, 2H), 7.29–7.37 (m, 2H), 7.23–7.27 (m, 1H), 3.27 (s, 3H), 2.47 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.6 (s), 138.7 (s), 138.4 (s), 135.7 (s), 134.4 (s), 133.4 (s), 131.9 (s), 129.4 (s), 129.0 (s), 128.4 (s), 128.0 (s), 127.8 (s), 126.6 (s), 126.2 (s), 125.9 (s), 125.7 (s), 124.9 (s), 51.5 (s), 19.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3053, 2948, 1726, 1587, 1508, 1435, 1394, 1111 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):276 (100) [M^+], 245 (50), 202 (12), 107 (6); **HRMS** (EI–TOF) calcd. for: $C_{19}H_{16}O_2$: 276.1150; found: 276.1138.

7.3.4.16. Synthesis of methyl–2'–(hydroxymethyl)–3–methylbiphenyl–2–carboxylate



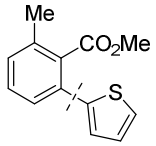
[CAS: 2051922-32-6]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 3–bromobenzyl alcohol (95.4 mg, 0.50 mmol). The title compound was isolated as colorless oil (66 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (dd, J = 7.7, 1.1 Hz, 1H), 7.32–7.42 (m, 2H), 7.23–7.32 (m, 2H), 7.10 (ddd, J = 12.4, 7.6, 0.9 Hz, 2H), 4.46–4.54 (m, 1H), 4.33–4.40 (m, 1H), 3.53 (s, 3H), 2.40 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.4 (s), 139.2 (s), 138.8 (s), 138.6 (s), 135.1 (s), 133.7 (s), 129.4 (s), 129.2 (s), 129.1 (s), 129.1 (s), 128.3 (s), 127.2 (s), 127.2 (s), 63.1 (s), 52.0 (s), 19.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3420, 2949, 1727, 1589, 1438, 1110, 1066, 1012 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 239 (29) [M^+–OH], 224 (100), 206.0 (60),

195 (59), 181 (38), 165 (25); **HRMS** (EI–TOF) calcd. for $C_{16}H_{14}O_2$: 238,0994; found: 238.0998 [M^+–(H_2O)].

7.3.4.17. Synthesis of methyl–2–methyl–6–(thiophen–2–yl)benzoate

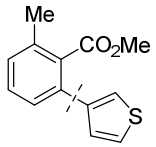


[CAS: 2051922-31-5]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 2–bromothiophene (83.2 mg, 49.5 µL, 0.50 mmol). The title compound was isolated as orange oil (100 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.36 (m, 3H), 7.18–7.24 (m, 1H), 7.08–7.11 (m, 1H), 7.03–7.07 (m, 1H), 3.76 (s, 3H), 2.38 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.2 (s), 141.9 (s), 135.3 (s), 133.3 (s), 132.0 (s), 129.5 (s), 129.3 (s), 127.5 (s), 127.4 (s), 125.9 (s), 52.1 (s), 19.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2948, 2920, 1727, 1589, 1432, 1266, 1119, 1072 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):232 (100) [M^+], 200 (70), 171 (12), 129 (6); **HRMS** (EI–TOF) calcd. for: $C_{13}H_{11}O_2S$: 231.0480; found: 231.0490 [M^+–H].

7.3.4.18. Synthesis of methyl–2–methyl–6–(thiophen–3–yl)benzoate

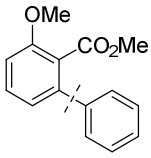


[CAS: 2022197-36-8]

The title compound was prepared following the general method A from 2–methylbenzoic acid (68.8 mg, 0.50 mmol) and 3–bromothiophene (84 mg, 48.3 µL, 0.50 mmol). The title compound was isolated as orange oil (79.0 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.32 (m, 2H), 7.20–7.25 (m, 2H), 7.13–7.17 (m, 1H), 7.10–7.13 (m, 1H), 3.66 (s, 3H), 2.33 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.5 (s), 140.9 (s), 135.2 (s), 134.3 (s), 133.0 (s), 129.4 (s), 129.0 (s), 127.9 (s), 126.8 (s), 125.6 (s), 122.3 (s), 52.0 (s), 19.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2948, 1723, 1591, 1461, 1437, 1265, 1119, 1090 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):232 (100) [M^+], 200 (85), 171 (13), 129.(7); **HRMS** (EI–TOF) calcd. for $C_{13}H_{12}O_2S$: 232.0558; found: 232.0564.

7.3.4.19. Synthesis of methyl–3–methoxylbiphenyl–2–carboxylate

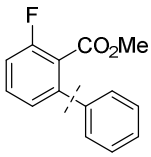


[CAS: 773134-32-0]

The title compound was prepared following the general method A from 2–methoxylbenzoic acid (76.8 mg, 0.50 mmol) and bromobenzene (119.0 mg, 79.8 µL, 0.75 mmol). The title compound was isolated as colorless solid (117 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.45 (m, 6H), 7.01 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.95 (dd, *J* = 8.3, 0.8 Hz, 1H), 3.90 (s, 3H), 3.64 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.5 (s), 156.4 (s), 141.2 (s), 140.0 (s), 130.5 (s), 128.3 (s), 128.2 (s), 127.6 (s), 123.0 (s), 122.0 (s), 109.8 (s), 56.0 (s), 52.1 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2947, 2839, 1730, 1570, 1462, 1257, 1128, 1108 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):242 (63) [M^+], 211 (100), 168 (12), 139 (8); **m.p.**: 84–85 °C. The analytical data matched those reported in the literature.[265]

7.3.4.20. Synthesis of methyl–3–fluorobiphenyl–2–carboxylate



[CAS: 1528793-42-1]

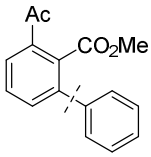
The title compound was prepared following the general method A from 2–fluorobenzoic acid (119 mg, 0.50 mmol) and bromobenzene (119.0 mg, 79.8 µL, 0.75 mmol). The title compound was isolated as colorless oil (102 mg, 88%).

The title compound was prepared following the general method B from 2–fluorobenzoic acid (119 mg, 0.50 mmol) and chlorobenzene (227.0 mg, 205 µL, 2 mmol). The title compound was isolated as colorless oil (108 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.50 (m, 6H), 7.21 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.14 (ddd, *J* = 9.3, 8.3, 1.0 Hz, 1H), 3.69 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.2 (s), 159.7 (d, *J* = 251.6 Hz) 142.5 (d, *J* = 2.7 Hz) 139.3 (d, *J* = 2.7 Hz) 131.2 (d, *J* = 8.2 Hz) 128.5 (s), 128.1 (s), 127.9 (s), 125.5 (d, *J* = 2.7 Hz) 121.4 (d, *J* = 16.3 Hz) 114.7 (s), 114.5 (s), 52.4 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –115.3 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2952, 1732,

1612, 1568, 1462, 1261, 1239, 1115 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):230 (79) [M^+], 199 (100), 170 (16). The analytical data matched those reported in the literature.[346]

7.3.4.21. Synthesis of methyl–3–acetylbiphenyl–2–carboxylate

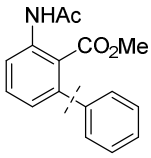


[CAS: 1097018-12-6]

The title compound was prepared following the general method A from 2–acetylbenzoic acid (82.9 mg, 0.50 mmol) and bromobenzene (119 mg, 80.0 µL, 0.75 mmol). The title compound was isolated as yellow solid (79 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.86 (m, 1H), 7.53–7.59 (m, 2H), 7.34–7.44 (m, 5H), 3.67 (s, 3H), 2.65 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 198.3 (s), 169.7 (s), 141.1 (s), 135.9 (s), 134.2 (s), 132.9 (s), 129.2 (s), 128.5 (s), 128.3 (s), 127.9 (s), 127.9 (s), 52.3 (s), 27.6 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2952, 1727, 1677, 1578, 1454, 1428, 1193, 1125 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 254 (10) [M^+], 239 (100), 207 (7), 179 (6), 152 (9); **HRMS** (EI–TOF) calcd. for $C_{16}H_{14}O_3$: 254.0943; found: 254.0945; **m.p.**: 92–93 °C. The analytical data matched those reported in the literature.[265]

7.3.4.22. Synthesis of methyl–3–acetamidobiphenyl–2–carboxylate



[CAS: 2051922-30-4]

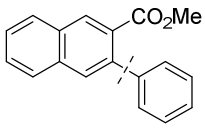
The title compound was prepared following the general method A from *N*–acetylanthranilic acid (90.5 mg, 0.50 mmol) and bromobenzene (91.0 mg, 0.50 mmol). The title compound was isolated as colorless solid (95 mg, 71%).

The title compound was prepared following the general method b from *N*–acetylanthranilic acid (90.5 mg, 0.50 mmol) and chlorobenzene (227 mg, 205 µL, 2.00 mmol). The title compound was isolated as colorless solid (78 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (br. s., 1H), 8.39 (d, J = 8.3 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.31–7.43 (m, 3H), 7.24–7.30 (m, 3H), 7.10–7.17 (m, 1H), 3.44 (s, 3H),

2.22 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9 (s), 168.6 (s), 143.0 (s), 141.9 (s), 137.8 (s), 131.6 (s), 128.2 (s), 127.9 (s), 127.2 (s), 125.6 (s), 120.5 (s), 119.6 (s), 51.9 (s), 25.1 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3236, 3037, 2949, 1722, 1548, 1466, 1369, 1266 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):269 (62) [M$^+$], 227 (68), 195 (100), 168 (22), 139 (9); **HRMS** (EI–TOF) calcd. for $C_{16}H_{15}NO_3$: 269.1052; found: 269.1063; **m.p.**: 162–163 °C.

7.3.4.23. Synthesis of methyl–3–phenylnaphthalene–2–carboxylate

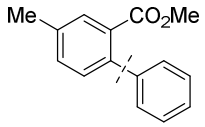


[CAS: 68376-11-4]

The title compound was prepared following the general method A from naphthalene–2–carboxylic acid (70.8 mg, 0.50 mmol) and bromobenzene (119.0 mg, 79.8 µL, 0.75 mmol). The title compound was isolated as colorless oil (115 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39–8.44 (m, 1H), 7.93–7.99 (m, 1H), 7.86–7.92 (m, 1H), 7.84 (s, 1H), 7.52–7.65 (m, 2H), 7.34–7.49 (m, 5H), 3.67–3.76 ppm (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.0 (s), 141.4 (s), 138.8 (s), 134.4 (s), 131.5 (s), 131.0 (s), 129.7 (s), 129.1 (s), 128.6 (s), 128.5 (s), 128.2 (s), 128.0 (s), 127.8 (s), 127.1 (s), 126.7 (s), 52.1 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3055, 3020, 2948, 1717, 1491, 1441, 1276, 1214 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):262 (100) [M$^+$], 231 (49), 202 (14). The analytical data matched those reported in the literature.[265]

7.3.4.24. Synthesis of methyl–4–methylbiphenyl–2–carboxylate



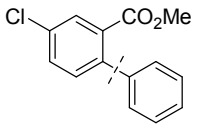
[CAS: 152620-33-2]

The title compound was prepared following the general method A from 3–methylbenzoic acid (68.8 mg, 0.50 mmol) and bromobenzene (119.0 mg, 79.8 µL, 0.75 mmol). The title compound was isolated as colorless oil (96 mg, 85%).

The title compound was prepared following the general method B from 3–methylbenzoic acid (68.8 mg, 0.50 mmol) and chlorobenzene (227 mg, 205 µL, 0.75 mmol). The title compound was isolated as colorless oil (67 mg, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 0.5 Hz, 1H), 7.27–7.44 (m, 7H), 3.64 (s, 3H), 2.44 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.4 (s), 141.3 (s), 139.6 (s), 137.1 (s), 130.7 (s), 130.6 (s), 130.3 (s), 128.4 (s), 128.0 (s), 127.1 (s), 51.9 (s), 21.0 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3027, 2949, 1717, 1482, 1434, 1296, 1243, 1089 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):226 (100) [M$^+$], 195 (67), 165 (13). The analytical data matched those reported in the literature.[346]

7.3.4.25. Synthesis of methyl–4–methylbiphenyl–2–carboxylate

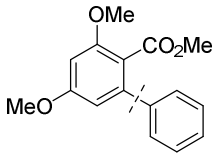


[CAS: 1092775-67-1]

The title compound was prepared following the general method A from 3–chlorobenzoic acid (79.1 mg, 0.50 mmol) and bromobenzene (79.3 mg, 53.2 µL, 0.50 mmol). The title compound was isolated as colorless oil (93.3 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.85 (m, 1H), 7.51 (dd, J = 8.2, 2.4 Hz, 1H), 7.35–7.45 (m, 3H), 7.33 (d, J = 8.3 Hz, 1H), 7.27–7.31 (m, 2H), 3.66 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.8 (s), 140.9 (s), 140.1 (s), 133.2 (s), 132.1 (s), 132.0 (s), 131.2 (s), 129.7 (s), 128.2 (s), 128.1 (s), 127.5 (s), 52.2 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3064, 2950, 1721, 1472, 1396, 1142, 1107, 1009 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 246 (94) [M$^+$], 215 (100), 152 (40), 76 (11). The analytical data matched those reported in the literature.[347]

7.3.4.26. Synthesis of methyl–3,5–dimethoxybiphenyl–2–carboxylate



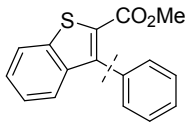
[CAS: 131035-40-0]

The title compound was prepared following the general method A from 2,4–dimethoxybenzoic acid (92.9 mg, 0.50 mmol) and bromobenzene (79.3 mg, 53.2 µL, 0.50 mmol). The title compound was isolated as purple oil (114 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.43 (m, 5H), 6.50 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.58 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.4 (s), 161.3 (s), 158.1 (s), 142.7 (s), 140.5 (s), 128.3 (s), 128.0 (s), 127.6 (s), 116.0 (s), 106.1 (s), 97.5 (s), 56.0 (s), 55.5 (s), 51.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2942, 2841, 1726, 1598, 1456, 1415, 1339, 12612 cm^{-1}; **MS** (EI,

70 eV) *m/z* (%):272 (71) [M^+], 241.2 (100). The analytical data matched those reported in the literature.[348]

7.3.4.27. Synthesis of methyl–3–phenyl–1–benzothiophene–2–carboxylate

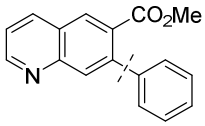


[CAS: 58878-44-7]

The title compound was prepared following the general method A from 1–benzothiophene–2–carboxylic acid (89.1 mg, 0.50 mmol) and bromobenzene (119 mg, 79.8 µL, 0.75 mmol). The title compound was isolated as colorless solid (73 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.92 (m, 1H), 7.34–7.57 (m, 8H), 3.80 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.9 (s), 144.2 (s), 140.4 (s), 134.5 (s), 129.6 (s), 128.1 (s), 128.0 (s), 127.8 (s), 127.2 (s), 125.3 (s), 124.8 (s), 122.5 (s), 120.0 (s), 52.2 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2943, 2845, 1700, 1516, 1440, 1291, 1177, 1155 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):268 (100) [M^+], 237 (72), 208 (7), 165 (15); **m.p.**: 65–66 °C. The analytical data matched those reported in the literature.[349]

7.3.4.28. Synthesis of methyl–7–phenylquinoline–6–carboxylate

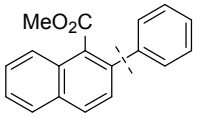


[CAS: 2051922-29-1]

The title compound was prepared following the general method A from 6–quinolinecarboxylic acid (89.3 mg, 0.50 mmol) and bromobenzene (79.3 mg, 53.2 µL, 0.50 mmol). The title compound was isolated as orange oil (53 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.03 (dd, J = 4.3, 1.8 Hz, 1H), 8.36 (s, 1H), 8.25–8.29 (m, 1H), 8.13 (s, 1H), 7.39–7.50 (m, 6H), 3.71 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.6 (s), 152.6 (s), 148.8 (s), 142.5 (s), 140.6 (s), 136.6 (s), 131.1 (s), 130.7 (s), 130.1 (s), 128.4 (s), 128.2 (s), 127.5 (s), 126.5 (s), 121.8 (s), 52.2 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2948, 1720, 1623, 1456, 1430, 1342, 1268, 1200 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):263 (100) [M^+], 232 (86), 204 (14), 176 (9); **HRMS** (EI–TOF) calcd. for $C_{17}H_{13}NO_2$: 263.0936; found: 263.0941.

7.3.4.29. Synthesis of methyl–2–phenylnaphthalene–1–carboxylate

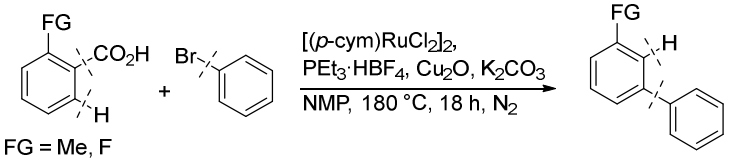


[CAS: 109251-89-0]

The title compound was prepared following the general method B from naphthalene–1–carboxylic acid (87.8 mg, 0.50 mmol) and chlorobenzene (227 mg, 205 µL, 2.00 mmol). The title compound was isolated as colorless solid (120 mg, 92%).

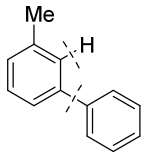
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.3 Hz, 2H), 7.89–7.94 (m, 1H), 7.37–7.63 (m, 8H), 3.71 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.0 (s), 140.9 (s), 138.0 (s), 132.3 (s), 130.0 (s), 129.9 (s), 128.5 (s), 128.4 (s), 128.1 (s), 127.6 (s), 127.5 (s), 127.4 (s), 126.3 (s), 125.0 (s), 52.2 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3051, 2997, 2946, 1716, 1427, 1371, 1341, 1036 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 262 (100) [M$^+$], 231 (85), 202 (15); **m.p.**: 75–76 °C. The analytical data matched those reported in the literature.[265]

7.3.5. Synthesis of the corresponding biaryls via ortho-C–H arylation with in situ protodecarboxylation



Standard procedure: An oven–dried 20 mL vessel was charged with [(*p*–cym)$RuCl_2$]$_2$ (12.2 mg, 0.02 mmol, 4 mol%), triethylphosphonium tetrafluoroborate (8.32 mg, 0.04 mmol, 8 mol%), K_2CO_3 (76 mg, 0.55 mmol, 1.1 eq.), Cu_2O (7.23 mg, 0.05 mmol, 10 mol%) and the *ortho*-substituted benzoic acid (0.50 mmol). After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, NMP (3 mL) and bromobenzene (79.3 mg, 53.2 µL, 0.50 mmol) were added *via* syringe. The resulting mixture was stirred at 180 °C for 18 h. After the reaction was complete, the mixture was allowed to cool to RT, then ethyl acetate (20 mL) was added and the resulting mixture was washed with water, aqueous LiCl solution (20%) and brine (20 mL each). The organic layer was dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient) yielding the corresponding biaryl.

7.3.5.1. Synthesis of 3–methyl–1,1'–biphenyl

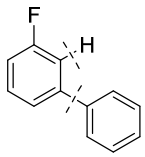


[CAS: 643-93-6]

The title compound was prepared following the general method for the *in situ ortho*–C–H arylation and protodecarboxylation, starting from 2–methylbenzoic acid (68.8 mg, 0.50 mmol). The title compound was isolated as colorless oil (45 mg, 54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.65 (m, 2H), 7.39–7.49 (m, 4H), 7.33–7.39 (m, 2H), 7.19 (d, *J* = 7.3 Hz, 1H), 2.45 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.3 (s), 141.2 (s), 138.3 (s), 128.7 (s), 128.6 (s), 128.0 (s), 127.2 (s), 127.1 (s), 124.2 (s), 21.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3057, 3031, 2916, 1601, 1481, 791, 752, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 168 (100) [M^+], 165 (19), 153 (15), 152 (18). The analytical data matched those reported in the literature.[350]

7.3.5.2. Synthesis of 3–fluoro–1,1'–biphenyl

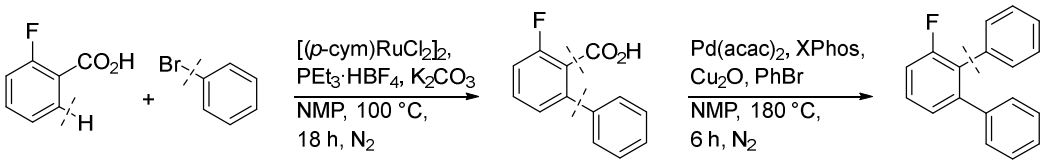


[CAS: 2367-22-8]

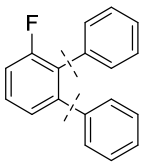
The title compound was prepared following the general method for the *in situ ortho*–C–H arylation and protodecarboxylation, starting from 2–fluorobenzoic acid (70.8 mg, 0.50 mmol). The title compound was isolated as colorless oil (61 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.65 (m, 2H), 7.40–7.49 (m, 5H), 7.32–7.39 (m, 2H), 7.19 (d, *J* = 7.3 Hz, 1H), 2.45 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 113.89 (d, *J* = 1.82 Hz, 1C), 114.12 (s), 122.75 (d, *J* = 2.73 Hz, 1C), 127.08 (s, 2C), 127.82 (s), 128.86 (s, 2C), 130.18 (d, *J* = 8.18 Hz, 1C), 139.92 (d, *J* = 2.73 Hz, 1C), 143.49 (d, *J* = 7.27 Hz, 1C), 164.39 ppm (d, *J* = 246.14 Hz, 1C); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –113.16 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3065, 3035, 1576, 1474, 1422, 1260, 1186, 1158, 1076, 877, 788, 755, 695 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 172 (100) [M^+], 154 (4), 98 (6), 85 (12), 74 (11). The analytical data matched those reported in the literature.[351]

7.3.6. Synthesis of 3'–fluoro–1,1':2',1''–terphenyl via ortho-C–H arylation followed by a one-pot decarboxylative cross-coupling



An oven–dried 20 mL vessel was charged with $[(p\text{–cym})RuCl_2]_2$ (12.2 mg, 0.02 mmol, 4 mol%), triethylphosphonium tetrafluoroborate (8.32 mg, 0.04 mmol, 8 mol%), K_2CO_3 (76 mg, 0.55 mmol, 1.1 eq.), and 2–fluorobenzoic acid (70.8 mg, 0.50 mmol). After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, NMP (3 mL) and bromobenzene (79.3 mg, 53.2 µL, 0.50 mmol) were added *via* syringe. The resulting mixture was stirred at 100 °C for 18 h. After the reaction time, the mixture was allowed to cool to RT, then a stock solution of $Pd(acac)_2$ (7.62 mg, 25.0 µmol, 5 mol%) and XPhos (12.0 mg, 25.0 µmol, 5 mol%) in NMP (1 mL), a slurry of Cu_2O (7.16 mg, 0.05 mmol, 10 mol%) in NMP (0.5 mL) and bromobenzene (64.0 µL, 0.6 mmol, 1.20 eq.) were added *via* syringe. The vessel was heated at 180 °C for 6 h, then allowed to cool to room temperature. Ethyl acetate (20 mL) was added and the resulting mixture was washed with water, aqueous LiCl solution (20%) and brine (20 mL each). The organic layer was dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, cyclohexane isocratic) yielding the title compound as colorless oil (68 mg, 55%).



[CAS: 2036084-12-3]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97–7.35 ppm (m, 13H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ =160.0 (d, J = 246.1 Hz), 143.3 (d, J = 2.7 Hz), 140.2 (d, J = 2.7 Hz), 134.2 (s), 130.9 (d, J = 1.9 Hz), 129.8 (s), 128.6 (d, J = 9.1 Hz), 128.2 (d, J = 15.4 Hz), 127.8 (s), 127.8 (s), 127.1 (s), 126.7 (s), 126.0 (d, J = 3.5 Hz), 114.6 ppm (d, J = 23.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = –115 ppm; **IR** (ATR): $\tilde{\nu}$ = 3053, 3021, 2916, 1601, 1487, 792, 752, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 248 (100) [M^+], 228 (5); **HRMS** (EI–TOF) calcd. for $C_{18}H_{13}F$: 248.1001; found: 248.0994.

7.4. Regioselective C–H Hydroarylation of Internal Alkynes with Arenecarboxylates: Carboxylates as Deciduous Directing Groups

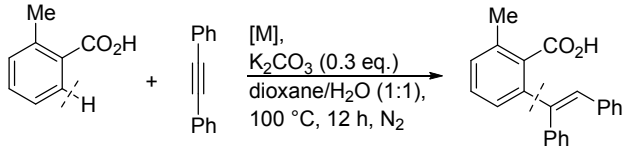
7.4.1. General Methods

Chemicals and solvents were either purchased (puriss p.A.) from commercial supplier or purified by standard techniques.[343] All reactions, if not stated otherwise, were performed in oven-dried glassware under a nitrogen atmosphere containing a Teflon-coated stirrer bar and dry septum. All reactions were monitored by GC using tetradecane as an internal standard. Response factors of the products with regard to *n*-tetradecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP–5 capillary column (Phenyl methyl siloxane, 30 m × 320 × 0.25, 100/2.3-30-300/3, 2 min at 60 °C, heating rate 30 °C/min, 3 or 10 min at 300 °C). Column chromatography was performed using a Combi Flash Companion-Chromatography-System (*Isco-Systems*) and *Reveleris* packed columns (12 g). NMR spectra were recorded on *Bruker Avance 400* at ambient temperature using $CDCl_3$ as solvent, with proton, carbon, and fluorine resonances at 400, 101, and 376 MHz respectively.

7.4.2. Catalyst development

7.4.2.1. Optimization of the non-decarboxylative hydroarylation

Table 10: Catalyst screening for the hydroarylation with diphenylacetylene.



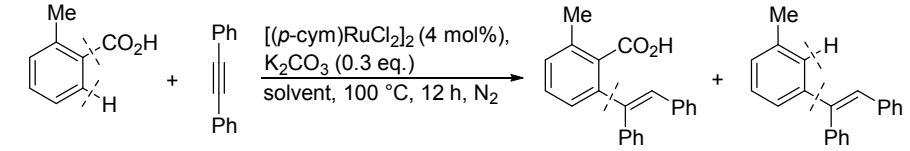
7.4.2.1.-1 **7.4.2.1.-2** **7.4.2.1.-3**

#	[M] /4 mol%	Yield/%[a]
1	$[(COD)RhCl]_2$	-
2	Rh_2OAc_4	-
3	$RhCl_3$	-
4	$[RhCp^*Cl_2]_2$	-
5	$[IrCp^*Cl_2]_2$	-
6	$[Ir(COD)]_2$	23

7	$Ru(CO)Cl(PPh_3)_3H$	-
8	$RuCl_2(PPh_3)_3$	-
9	$RuCl_3$	-
10	$[(p\text{–cym})RuCl_2]_2$	96

Reaction conditions: ***7.4.2.1.-1*** *(0.5 mmol),* ***7.4.2.1.-2*** *(0.5 mmol), [M]-catalyst (4 mol%), K_2CO_3 (0.3 eq.) and dioxane/H_2O = 10:1 (1.1 mL), 100 °C, 12 h. [a] Yields of corresponding methyl esters determined by GC after esterification with K_2CO_3 (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard.*

Table 11: Solvent screening for the hydroarylation with diphenylacetylene.

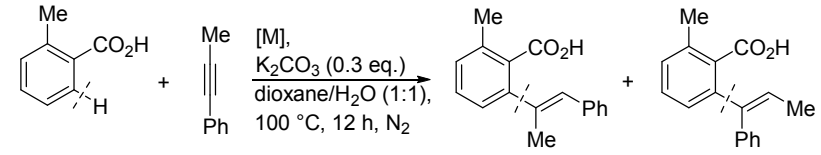


7.4.2.1.-1 **7.4.2.1.-2** **7.4.2.1.-3** **7.4.2.1.-4**

#	**solvent (10/1) /1.1 mL**	**Yield/%[a]**	
		7.4.2.1.-3	**7.4.2.1.-4**
1	dioxane/H_2O	96	-
2	NMP/H_2O	32	34
3	DMSO/H_2O	-	-
4	DMF/H_2O	-	-
5	MeCN/H_2O	8	-
6	toluene/H_2O	64	29
7	^{i}PrOH/H_2O	100	-
8	^{t}AmOH/H_2O	100	-
9	quin/H_2O	2	8
10	H_2O	25	9
11	toluene	11	20
12	^{i}PrOH	64	-
13	^{t}AmOH	88	12

Reaction conditions: ***7.4.2.1.-1*** *(0.5 mmol),* ***7.4.2.1.-2*** *(0.5 mmol), $[(p\text{–cym})RuCl_2]_2$ (4 mol%), K_2CO_3 (0.3 eq.) and solvent (1.1 mL), 100 °C, 12 h. [a] Yields of corresponding methyl esters determined by GC after esterification with K_2CO_3 (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard.*

Table 12: Catalyst screening for the hydroarylation with 1−phenyl−1−propyne.

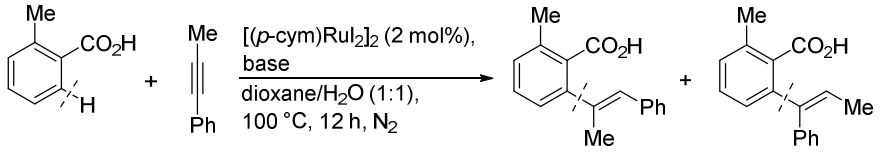


7.4.2.1.-1 **7.4.2.1.-5** **7.4.2.1.-6** **7.4.2.1.-7**

#	**[M] /4 mol%**	**Yield/%[a]**	
		7.4.2.1.-6	**7.4.2.1.-7**
1	$[(COD)RhCl]_2$	-	-
2	Rh_2OAc_4	-	-
3	$RhCl_3$	-	-
4	$[RhCp^*Cl_2]_2$	-	-
5	$[IrCp^*Cl_2]_2$	-	-
6	$[Ir(COD)]_2$	28	4
7	$Ru(CO)Cl(PPh_3)_3H$	-	-
8	$RuCl_2(PPh_3)_3$	-	-
9	$RuCl_3$	6	-
10	$Ru(acac)_3$	11	6
11	$(COD)Ru(2-methylallyl)_2$	26	10
12	$(NBD)RuCl_2$	37	10
13	$[(C_6H_6)RuCl_2]_2$	43	17
14	$[(p-cym)RuCl_2]_2$	43	5
15	$[(p-cym)RuI_2]_2$	52	10
16[b]	"	60	6

Reaction conditions: ***7.4.2.1.-1*** *(0.5 mmol),* ***7.4.2.1.-5*** *(0.5 mmol), [M]-catalyst (4 mol%), K_2CO_3 (0.3 eq.) and dioxane/H_2O = 10:1 (1.1 mL), 100 °C, 12 h. [a] Yields of corresponding methyl esters determined by GC after esterification with K_2CO_3 (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard. [b] [M]-catalyst (2 mol%).*

Table 13: Base screening for the hydroarylation with 1−phenyl−1−propyne.

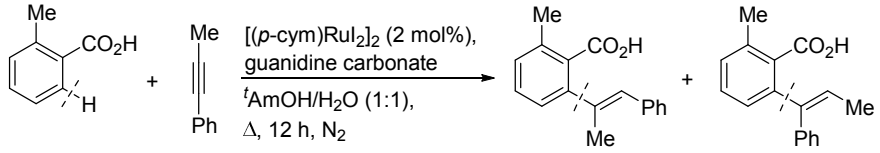


7.4.2.1.-1 **7.4.2.1.-5** **7.4.2.1.-6** **7.4.2.1.-7**

#	base /eq.	Yield/%[a]	
		7.4.2.1.-6	**7.4.2.1.-7**
1	K_2CO_3 /0.3	60	6
2	Li_2CO_3 /0.3	46	8
3	Na_2CO_3 /0.3	50	7
4	Cs_2CO_3 /0.3	57	5
5	guanidine carbonate /0.3	61	6
6	$(NH_4)_2CO_3$ /0.3	-	-
7	TBAOAc /0.3	51	6
8	NH_4OAc /0.3	-	-
9	KOAc /0.3	47	19
10	K_3PO_4 /0.3	54	15
11	KOPiv /0.3	52	6
12	KOTf /0.3	-	-
13	KOH /0.3	54	15
14	guanidine carbonate /0.5	68	7
15	guanidine carbonate /1.0	-	-
16[b]	guanidine carbonate /0.5	74	5

Reaction conditions: ***7.4.2.1.-1*** *(0.5 mmol),* ***7.4.2.1.-5*** *(0.5 mmol), [(p–cym)RuI_2]$_2$ (2 mol%), base (0.3 eq.) and dioxane/H_2O = 10:1 (1.1 mL), 100 °C, 12 h. [a] Yields of corresponding methyl esters determined by GC after esterification with K_2CO_3 (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard. [b] ^{t}AmOH/H_2O = 10:1 (1.1 mL) as the solvent.*

Table 14: Screening of the amount of base, temperature and ratio of the reactants.



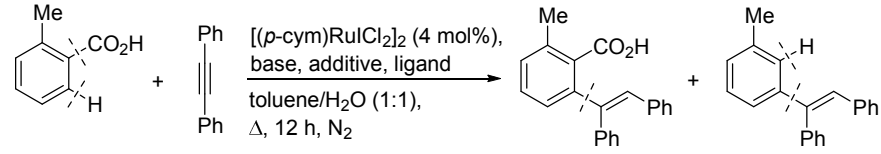
7.4.2.1.-1 **7.4.2.1.-5** **7.4.2.1.-6** **7.4.2.1.-7**

#	eq. guanidine carbonate	T/°C	Yield/%[a]	
			7.4.2.1.-6	7.4.2.1.-7
1	0.1	100	48	9
2	0.5	"	74	5
3	0.7	"	-	-
4	0.1	90	47	4
5	0.5	"	56	3
6	0.7	"	-	-
7	0.5	110	70	13
8[b]	"	100	73	6
9[c]	"	"	90(93)	5

Reaction conditions: ***7.4.2.1.-1*** *(0.5 mmol),* ***7.4.2.1.-5*** *(0.5 mmol), [(p–cym)RuI$_2$]$_2$ (2 mol%), guanidine carbonate as the base and ^{t}AmOH/H$_2$O = 10:1 (1.1 mL), 12 h. [a] Yields of corresponding methyl esters determined by GC after esterification with K$_2$CO$_3$ (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard. [b]* ***7.4.2.1.-5*** *(0.6 mmol). [c]* ***7.4.2.1.-5*** *(0.75 mmol).*

7.4.2.2. Optimization of the decarboxylative hydroarylation

Table 15: Evaluation of the catalyst system for the decarboxylative hydroarylation.

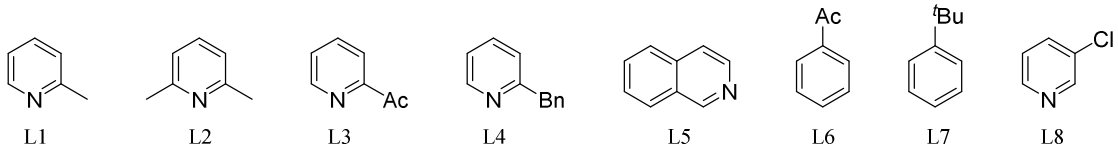


7.4.2.2.-1 **7.4.2.2.-2** **7.4.2.2.-3** **7.4.2.2.-4**

#	base /eq.	ligand/0.2 eq.	additive /eq.	T/°C	Yield/%[a]	
					7.4.2.2.-3	7.4.2.2.-4
1	K_2CO_3 /0.3	-	-	100	64	29
2	"	L1	-	"	-	22
3	guanidine carbonate /0.3	"	-	"	trace	29
4	guanidine carbonate /0.2	"	-	"	"	34

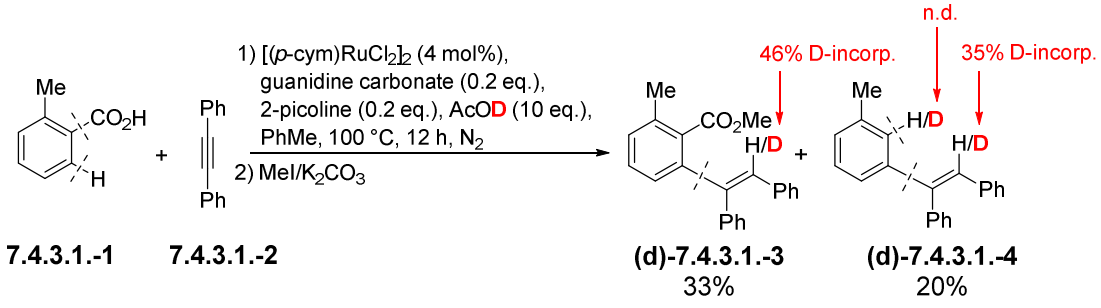
5	"	L2	-	"	"	31
6	"	L3	-	"	"	26
7	"	L4	-	"	"	32
8	"	L5	-	"	"	28
9	"	L6	-	"	"	28
10	"	L7	-	"	5	32
11	"	L8	-	"	trace	32
12	"	L1	HOAc/1 eq.	"	15	37
13[b]	"	"	"	"	21	53
14[b]	"	-	"	"	28	52
15[b]	"	-	HOAc/2 eq.	"	11	50
16[b]	"	-	PivOH/1 eq.	"	18	50
17[b]	"	-	TFA/1 eq.	"	-	-
18[b]	"	L1	HOAc/1 eq.	120	<5	80
19[b]	"	-	"	"	13	78
20[c]	"	L1	"	"	<5	87(73)

Reaction conditions: ***7.4.2.2.-1*** *(0.5 mmol),* ***7.4.2.2.-2*** *(0.5 mmol), [(p–cym)$RuCl_2]_2$ (4 mol%), base, ligand and toluene/H_2O = 10:1 (1.1 mL), 12 h. [a] Yields of corresponding methyl esters determined by GC after esterification with K_2CO_3 (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard. [b] Toluene (1 mL) was used as the solvent. [c] Toluene (2 mL) was used as the solvent.*



7.4.3. Mechanistic control experiments for the decarboxylative hydroarylation

7.4.3.1. H/D-scrambling experiments



Scheme 47: H/D-scrambling experiment in the presence of deuterated acetic acid.

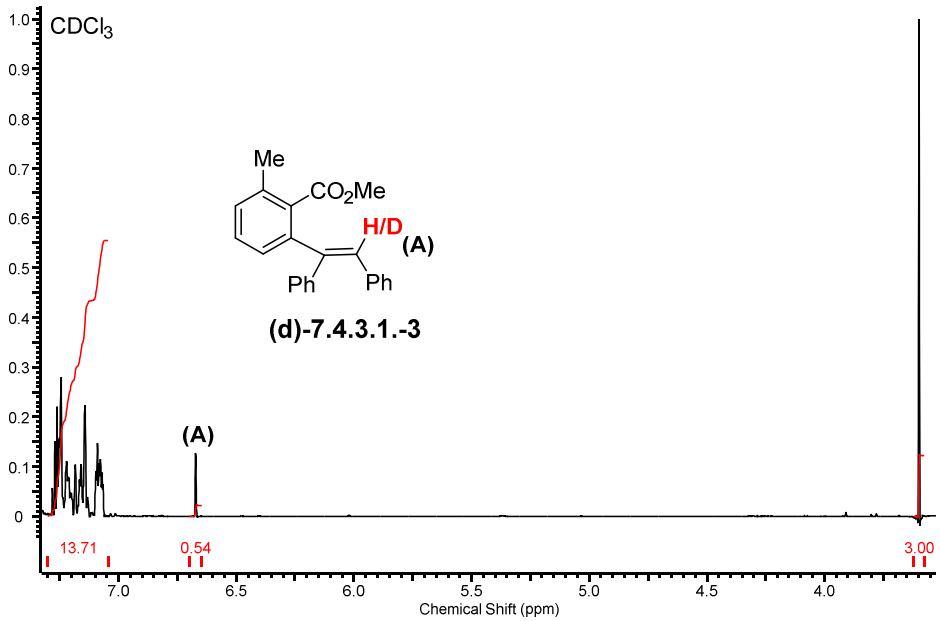


Figure 1: ^{1}H–NMR profile of **(d)–7.4.3.1.-3** after the H/D-scrambling experiment in the presence deuterated acetic acid.

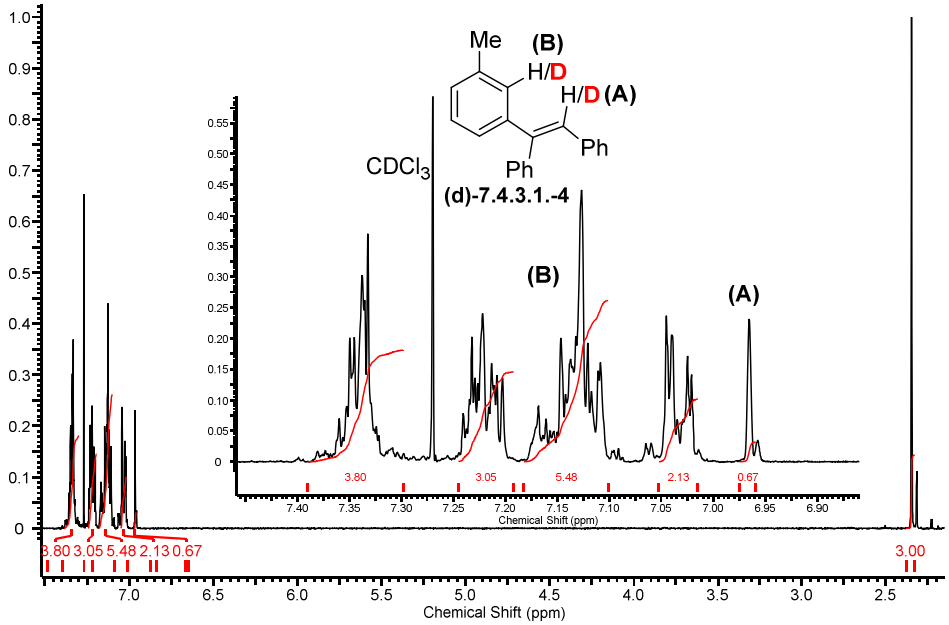
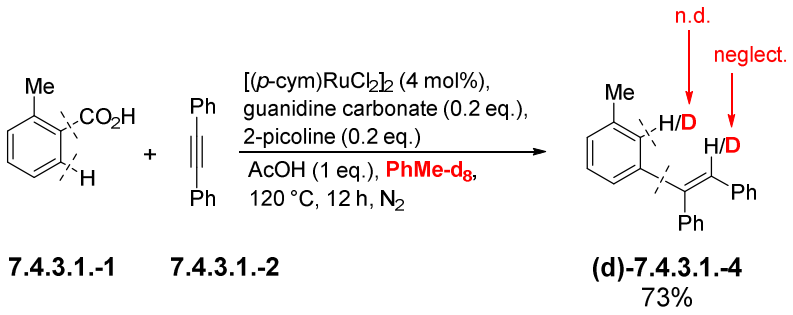


Figure 2: ^{1}H–NMR profile of **(d)–7.4.3.1.-4** after the H/D-scrambling experiment in the presence of deuterated acetic acid.



7.4.3.1.-1 **7.4.3.1.-2** **(d)-7.4.3.1.-4**
73%

Scheme 48: H/D-scrambling experiment in the presence of deuterated toluene.

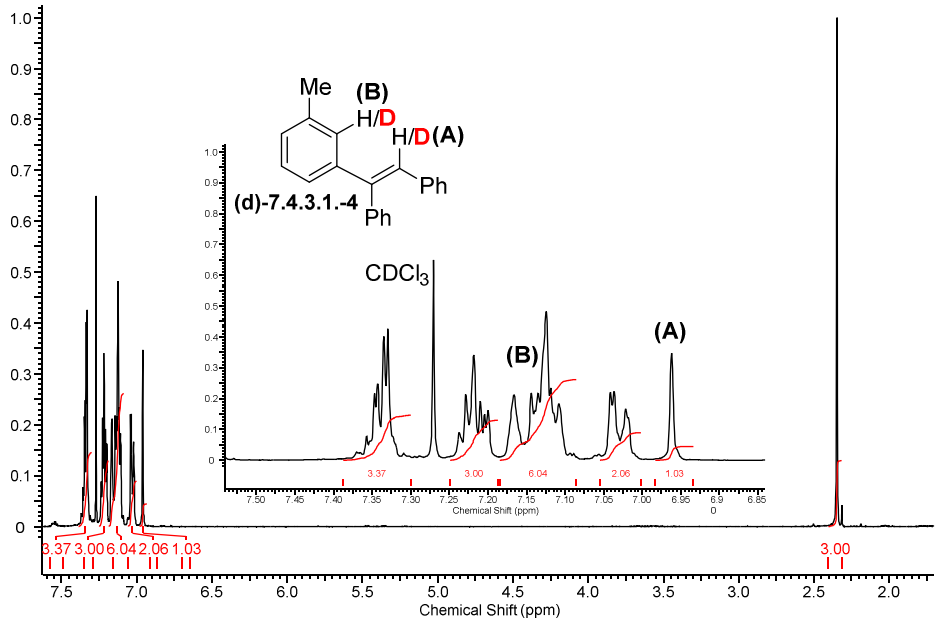
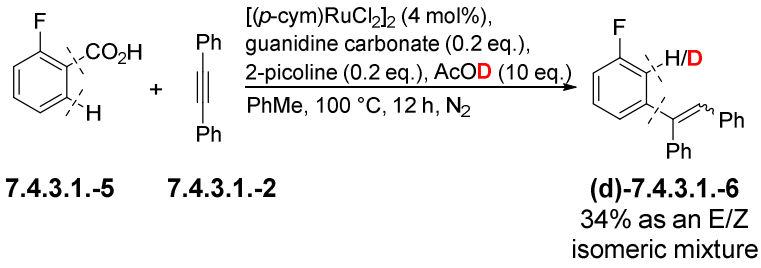


Figure 3: ^{1}H–NMR profile of **(d)–7.4.3.1.-4** after the H/D-scrambling experiment in the presence of deuterated toluene.



7.4.3.1.-5 **7.4.3.1.-2** **(d)-7.4.3.1.-6**
34% as an E/Z
isomeric mixture

Scheme 49: H/D-scrambling experiment of *o*–fluoro benzoic acid in the presence of deuterated acetic acid.

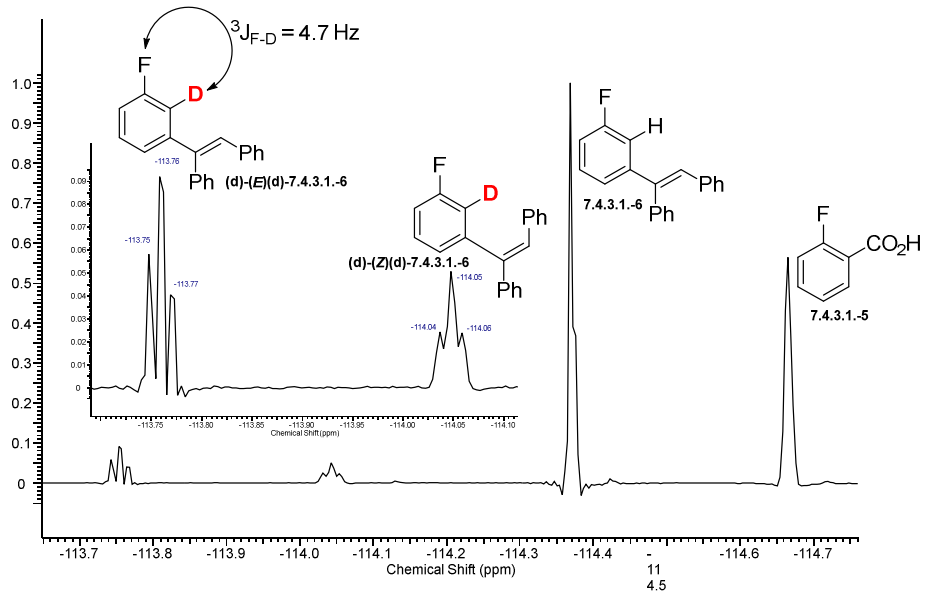
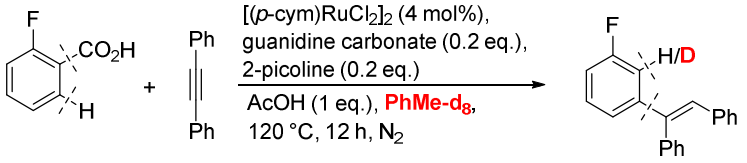


Figure 4: ^{19}F–NMR (H–decoupled) profile of **(d)–7.4.3.1.-6** after the H/D-scrambling experiment in the presence of deuterated acetic acid. E/Z isomeric mixture is caused by the excess of AcO**D**.



7.4.3.1.-5 **7.4.3.1.-2** **(d)-7.4.3.1.-6**
46%

Scheme 50: H/D-scrambling experiment of *o*-fluoro benzoic acid in the presence of deuterated toluene.

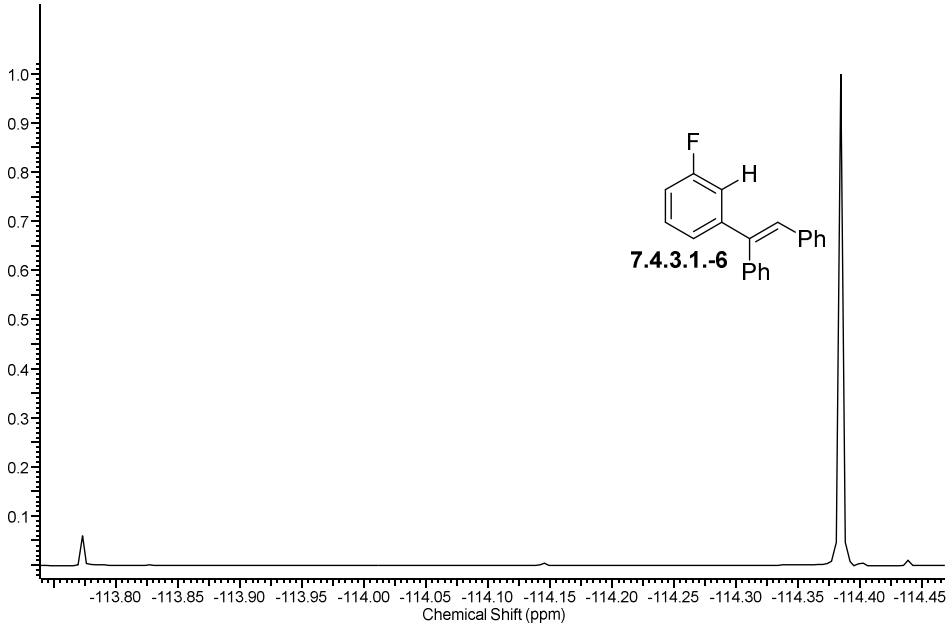
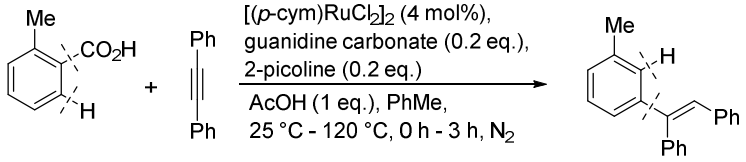


Figure 5: ^{19}F–NMR (H–decoupled) profile of **(d)–7.4.3.1.-6** after the H/D-scrambling experiment in the presence of deuterated toluene. No signal for the F-D$_{ortho}$ coupling was detected.

7.4.3.2. ESI-MS measurements



Scheme 51: Standard decarboxylative hydroarylation reaction set-up for *in situ* ESI-MS experiments.

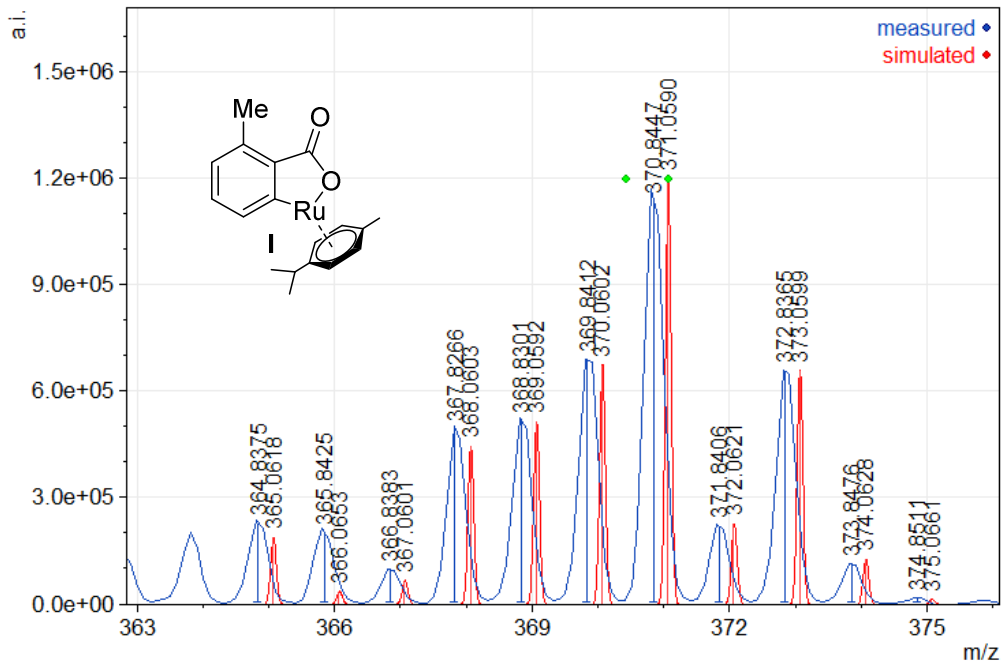


Figure 6: ESI-MS measurement of the reaction mixture (t = 0, room temperature).

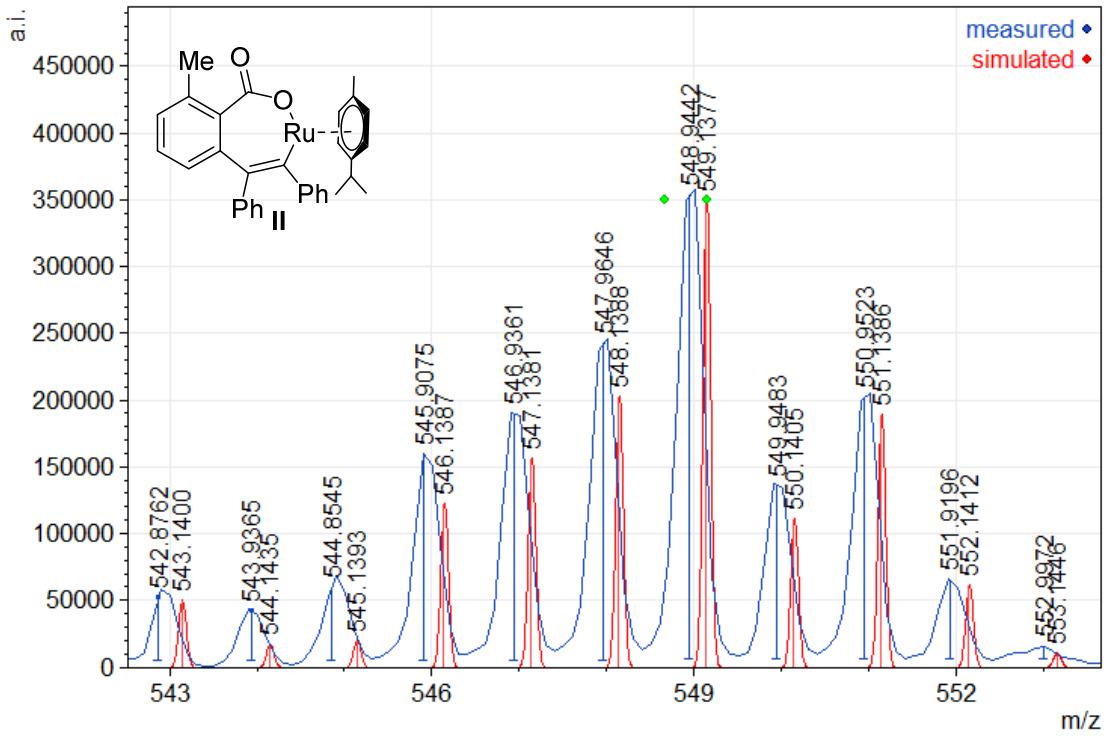


Figure 7: ESI-MS measurement of the reaction mixture (t = 0, 120 °C).

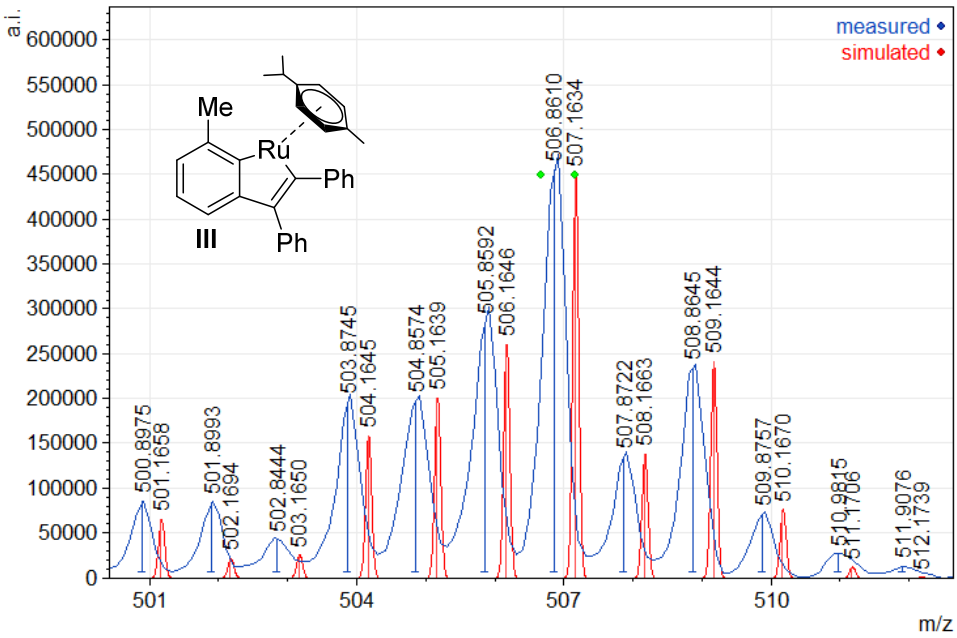
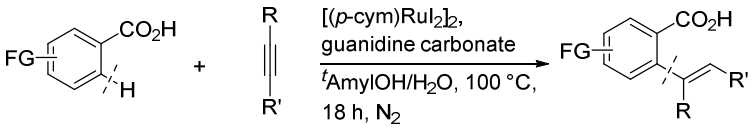


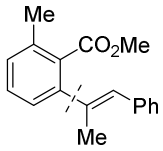
Figure 8: ESI-MS measurement of the reaction mixture (t = 3 h, 120 °C).

7.4.4. Synthesis of the corresponding vinylarene carboxylic acids via non-decarboxylative ortho-C–H hydroarylation



Standard procedure: An oven–dried 20 mL vessel was charged with $[(p\text{–cym})RuI_2]_2$ (9.8 mg, 0.01 mmol, 2 mol%), guanidine carbonate (46 mg, 0.25 mmol, 0.5 eq.) and the benzoic acid (0.50 mmol). After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, a degassed mixture of ^{t}AmylOH (1 mL) and H_2O (0.1 mL), and the alkyne (0.75 mmol, 1.5 eq.) was added *via* syringe. The resulting mixture was stirred at 100 °C for 18 h. After the reaction was complete, the mixture was allowed to cool to room temperature. MeCN (2 mL), K_2CO_3 (1 mmol) and MeI (2.5 mmol) were added and the mixture was stirred at 50 °C for another 2 h. The mixture was allowed to cool to room temperature, brine (20 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient) yielding the hydroarylation products in the form of its methyl ester.

7.4.4.1. Synthesis of (E)–methyl–2–methyl–6–(1–phenylprop–1–en–2–yl)–benzoate

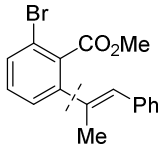


[CAS: 1642792-71-9]

The title compound was prepared starting from 2–methylbenzoic acid (68.8 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as yellow liquid (124 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 5H), 7.25–7.22 (m, 1H), 7.17–7.12 (m, 2H), 6.40 (d, J = 0.8 Hz, 1H), 3.80 (s, 3H), 2.37 (s, 3H), 2.20 ppm (d, J = 1.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.3 (s), 143.9 (s), 138.1 (s), 137.8 (s), 135.4 (s), 132.5 (s), 129.2 (s), 129.2 (s), 128.8 (s), 128.7 (s), 128.2 (s), 126.6 (s), 125.3 (s), 52.0 (s), 19.8 (s), 19.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2922, 1727, 1438, 1265, 1098, 1069, 787, 730, 697 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 266 (100) [M^+], 234 (85), 191 (15); **HRMS** (EI–TOF) calcd. for $C_{18}H_{18}O_2$: 266.1307; found: 266.1322.

7.4.4.2. Synthesis of (E)–methyl–2–bromo–6–(1–phenylprop–1–en–2–yl)–benzoate

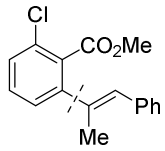


[CAS: 1914996-24-9]

The title compound was prepared starting from 2–bromobenzoic acid (104 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as colorless solid (111 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (dd, J = 7.2 Hz, 1.2 Hz, 1H), 7.38 (t, J = 7.2 Hz, 2H), 7.31–7.27 (m, 5H), 6.48 (s, 1H), 3.86 (s, 3H), 2.20 ppm (d, J = 1.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.3 (s), 145.6 (s), 137.3 (s), 136.5 (s), 134.6 (s), 131.1 (s), 130.5 (s), 130.4 (s), 128.9 (s), 128.3 (s), 126.91 (s), 126.87 (s), 119.4 (s), 52.5 (s), 19.6 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2950, 1729, 1436, 1265, 1117, 1061, 866, 783, 751 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 331 (82) [M^+], 329 (78) [M^+], 300 (65), 299 (100), 298 (65), 297 (93), 191 (64); **HRMS** (EI–TOF) calcd. for $C_{17}H_{15}BrO_2$: 332.0235/330.0255; found: 332.0237/330.0257; **m.p.**: 74–76 °C.

7.4.4.3. Synthesis of (E)–methyl–2–chloro–6–(1–phenylprop–1–en–2–yl)–benzoate

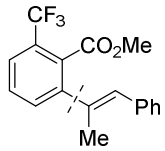


[CAS: 1914996-27-2]

The title compound was prepared starting from 2–chlorobenzoic acid (79.9 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as yellow solid (95 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 4H), 7.24–7.23 (m, 1H), 7.22–7.20 (m, 1H), 7.19–7.17 (m, 2H), 6.40 (s, 1H), 3.78 (s, 3H), 2.12 ppm (d, J = 1.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.7 (s), 145.5 (s), 137.3 (s), 136.5 (s), 132.5 (s), 130.9 (s), 130.4 (s), 130.2 (s), 128.9 (s), 128.3 (s), 127.9 (s), 126.9 (s), 126.3 (s), 52.5 (s), 19.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2952, 1731, 1438, 1263, 1188, 1117, 1063, 954, 787, 754, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 286 (100) [M^+], 256 (36), 255 (62), 254 (66), 227 (32), 219 (40), 191 (40); **HRMS** (EI–TOF) calcd. for $C_{17}H_{15}ClO_2$: 286.0761; found: 286.0760; **m.p.**: 73–75 °C.

7.4.4.4. Synthesis of (E)–methyl–2–(1–phenylprop–1–en–2–yl)–6–(trifluoromethyl)benzoate



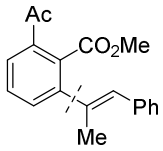
[CAS: 1914996-28-3]

The title compound was prepared starting from 2–(trifluoromethyl)benzoic acid (97 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as yellow liquid (120 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, J = 8.8 Hz, 4.0 Hz, 1H), 7.57–7.54 (m, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.32–7.26 (m, 4H), 6.46 (s, 1H), 3.85 (s, 3H), 2.22 ppm (d, J = 1.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.9 (s), 145.0 (s), 137.2 (s), 136.2 (s), 131.7 (d, J = 1 Hz, 1C), 130.9 (d, J = 2 Hz, 1C), 130.8 (s), 129.4 (s), 128.8 (s), 128.3 (s), 127.5 (s), 127.0 (s), 124.6 (q, J = 4 Hz, 1C), 123.44 (d, J = 278 Hz, 1C), 52.7 (s), 19.8 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2952, 1738, 1321, 1168, 1128, 1066, 806, 733, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 321 (23)

[M^+], 320 (100), 289 (8), 288 (12), 269 (12), 268 (11), 267 (9); **HRMS** (EI–TOF) calcd. for $C_{18}H_{15}F_3O_2$: 320.1024; found: 320.1017.

7.4.4.5. Synthesis of (E)–methyl–2–acetyl–6–(1–phenylprop–1–en–2–yl)–benzoate

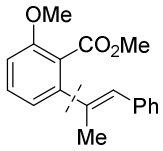


[CAS: 1914996-32-9]

The title compound was prepared starting from 2–acetylbenzoic acid (82.9 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as colorless solid (77 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 77.76 (dd, J = 6.0 Hz, 2.8 Hz, 1H), 7.54–7.49 (m, 2H), 7.40–7.36 (m, 2H), 7.32–7.31 (m, 2H), 7.29–7.24 (m, 1H), 6.43 (s, 1H), 3.85 (s, 3H), 2.63 (s, 3H), 2.20 ppm (d, J = 1.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 198.5 (s), 169.8 (s), 144.8 (s), 137.4 (s), 136.21 (s), 136.20 (s), 132.4 (s), 132.3 (s), 130.5 (s), 129.1 (s), 128.9 (s), 128.2 (s), 127.5 (s), 126.8 (s), 52.4 (s), 27.6 (s), 19.8 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2953, 1728, 1683, 1443, 1261, 1122, 1072, 800, 761, 702 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 294 (8) [M^+], 263 (30), 262 (100), 247 (39), 219 (46), 191 (20), 44 (12), 43 (24); **HRMS** (EI–TOF) calcd. for $C_{19}H_{18}O_3$: 294.1256; found: 294.1275; **m.p.**: 95–96 °C.

7.4.4.6. Synthesis of (E)–methyl–2–methoxy–6–(1–phenylprop–1–en–2–yl)–benzoate



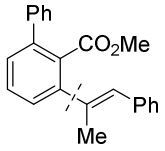
[CAS: 1914996-34-1]

The title compound was prepared starting from 2–methoxybenzoic acid (76.8 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as yellow liquid (101 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.27 (m, 2H), 7.26 (t, J = 2.0 Hz, 1H), 7.23–7.21 (m, 2H), 7.18–7.14 (m,1H), 6.86 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.39 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 2.11 ppm (d, J = 1.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 168.5 (s), 156.4 (s), 145.1 (s), 137.7 (s), 137.1 (s), 130.3 (s), 129.6 (s), 128.9 (s), 128.1 (s),

126.6 (s), 122.4 (s), 120.1 (s), 109.4 (s), 56.0 (s), 52.2 (s), 19.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2954, 1727, 1573, 1428, 1252, 1102, 1050, 867, 795, 699 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 283 (20), 281 (100) [M^+], 267 (20), 251 (56), 250 (39), 223 (35), 221 (19); **HRMS** (EI–TOF) calcd. for $C_{18}H_{18}O_3$: 282.1256; found: 282.1257.

7.4.4.7. Synthesis of (E)–methyl–3–(1–phenylprop–1–en–2–yl)biphenyl–2–carboxylate

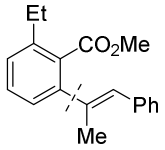


[CAS: 1914996-37-4]

The title compound was prepared starting from biphenyl–2–carboxylic acid (101 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as yellow liquid (155 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (t, *J* = 4.0 Hz, 1H), 7.42–7.41 (m, 4H), 7.38–7.36 (m, 3H), 7.34–7.31 (m, 4H), 7.27–7.23 (m, 1H), 6.46 (s, 1H), 3.56 (s, 3H), 2.27 ppm (d, *J* = 1.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.0 (s), 144.2 (s), 140.6 (s), 140.3 (s), 137.7 (s), 137.7 (s), 132.2 (s), 129.6 (s), 129.2 (s), 128.9 (s), 128.4 (s), 128.3 (s), 128.27 (s), 128.2 (s), 127.5 (s), 127.0 (s), 126.6 (s), 51.9 (s), 19.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2984, 1725, 1436, 1260, 1120, 1068, 869, 759, 702 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 328 (61) [M^+], 297 (24), 296 (28), 281 (24), 207 (62), 44 (100), 40 (46); **HRMS** (EI–TOF) calcd. for $C_{23}H_{20}O_2$: 328.1463; found: 328.1461.

7.4.4.8. Synthesis of (E)–methyl–2–ethyl–6–(1–phenylprop–1–en–2–yl)–benzoate



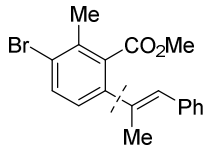
[CAS: 1914996-39-6]

The title compound was prepared starting from 2–ethylbenzoic acid (75.1 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as yellow liquid (127 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 3H), 7.34–7.31 (m, 2H), 7.27–7.2 (m, 1H), 7.21–7.18 (m, 2H), 6.42 (s, 1H), 3.81 (s, 3H), 2.71 (q, *J* = 7.6 Hz, 2H), 2.22 (d, *J* = 1.2 Hz,

3H), 1.26 ppm (t, J = 7.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.4 (s), 143.9 (s), 141.6 (s), 138.1 (s), 137.8 (s), 132.1 (s), 129.32 (s), 129.29 (s), 128.9 (s), 128.2 (s), 127.2 (s), 126.6 (s), 125.3 (s), 52.0 (s), 26.8 (s), 19.8 (s), 15.6 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2968, 1726, 1444, 1246, 1076, 729, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 280 (61) [M^+], 248 (24), 233 (28), 219 (24), 189 (62), 178 (100), 115 (46), 91 (27); **HRMS** (EI–TOF) calcd. for $C_{19}H_{20}O_2$: 280.1463; found: 280.1471.

7.4.4.9. Synthesis of (E)–methyl–3–bromo–2–methyl–6–(1–phenylprop–1–en–2–yl)–benzoate

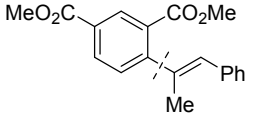


[CAS: 1914996-41-0]

The title compound was prepared starting from 3–bromo–2–methylbenzoic acid (111 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as colorless liquid (158 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 7.2 Hz, 2H), 7.27–7.20 (m, 3H), 7.00 (d, J = 7.2 Hz, 1H), 6.39 (d, J = 8.4 Hz, 1H), 6.33 (s, 1H), 3.78 (s, 3H), 2.39 (s, 3H), 2.15 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.4 (s), 142.9 (s), 137.4 (s), 136.9 (s), 134.7 (s), 134.5 (s), 133.2 (s), 129.8 (s), 128.8 (s), 128.2 (s), 126.8 (s), 126.7 (s), 124.0 (s), 52.2 (s), 20.4 (s), 19.6 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2949, 1728, 1434, 1251, 1153, 1089, 1017, 814, 732, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 346 (100) [M^+], 344 (99) [M^+], 314 (63), 313 (45), 312 (53), 233 (57), 206 (55); **HRMS** (EI–TOF) calcd. for $C_{17}H_{15}BrO_2$: 344.0412; found: 344.0418.

7.4.4.10. Synthesis of (E)–dimethyl–4–(1–phenylprop–1–en–2–yl)–isophthalate

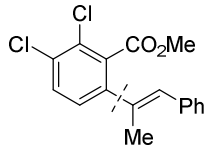


[CAS: 1914996-44-3]

The title compound was prepared starting from *mono*–methyl isophthalate (92.9 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as yellow liquid (116 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 2.0 Hz, 1H), 8.16 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.39–7.38 (m, 4H), 7.30–7.24 (m, 1H), 6.39 (d, *J* = 1.2 Hz, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 2.23 ppm (d, *J* = 1.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 167.7 (s), 166.1 (s), 151.3 (s), 138.5 (s), 137.5 (s), 132.4 (s), 131.3 (s), 130.1 (s), 129.6 (s), 129.0 (s), 128.81 (s), 128.80 (s), 128.2 (s), 126.8 (s), 52.35 (s), 52.32 (s), 19.8 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2952, 1722, 1435, 1306, 1235, 1114, 990, 769. 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 310 (99) [M^+], 279 (49), 278 (100), 251 (82), 219 (82), 207 (29), 191 (35); **HRMS** (EI–TOF) calcd. for $C_{19}H_{18}O_4$: 310.1205; found: 310.1217.

7.4.4.11. Synthesis of (E)–methyl–2,3–dichloro–6–(1–phenylprop–1–en–2–yl)–benzoate

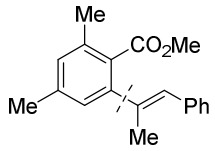


[CAS: 1914996-46-5]

The title compound was prepared starting from 2,3–dichlorobenzoic acid (97.5 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as yellow liquid (77 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.4 Hz, 1H), 7.36–7.233 (m, 2H), 7.27–7.22 (m, 3H), 7.17 (d, *J* = 8.4 Hz, 1H), 6.45 (s, 1H), 3.83 (s, 3H), 2.15 ppm (d, *J* = 1.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 166.9 (s), 143.5 (s), 137.0 (s), 135.5 (s), 134.4 (s), 131.7 (s), 130.9 (s), 130.8 (s), 129.3 (s), 128.8 (s), 128.3 (s), 127.3 (s), 127.1 (s), 52.7 (s), 19.4 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2951, 1735, 1433, 1243, 1149, 1105, 966, 750, 700 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 322 (73) [M^+], 320 (100) [M^+], 290 (45), 289 (62), 288 (55), 261 (72), 253 (49); **HRMS** (EI–TOF) calcd. for $C_{17}H_{14}Cl_2O_2$: 320.0371; found: 320.0362.

7.4.4.12. Synthesis of (E)–methyl–2,4–dimethyl–6–(1–phenylprop–1–en–2–yl)–benzoate

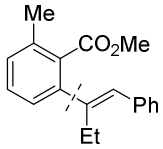


[CAS: 1914996-48-7]

The title compound was prepared starting from 2,4–dimethylbenzoic acid (76.6 mg, 0.5 mmol) and 1–phenyl–1–propyne (94.3 mg, 0.75 mmol). The title compound was isolated as yellow liquid (124 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 4H), 7.21–7.18 (m, 1H), 6.94 (d, J = 10.8 Hz, 2H), 6.38 (s, 1H), 3.75 (s, 3H), 2.33 (s, 3H), 2.30 (s, 3H), 2.18 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.3 (s), 144.1 (s), 139.1 (s), 138.2 (s), 137.8 (s), 135.5 (s), 129.6 (s), 128.8 (s), 128.77 (s), 128.1 (s), 126.4 (s), 125.9 (s), 51.8 (s), 21.1 (s), 19.7 (s), 19.6 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2949, 1724, 1603, 1439, 1264, 1080, 856, 750, 699 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 281 (27), 280 (100) [M^+], 279. (7), 249 (11), 248 (8), 233 (10), 189 (9); **HRMS** (EI–TOF) calcd. for $C_{19}H_{20}O_2$: 280.1463; found: 280.1456.

7.4.4.13. Synthesis of (E)–methyl–2–methyl–6–(1–phenylbut–1–en–2–yl)–benzoate



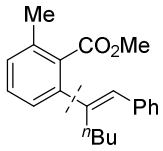
[CAS: 1914996-51-2]

The title compound was prepared starting from 2–methylbenzoic acid (68.8 mg, 0.5 mmol) and 1–butinylbenzene (99.6 mg, 0.75 mmol). The title compound was isolated as colorless liquid (98.3 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, J = 7.6 Hz, 2H), 7.27 (t, J = 7.6 Hz, 3H), 7.24–7.20 (m, 1H), 7.14 (t, J = 7.2 Hz, 2H), 6.39 (s, 1H), 3.77 (s, 3H), 2.62 (q, J = 7.2 Hz, 2H), 2.36 (s, 3H), 1.02 ppm (t, J = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.3 (s), 143.9 (s), 141.9 (s), 137.8 (s), 135.3 (s), 133.4 (s), 129.1 (s), 128.9 (s), 128.7 (s), 128. 6 (s), 128.2 (s), 126.6 (s), 125.4 (s), 51.8 (s), 25.4 (s), 19.8 (s), 12.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2970, 1726, 1437, 1263, 1105, 1070, 785, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 280 (70) [M^+], 249 (30), 248

(100), 233 (51), 205 (26), 189 (93), 157 (29); **HRMS** (EI–TOF) calcd. for $C_{19}H_{20}O_2$: 280.1463; found: 280.1461.

7.4.4.14. Synthesis of (E)–methyl–2–methyl–6–(1–phenylhex–1–en–2–yl)–benzoate

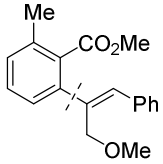


[CAS: 1914996-53-4]

The title compound was prepared starting from 2–methylbenzoic acid (68.8 mg, 0.5 mmol) and 1–phenyl–1–hexin (119 mg, 0.75 mmol). The title compound was isolated as yellow liquid (81 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (t, J = 7.6 Hz, 2H), 7.31–7.28 (m, 2H), 7.26–7.22 (m, 2H), 7.18–7.14 (m, 2H), 6.42 (s, 1H), 3.80 (s, 3H), 2.59 (t, J = 8.0 Hz, 2H), 2.38 (s, 3H), 1.44–1.38 (m, 2H), 1.33–1.27 (m, 2H), 0.85 ppm (t, J = 8.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.3 (s), 142.8 (s), 142.2 (s), 137.8 (s), 135.3 (s), 133.3 (s), 129.4 (s), 128.9 (s), 128.7 (s), 128.6 (s), 128.2 (s), 126.6 (s), 125.4 (s), 51.8 (s), 32.1 (s), 30.5 (s), 22.9 (s), 19.8 (s), 13.8 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2955, 1728, 1437, 1264, 1109, 1070, 785, 735, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 308 (28) [M^+], 234 (34), 233 (8), 219 (16), 218 (21), 217 (100), 185 (48); **HRMS** (EI–TOF) calcd. for $C_{21}H_{24}O_2$: 308.1776; found: 308.1779.

7.4.4.15. Synthesis of (Z)–methyl–2–(3–methoxy–1–phenylprop–1–en–2–yl)–6–methylbenzoate



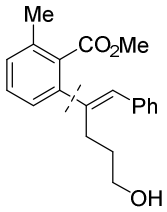
[CAS: 1914996-55-6]

The title compound was prepared starting from 2–methylbenzoic acid (68.8 mg, 0.5 mmol) and (3–methoxyprop–1–ynyl)–benzene (110 mg, 0.75 mmol). The title compound was isolated as yellow liquid (123 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.35 (m, 4H), 7.32–7.29 (m, 3H), 7.20–7.17 (m, 1H), 6.71 (s, 1H), 4.29 (s, 2H), 3.83 (s, 3H), 3.34 (s, 3H), 2.40 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.3 (s), 140.8 (s), 138.3 (s), 136.6 (s), 135.5 (s), 133.9 (s), 132.8 (s), 129.14 (s),

129.13 (s), 128.9 (s), 128.3 (s), 127.4 (s), 126.2 (s), 71.3 (s), 58.4 (s), 52.0 (s), 19.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2934, 2225, 1724, 1443, 1266, 1070, 757, 700 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 264 (100) [M^+–OMe], 249 (88), 237 (68), 234 (68), 221 (66), 177 (55), 162 (90); **HRMS** (EI–TOF) calcd. for $C_{19}H_{20}O_3$: 296.1412; found: 296.1416.

7.4.4.16. Synthesis of (E)–methyl–2–(5–hydroxy–1–phenylpent–1–en–2–yl)–6—benzoate

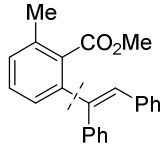


[CAS: 1914996-58-9]

The title compound was prepared starting from 2–methylbenzoic acid (68.8 mg, 0.5 mmol) and 5–phenylpent–4–yn–1–ol (120 mg, 0.75 mmol). The title compound was isolated as colorless liquid (103 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.6 Hz, 2H), 7.29–6.20 (m, 4H), 7.14 (t, *J* = 7.6 Hz, 2H), 6.44 (s, 1H), 3.79 (s, 3H), 3.53 (t, *J* = 5.6 Hz, 2H), 2.66 (t, *J* = 8.0 Hz, 2H), 2.35 (s, 3H), 1.68–1.61 ppm (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.4 (s), 141.8 (s), 141.7 (s), 137.6 (s), 135.4 (s), 133.3 (s), 130.1 (s), 129.0 (s), 128.9 (s), 128.6 (s), 128.3 (s), 126.7 (s), 125.3 (s), 62.6 (s), 51.9 (s), 31.3 (s), 28.4 (s), 19.8 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3391, 2949, 1725, 1439, 1265, 1069, 920, 787, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 311 (100) [M^+], 278 (88), 234 (68), 189 (68), 115 (66), 91 (55); **HRMS** (EI–TOF) calcd. for $C_{20}H_{22}O_3$: 310.1569; found: 310.1570.

7.4.4.17. Synthesis of (E)–methyl–2–(1,2–diphenylvinyl)–6–benzoate

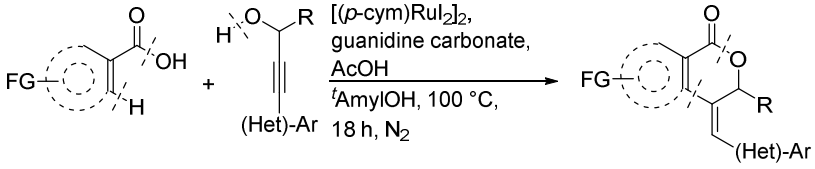


[CAS: 1914996-60-3]

The title compound was prepared starting from 2–methylbenzoic acid (68.8 mg, 0.5 mmol) and diphenylacetylene (90 mg, 0.5 mmol). The title compound was isolated as colorless solid (162 mg, 99%).

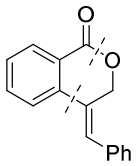
^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.35–7.24 (m, 5H), 7.17–7.13 (m, 3H), 7.10–7.09 (m, 2H), 7.06–7.01 (m, 3H), 6.58 (s, 1H), 3.52 (s, 3H), 2.27 ppm (s, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 169.2 (s), 142.0 (s), 141.4 (s), 139.5 (s), 136.6 (s), 134.8 (s), 133.2 (s), 129.8 (s), 129.7 (s), 129.30 (s), 129.28 (s), 129.0 (s), 128.4 (s), 128.1 (s), 127.6 (s), 127.1 (s), 127.1 (s) 51.8 (s), 19.3 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2950, 1720, 1443, 1263, 1109, 1066, 918, 769, 696 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 328 (82) [M$^+$], 295 (78), 269 (65), 252 (100), 165 (65), 126 (93), 105 (64), 77 (23); **HRMS** (EI–TOF) calcd. for $C_{23}H_{20}O_2$: 328.1463; found: 328.1450; **m.p.**: 104–105 °C.

7.4.5. Synthesis of the corresponding γ–alkylidene–δ–lactones via ortho–C–H hydroarylation followed by in situ esterification with propargylic alcohols



Standard procedure: An oven–dried 20 mL vessel was charged with [(*p*–cym)RuI_2]$_2$ (9.8 mg, 0.01 mmol, 2 mol%), guanidine carbonate (46 mg, 0.25 mmol, 0.5 eq.) and the acid (0.50 mmol). After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, degassed ^{t}AmylOH (1 mL), AcOH (28.9 µL, 0.5 mmol, 1 eq.) and the propargylic alcohol (0.75 mmol, 1.5 eq.) was added *via* syringe. The resulting mixture was stirred at 100 °C for 18 h. After the reaction was complete, the mixture was allowed to cool to room temperature. Brine (20 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient) yielding the corresponding isochromanones.

7.4.5.1. Synthesis of (Z)–4–benzylideneisochroman–1–one

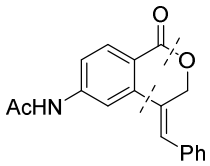


[CAS: 90992-13-5]

The title compound was prepared starting from benzoic acid (123 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as yellow solid (212 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (dd, J = 7.6 Hz, 0.4 Hz, 1H), 7.67–7.60 (m, 2H), 7.47–7.39 (m, 3H), 7.36–7.32 (m, 1H), 7.23 (t, J = 4.8 Hz, 3H), 5.29 ppm (d, J = 1.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.1 (s), 138.2 (s), 135.0 (s), 133.9 (s), 130.2 (s), 129.7 (s), 129.1 (s), 128.7 (s), 128.5 (s), 128.2 (s), 127.7 (s), 123.4 (s), 123.3 (s), 66.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1709, 1600, 1270, 1091, 890, 704, 684 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 236 (100) [M^+], 207 (85), 178 (15), 105 (45), 76 (27); **HRMS** (EI–TOF) calcd. for $C_{16}H_{12}O_2$: 236.0837; found: 236.0832; **m.p.**: 122–123 °C.

7.4.5.2. Synthesis of (Z)–N–(4–benzylidene–1–oxoisochroman–6–yl)–acetamide



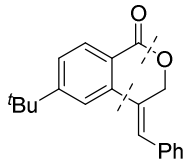
[CAS: 1914996-65-8]

The title compound was prepared starting from 4–acetamidobenzoic acid (90.5 mg, 0.5 mmol) and 3–phenyl–2–propyn–1–ol (99 mg, 0.75 mmol). The title compound was isolated as colorless solid (93.3 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 0.8 Hz, 1H), 8.20 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.44–7.34 (m, 4H), 7.19 (d, J = 7.2 Hz, 2H), 5.29 (d, J = 1.2 Hz, 2H), 2.26 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.2 (s), 164.4 (s), 143.5 (s), 139.9 (s), 135.0 (s), 131.6 (s), 130.6 (s), 129.2 (s), 128.6 (s), 128.4 (s), 127.6 (s), 119.5 (s), 118.6 (s), 113.3 (s), 67.2 (s), 24.8 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3296, 1706, 1680, 1586, 1538, 1368, 1262, 1101, 1004, 777, 694 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 293 (100) [M^+], 164 (85), 222 (15), 194 (45), 165 (27),

105 (13); **HRMS** (EI–TOF) calcd. for $C_{18}H_{15}NO_3$: 293.1052; found: 293.1048; **m.p.**: 196–197 °C.

7.4.5.3. Synthesis of (Z)–4–benzylidene–6–tert–butylisochroman–1–one

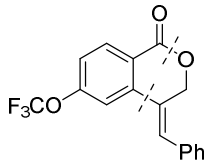


[CAS: 1914996-67-0]

The title compound was prepared starting from 4–*tert*–butylbenzoic acid (90 mg, 0.5 mmol) and 3–phenyl–2–propyn–1–ol (99 mg, 0.75 mmol). The title compound was isolated as yellow solid (111 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.54 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.44 (t, J = 7.2 Hz, 2H), 7.39–7.35 (m, 1H), 7.27 (t, J = 7.2 Hz, 3H), 5.31 (d, J = 1.2 Hz, 2H), 1.41 ppm (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.4 (s), 157.9 (s), 138.1 (s), 135.2 (s), 130.2 (s), 129.4 (s), 129.2 (s), 128.60 (s), 128.58 (s), 128.3 (s), 126.5 (s), 120.9 (s), 120.0 (s), 67.1 (s), 35.4 (s), 31.0 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2963, 1711, 1601, 1247, 1094, 1006, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 263 (100) [M^+-2CH_3], 231 (76), 203 (68), 101 (45); **HRMS** (EI–TOF) calcd. for $C_{20}H_{20}O_2$: 292.1463; found: 292.1473; **m.p.**: 127–129 °C.

7.4.5.4. Synthesis of (Z)–4–benzylidene–6–(trifluoromethoxy)–1–one



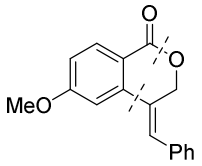
[CAS: 1914996-70-5]

The title compound was prepared starting from 4–(trifluoromethoxy)–benzoic acid (107 mg, 0.5 mmol) and 3–phenyl–2–propyn–1–ol (99 mg, 0.75 mmol). The title compound was isolated as colorless solid (125 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.8 Hz, 1H), 7.49–7.44 (m, 3H), 7.42–7.38 (m, 1H), 7.33–7.29 (m, 2H), 7.26–7.25 (m, 2H), 5.35 ppm (d, J = 1.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.1 (s), 153.3 (d, J = 1.8 Hz, 1C), 140.7 (s), 134.6 (s), 132.97 (s),

131.5 (s), 129.3 (s), 128.8 (s), 128.76 (s), 126.91 (s), 121.8 (s), 120.7 (s), 119.8 (d, *J* = 89 Hz, 1C), 115.0 (s), 67.1 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3053, 1708, 1211, 1162, 1007, 886, 773, 703 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 320 (100) [M^+], 291 (76), 214 (68), 165 (45), 105 (27); **HRMS** (EI–TOF) calcd. for $C_{17}H_{11}F_3O_3$: 320.0660; found: 320.0662; **m.p.**: 147–148 °C.

7.4.5.5. Synthesis of (Z)–4–benzylidene–6–methoxyisochroman–1–one

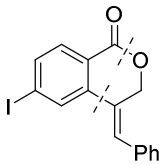


[CAS: 1914996-72-7]

The title compound was prepared starting from 4–methoxybenzoic acid (152 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as yellow solid (216 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.8 Hz, 1H), 7.43–7.39 (m, 2H), 7.36–7.32 (m, 1H), 7.24–7.21 (m, 3H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 5.25 (d, *J* = 1.2 Hz, 2H), 3.90 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.0 (s), 163.9 (s), 140.2 (s), 134.9 (s), 132.4 (s), 129.6 (s), 129.0 (s), 128.4 (s), 128.2 (s), 128.1 (s), 116.1 (s), 115.1 (s), 107.4 (s), 66.8 (s), 55.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2848, 1700, 1596, 1341, 1260, 1226, 1103, 993, 869, 694 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 266 (100) [M^+], 237 (76), 165 (45); **HRMS** (EI–TOF) calcd. for $C_{17}H_{14}O_3$: 266.0943; found: 266.0948; **m.p.**: 115–117 °C.

7.4.5.6. Synthesis of (Z)–4–benzylidene–6–iodoisochroman–1–one



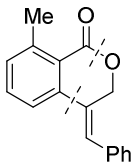
[CAS: 1914996-74-9]

The title compound was prepared starting from 4–iodobenzoic acid (253 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as colorless solid (218 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 0.8 Hz, 1H), 7.85–7.80 (m, 2H), 7.46–7.36 (m, 3H), 7.24 (t, *J* = 7.2 Hz, 3H), 5.30 ppm (d, *J* = 1.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ

= 163.7 (s), 139.6 (s), 137.9 (s), 134.6 (s), 132.5 (s), 131.5 (s), 131.0 (s), 129.1 (s), 128.6 (s), 128.6 (s), 126.4 (s), 122.6 (s), 102.1 (s), 66.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1702, 1582, 1247, 1009, 773, 751, 697, 679 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 361 (100) [M^+], 333 (76), 178 (45), 127 (33), 105 (15); **HRMS** (EI–TOF) calcd. for $C_{16}H_{11}IO_2$: 361.9804; found: 361.9807; **m.p.**: 169–170 °C.

7.4.5.7. Synthesis of (Z)–4–benzylidene–8–methylisochroman–1–one

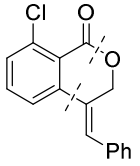


[CAS: 1914996-77-2]

The title compound was prepared starting from 2–methylbenzoic acid (68.8 mg, 0.5 mmol) and 3–phenyl–2–propyn–1–ol (99 mg, 0.75 mmol). The title compound was isolated as yellow solid (103 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.48 (m, 2H), 7.45–7.40 (m, 2H), 7.38–7.34 (m, 1H), 7.31–7.29 (m, 1H), 7.25–7.23 (m, 3H), 5.20 (d, *J* = 1.2 Hz, 2H), 2.74 ppm (d, *J* = 0.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.5 (s), 142.9 (s), 139.9 (s), 135.2 (s), 132.9 (s), 132.3 (s), 129.6 (s), 129.2 (s), 129.0 (s), 128.5 (s), 128.1 (s), 122.0 (s), 121.9 (s), 66.1 (s), 22.4 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1704, 1593, 1470, 1257, 1074, 989, 779, 695 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 250 (23) [M^+], 232 (85), 178 (74), 115 (100), 89 (27); **HRMS** (EI–TOF) calcd. for $C_{17}H_{14}O_2$: 250.0994; found: 250.1010; **m.p.**: 111–112 °C.

7.4.5.8. Synthesis of (Z)–4–benzylidene–8–chloroisochroman–1–one

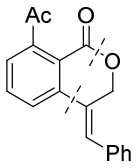


[CAS: 1914996-80-7]

The title compound was prepared starting from 4–iodobenzoic acid (160 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as yellow solid (189 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.50 (m, 3H), 7.45–7.41 (m, 2H), 7.38–7.35 (m, 1H), 7.28 (s, 1H), 7.23 (d, J = 7.2 Hz, 2H), 5.18 ppm (d, J = 0.8 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 160.7 (s), 141.6 (s), 136.7 (s), 134.7 (s), 133.5 (s), 132.0 (s), 131.3 (s), 129.1 (s), 128.6 (s), 128.5 (s), 128.1 (s), 122.8 (s), 121.248 (s), 66.1 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1717, 1588, 1220, 1110, 1066, 1007, 796, 703 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 270 (100) [M$^+$], 241 (76), 207 (45), 178 (33), 151 (15), 105 (10); **HRMS** (EI–TOF) calcd. for $C_{16}H_{11}ClO_2$: 270.0448/272.0423; found: 270.0423/272.0422; **m.p.**: 159–160 °C.

7.4.5.9. Synthesis of (Z)–8–acetyl–4–benzylideneisochroman–1–one

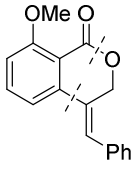


[CAS: 1914996-82-9]

The title compound was prepared starting from 2–acetylbenzoic acid (166 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as yellow solid (189 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.66 (m, 2H), 7.46–7.36 (m, 3H), 7.33–7.24 (m, 4H), 5.31 (d, J = 1.5 Hz, 2H), 2.57 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 204.0 (s), 162.9 (s), 146.0 (s), 139.2 (s), 134.74 (s), 133.9 (s), 131.4 (s), 129.1 (s), 128.7 (s), 128.6 (s), 127.3 (s), 126.0 (s), 124.4 (s), 120.2 (s), 66. 8 (s), 30.8 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1695, 1580, 1359, 1266, 1116, 1067, 752, 695 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 278 (100) [M$^+$], 178 (33), 151 (15), 105 (10); **HRMS** (EI–TOF) calcd. for $C_{18}H_{14}O_3$: 278.0943; found: 278.0936; **m.p.**: 167–168 °C.

7.4.5.10. Synthesis of (Z)–4–benzylidene–8–methoxyisochroman–1–one

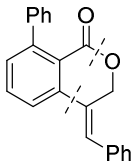


[CAS: 1914996-85-2]

The title compound was prepared starting from 2–methoxybenzoic acid (154 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as colorless solid (207 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.0 Hz, 1H), 7.35–7.22 (m, 3H), 7.19–7.10 (m, 4H), 6.92 (d, J = 8.4 Hz, 1H), 5.05 (d, J = 0.8 Hz, 2H), 3.87 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.0 (s), 160.8 (s), 141.0 (s), 134.8 (s), 134.5 (s), 129.9 (s), 128.8 (s), 128.7 (s), 128.2 (s), 127.9 (s), 115.6 (s), 111.8 (s), 111.7 (s), 65.7 (s), 55.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2838, 1717, 1577, 1466, 1256, 1212, 1063, 982, 804, 776, 692 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 266 (100) [M^+], 237 (76), 165 (45), 115 (30), 76 (23); **HRMS** (EI–TOF) calcd. for $C_{17}H_{14}O_3$: 266.0943; found: 266.0941; **m.p.**: 129–130 °C.

7.4.5.11. Synthesis of (Z)–4–benzylidene–8–phenylisochroman–1–one

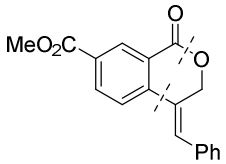


[CAS: 1914996-87-4]

The title compound was prepared starting from 2–biphenylcarboxylic acid (198 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as yellow solid (162 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.64 (m, 2H), 7.50–7.41 (m, 9H), 7.37 (s, 1H), 7.32–7.30 (m, 2H), 5.31 ppm (d, J = 1.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.6 (s), 145.7 (s), 141.1 (s), 140.1 (s), 135.0 (s), 132.7 (s), 131.9 (s), 130.4 (s), 129.0 (s), 128.5 (s), 128.3 (s), 128.2 (s), 127.9 (s), 127.2 (s), 122.9 (s), 121.8 (s), 66.1 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1716, 1573, 1466, 1252, 1220, 1107, 994, 752, 695 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 312 (66) [M^+], 294 (100), 265 (45), 178 (30), 105 (25); **HRMS** (EI–TOF) calcd. for $C_{22}H_{16}O_2$: 312.1150; found: 312.1125; **m.p.**: 184–185 °C.

7.4.5.12. Synthesis of (Z)–methyl–4–benzylidene–1–oxoisochroman–7–carboxylate

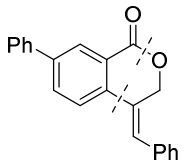


[CAS: 1914996-90-9]

The title compound was prepared starting from *mono*–methyl isophthalate (186 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as colorless solid (256 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (d, J = 1.2 Hz, 1H), 8.11 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.33–7.29 (m, 2H), 7.27–7.23 (m, 2H), 7.12 (d, J = 6.8 Hz, 2H), 5.20 (d, J = 1.6 Hz, 2H), 3.80 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.4 (s), 159.7 (s), 138.7 (s), 134.0 (s), 130.7 (s), 130.3 (s), 129.6 (s), 128.6 (s), 127.7 (s), 126.2 (s), 123.4 (s), 123.2 (s), 114.1 (s), 67.2 (s), 55.3 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2960, 1730, 1712, 1605, 1428, 1305, 1218, 1091, 767, 688 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 294 (66) [M^+], 265 (100), 178 (45), 152 (30), 105 (25); **HRMS** (EI–TOF) calcd. for $C_{18}H_{14}O_4$: 294.0892; found: 294.0903; **m.p.**: 115–117 °C.

7.4.5.13. Synthesis of (Z)–4–benzylidene–7–phenylisochroman–1–one

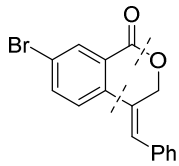


[CAS: 1914996-93-2]

The title compound was prepared starting from biphenyl–3–carboxylic acid (198 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as yellow solid (154 mg, 49%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.70–7.67 (m, 2H), 7.52–7.44 (m, 4H), 7.44–7.37 (m, 4H), 7.33 (s, 1H), 7.28–7.27 (m, 2H), 5.38 ppm (d, J = 1.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.3 (s), 141.8 (s), 139.1 (s), 137.1 (s), 135.2 (s), 132.5 (s), 129.7 (s), 129.2 (s), 129.0 (s), 128.7 (s), 128.6 (s), 128.4 (s), 128.1 (s), 127.7 (s), 126.9 (s), 124.1 (s), 123.8 (s), 67.2 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3031, 1713, 1449, 1221, 1096, 1004, 831, 764, 693 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 312 (65) [M^+], 294 (100), 265 (55), 178 (30), 105 (25); **HRMS** (EI–TOF) calcd. for $C_{22}H_{16}O_2$: 312.1150; found: 312.1139; **m.p.**: 185–186 °C.

7.4.5.14. Synthesis of (Z)–4–benzylidene–7–bromoisochroman–1–one

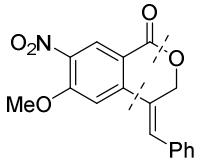


[CAS: 1914996-96-5]

The title compound was prepared starting from 3–bromobenzoic acid (205 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as colorless solid (239 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.48–7.37 (m, 3H), 7.29 (s, 1H), 7.25 (d, J = 7.6 Hz, 2H), 5.34 ppm (d, J = 1.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.0 (s), 137.2 (s), 137.0 (s), 134.8 (s), 133.1 (s), 130.6 (s), 129.2 (s), 128.7 (s), 128.6 (s), 127.0 (s), 125.2 (s), 124.9 (s), 122.9 (s), 67.1 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2924, 1713, 1590, 1422, 1233, 1093, 1007, 821 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 314 (65) [M^+], 269 (100), 207 (55), 178 (30), 152 (25), 105 (13); **HRMS** (EI–TOF) calcd. for $C_{16}H_{11}BrO_2$: 313.9942/315.9924; found: 313.9934/315.9916; **m.p.**: 140–141 °C.

7.4.5.15. Synthesis of (Z)–4–benzylidene–6–methoxy–7–nitroisochroman–1–one



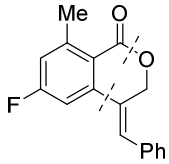
[CAS: 1914996-99-8]

The title compound was prepared starting from 4–methoxy–3–nitrobenzoic acid (201 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as yellow solid (139 mg, 45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 7.50–7.38 (m, 4H), 7.30–7.24 (m, 3H), 5.33 (d, J = 1.2 Hz, 2H), 4.11 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.2 (s), 156.6 (s), 144.0 (s), 139.6 (s), 134.2 (s), 133.4 (s), 129.3 (s), 129.2 (s), 128.8 (s), 128.4 (s), 126.5 (s), 115.9 (s), 107.5 (s), 66.9 (s), 57.0 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2929, 1705, 1603, 1520, 1294, 1237, 1026, 691 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 311 (100) [M^+], 282 (76), 235 (55), 178 (30),

105 (13); **HRMS** (EI–TOF) calcd. for $C_{17}H_{13}NO_5$: 311.0794; found: 311.0807; **m.p.**: 161–163 °C.

7.4.5.16. Synthesis of (Z)–4–benzylidene–6–fluoro–8–methylisochroman–1–one

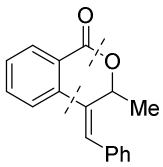


[CAS: 1914997-02-6]

The title compound was prepared starting from 4–fluoro–2–methylbenzoic acid (156 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as colorless solid (220 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.35 (m, 3H), 7.25–7.22 (m, 3H), 7.16 (dd, *J* = 9.6 Hz, 2.4 Hz, 1H), 6.99 (dd, *J* = 9.6 Hz, 2.0 Hz, 1H), 5.19 (d, *J* = 1.2 Hz, 2H), 2.72 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 165.9 (s), 163.3 (s), 162.8 (s), 147.1 (d, *J* = 7 Hz, 1C), 142.7 (d, *J* = 9 Hz, 1C), 134.8 (s), 130.8 (s), 129.1 (s), 128.62 (s), 128.58 (s), 128.4 (s), 119.3 (d, *J* = 21 Hz, 1C), 118.6 (d, *J* = 3 Hz, 1C), 108.5 (d, *J* = 22 Hz, 1C), 66.0 (s), 22.8 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2342, 1704, 1585, 1495, 1239, 1093, 881, 750, 697 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 268 (100) [M^+], 239 (76), 196 (55), 133 (30), 107 (13); **HRMS** (EI–TOF) calcd. for $C_{17}H_{13}FO_3$: 268.0900; found: 268.0886; **m.p.**: 153–155 °C.

7.4.5.17. Synthesis of (Z)–4–benzylidene–3–methylisochroman–1–one



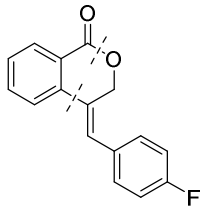
[CAS: 334872-10-5]

The title compound was prepared starting from benzoic acid (61.7 mg, 0.5 mmol) and 4–phenylbut–3–yn–2–ol (113 mg, 0.75 mmol). The title compound was isolated as yellow solid (75.3 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.0 Hz, 1H), 7.68–7.67 (m, 2H), 7.52–7.42 (m, 3H), 7.40–7.36 (m, 1H), 7.30–7.27 (m, 2H), 7.14 (s, 1H), 5.75 (q, *J* = 6.8 Hz, 1H), 1.64 ppm (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.7 (s), 137.3 (s), 135.2 (s), 134.2

(s), 132.9 (s), 130.0 (s), 129.0 (s), 128.8 (s), 128.7 (s), 128.2 (s), 124.4 (s), 123.6 (s), 73.9 (s), 21.8 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2980, 1705, 1599, 1372, 1238, 1094, 1043, 933, 755, 701 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 250 (23) [M^+], 207 (85), 178 (74), 152 (100), 77 (27); **HRMS** (EI–TOF) calcd. for $C_{17}H_{14}O_2$: 250.0994; found: 250.0992; **m.p.**: 160–162 °C.

7.4.5.18. Synthesis of (Z)–4–(4–fluorobenzylidene)–isochroman–1–one

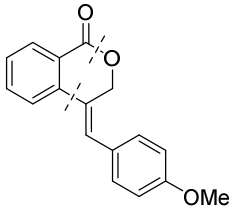


[CAS: 1914997-05-9]

The title compound was prepared starting from benzoic acid (61.7 mg, 0.5 mmol) and 3–(4–fluorophenyl)–prop–2–yn–1–ol (113 mg, 0.75 mmol). The title compound was isolated as yellow solid (71 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.0 Hz, 1H), 7.68–7.66 (m, 2H), 7.53–7.48 (m, 1H), 7.25–7.22 (m, 3H), 7.16–7.12 (m, 2H), 5.30 ppm (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.1 (s), 163.7 (s), 161.2 (s), 138.2 (s), 134.1 (s), 131.2 (d, *J* = 4 Hz, 1C), 130.9 (d, *J* = 8 Hz, 1C), 130.4 (s), 129.0 (s), 128.6 (s), 128.01 (s), 123.4 (s), 115.7 (d, *J* = 21 Hz, 1C), 66.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1709, 1596, 1505, 1224, 1099, 873, 759 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 254 (100) [M^+], 225 (85), 196 (74), 145 (75), 102 (45); **HRMS** (EI–TOF) calcd. for $C_{16}H_{11}FO_2$: 254.0739; found: 254.0743; **m.p.**: 139–141 °C.

7.4.5.19. Synthesis of (Z)–4–(4–methoxybenzylidene)–isochroman–1–one

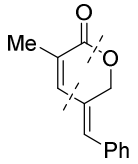


[CAS: 1914997-08-2]

The title compound was prepared starting from benzoic acid (61.7 mg, 0.5 mmol) and 3–(4–methoxyphenyl)–prop–2–yn–1–ol (122 mg, 0.75 mmol). The title compound was isolated as yellow solid (104 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, J = 8.0 Hz, 1.6 Hz, 1H), 8.29 (dd, J = 1.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.47–7.44 (m, 2H), 7.41–7.38 (m, 2H), 7.26 (d, J = 7.6 Hz, 2H), 5.35 (d, J = 1.2 Hz, 2H), 3.96 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.4 (s), 159.7 (s), 138.7 (s), 134.0 (s), 130.7 (s), 130.3 (s), 129.6 (s), 128.6 (s), 127.8 (s), 126.3 (s), 123.4 (s), 123.2 (s), 114.1 (s), 67.2 (s), 55.4 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2840, 1711, 1599, 1510, 1256, 1234, 1092, 985, 828, 756, 687 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 266 (100) [M^+], 237 (72), 219 (82), 165 (39), 108 (45), 69 (28); **HRMS** (EI–TOF) calcd. for $C_{17}H_{14}O_3$: 266.0943; found: 266.0943; **m.p.**: 118–119 °C.

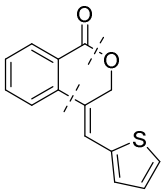
7.4.5.20. Synthesis of (Z)–5–benzylidene–3–methyl–5,6–dihydro–2H–pyran–2–one



The title compound was prepared starting from methacrylic acid (86.1 mg, 1.0 mmol) and 3–phenyl–2–propyn–1–ol (198 mg, 1.5 mmol). The title compound was isolated as yellow solid (124 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.37 (m, 2H), 7.33–7.29 (m, 1H), 7.15 (d, J = 7.6 Hz, 2H), 6.92–6.91 (m, 1H), 6.62 (s, 1H), 5.33 (d, J = 2.0 Hz, 2H), 2.02 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.4 (s), 141.4 (s), 134.9 (s), 132.0 (s), 128.9 (s), 128.86 (s), 128.7 (s), 128.3 (s), 125.9 (s), 67.8 (s), 17.2 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1701, 1451, 1212, 1114, 1042, 929, 761, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 200 (100) [M^+], 171 (76), 128 (55), 105 (13); **HRMS** (EI–TOF) calcd. for $C_{13}H_{12}O_2$: 200.0837; found: 200.0851; **m.p.**: 146–147 °C.

7.4.5.21. Synthesis of (Z)–4–(thiophen–2–ylmethylene)–isochroman–1–one

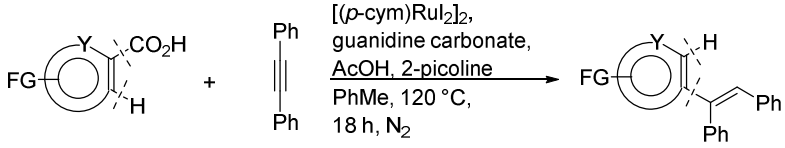


[CAS: 1914997-10-6]

The title compound was prepared starting from benzoic acid (61.7 mg, 0.5 mmol) and 3–(thiphen–2–yl)–prop–2–yn–1–ol (104 mg, 0.75 mmol). The title compound was isolated as yellow solid (61 mg, 51%).

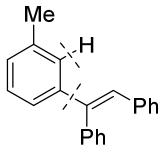
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (dd, J = 8.4 Hz, 0.8 Hz, 1H), 7.68–7.62 (m, 2H), 7.49–7.45 (m, 2H), 7.32 (s, 1H), 7.14–7.12 (m, 2H), 5.49 ppm (d, J = 1.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 164.0 (s), 138.1 (s), 137.9 (s), 134.0 (s), 130.5 (s), 130.1 (s), 128.7 (s), 127.9 (s), 127.8 (s), 125.5 (s), 123.02 (s), 122.97 (s), 121.1 (s), 67.2 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1712, 1460, 1254, 1098, 978, 757, 718 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 242 (100) [M$^+$], 213 (72), 197 (82), 184 (39), 152 (45), 130 (28); **HRMS** (EI–TOF) calcd. for $C_{13}H_{12}SO_2$: 242.0402; found: 242.0397; **m.p.**: 154–156 °C.

7.4.6. Synthesis of the corresponding vinylarenes via decarboxylative ortho-C–H hydroarylation



Standard procedure: An oven–dried 20 mL vessel was charged with [(*p*–cym)$RuCl_2$]$_2$ (12.2 mg, 0.02 mmol, 4 mol%), guanidine carbonate (18.2 mg, 0.1 mmol, 0.2 eq.), the (hetero)–arenecarboxylic acid (0.50 mmol) and diphenylacetylene (90 mg, 0.5 mmol, 1 eq.). After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, degassed toluene (2 mL), AcOH (28.9 µL, 0.5 mmol, 1 eq.) and 2-picoline (9.9 µL, 0.1 mmol, 0.2 eq.) was added *via* syringe. The resulting mixture was stirred at 120 °C for 18 h. After the reaction was complete, the mixture was allowed to cool to room temperature. Brine (20 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate/hexane gradient) yielding the corresponding vinylarenes.

7.4.6.1. Synthesis of (E)–(1–m–tolylethene–1,2–diyl)–dibenzene

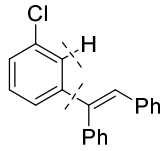


[CAS: 70603-13-3]

The title compound was prepared starting from 2–methylbenzoic acid (68.8 mg, 0.5 mmol) and diphenylacetylene (89.1 mg, 0.5 mmol). The title compound was isolated as colorless liquid (99 mg, 73%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.43–7.37 (m, 3H), 7.23 (t, J = 7.6 Hz, 1H), 7.15–7.10 (m, 7H), 7.07–7.05 (m, 2H), 7.01–6.99 (m, 2H), 2.29 ppm (s, 3H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 142.5 (s), 141.8 (s), 140.0 (s), 137.4 (s), 136.9 (s), 129.7 (s), 129.2 (s), 128.9 (s), 128.3 (s), 128.2 (s), 128.0 (s), 127.6 (s), 127.57 (s), 126.9 (s), 124.4 (s), 21.09 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1600, 1492, 1444, 782, 692 cm^{-1}. The analytical data matched those reported in the literature.[352]

7.4.6.2. Synthesis of (E)–(1–(3–chlorophenyl)–ethene–1,2–diyl)–dibenzene

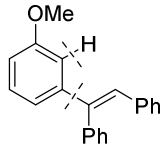


[CAS: 1892558-41-6]

The title compound was prepared starting from 2–chlorobenzoic acid (79.9 mg, 0.5 mmol) and diphenylacetylene (89.1 mg, 0.5 mmol). The title compound was isolated as colorless liquid (140 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 4H), 7.20–7.17 (m, 2H), 7.15–7.11 (m, 3H), 7.09–7.05 (m, 3H), 6.97–6.95 (m, 2H), 6.90 ppm (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 145.3 (s), 141.3 (s), 139.6 (s), 136.9 (s), 134.2 (s), 130.3 (s), 129.6 (s), 129.4 (s), 129.2 (s), 128.8 (s), 128.0 (s), 127.7 (s), 127.6 (s), 127.4 (s), 127.1 (s), 125.8 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1590, 1472, 14445, 1076, 873, 779, 706, 690 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 292 (75) [M^+], 290 (10); **HRMS** (EI–TOF) calcd. for $C_{20}H_{15}Cl$: 290.0862; found: 290.0860.

7.4.6.3. Synthesis of (E)–(1–(3–methoxyphenyl)–ethene–1,2–diyl)–dibenzene



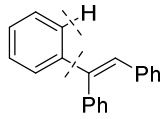
[CAS: 479206-43-4]

The title compound was prepared starting from 2–methoxybenzoic acid (76.1 mg, 0.5 mmol) and diphenylacetylene (89.1 mg, 0.5 mmol). The title compound was isolated as colorless liquid (109 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.35 (m, 3H), 7.29–7.28 (m, 1H), 7.26–7,24 (m, 2H), 7.20–7.14 (m, 3H), 7.08–7.06 (m, 2H), 7.02 (s, 1H), 6.98–6.95 (m, 1H), 6.93 (t, J = 2.1 Hz,

1H), 6.90–6.87 (m, 1H), 3.83 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.4 (s), 144.9 (s), 142.4 (s), 140.2 (s), 137.2 (s), 130.3 (s), 129.5 (s), 129.1 (s), 128.6 (s), 128.3 (s), 127.9 (s), 127.4 (s), 126.7 (s), 120.2 (s), 113.4 (s), 112.8 (s), 55.1 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1594, 1484, 1267, 1209, 1045, 870, 776, 691 cm^{-1}. The analytical data matched those reported in the literature.[353]

7.4.6.4. Synthesis of ethane–1,1,2–triyltribenzene

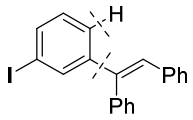


[CAS: 58-72-0]

The title compound was prepared starting from 2–methoxybenzoic acid (76.1 mg, 0.5 mmol) and diphenylacetylene (89.1 mg, 0.5 mmol). The title compound was isolated as colorless liquid (109 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.31 (m, 8H), 7.26–7.23 (m, 2H), 7.19–7.13 (m, 3H), 7.08–7.05 (m, 2H), 7.00 ppm (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 143.4 (s), 142.6 (s), 140.3 (s), 137.4 (s), 130.4 (s), 129.5 (s), 128.6 (s), 128.2 (s), 128.1 (s), 127.4 (s), 127.6 (s), 127.5 (s), 127.4 (s), 126.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3022, 1598, 1491, 1444, 1074, 758, 690 cm^{-1}. The analytical data matched those reported in the literature.[354]

7.4.6.5. Synthesis of (E)–(1–(3–iodophenyl)–ethene–1,2–diyl)–dibenzene



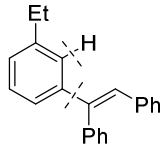
[CAS: 1914997-23-1]

The title compound was prepared starting from 4–iodobenzoic acid (127 mg, 0.5 mmol) and diphenylacetylene (89.1 mg, 0.5 mmol). The title compound was isolated as colorless solid (98.2 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (t, J = 1.2 Hz, 1H), 7.62 (dt, J = 7.6 Hz, 1.2 Hz, 1H), 7.36–7.33 (m, 3H), 7.26–7.23 (m, 1H), 7.20–7.18 (m, 2H), 7.15–7.12 (m, 3H), 7.06–7.01 (m, 3H), 6.94 ppm (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 145.8 (s), 141.1 (s), 139.6 (s), 136.9 (s), 136.3 (s), 130.3 (s), 129.8 (s), 129.6 (s), 129.2 (s), 128.8 (s), 128.0 (s), 127.7 (s), 127.1 (s), 127.0 (s), 94.4 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1580, 1487, 1064, 869, 780, 759, 690 cm^{-1}; **MS**

(EI, 70 eV) *m/z* (%): 382 (75) [M^+], 256 (10), 179 (100); **HRMS** (EI–TOF) calcd. for $C_{20}H_{15}I$: 382.0219; found: 382.0206; **m.p.**: 97–98 °C.

7.4.6.6. Synthesis of (E)–(1–(3–ethylphenyl)–ethene–1,2–diyl)–dibenzene

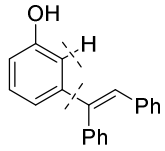


[CAS: 1914997-22-0]

The title compound was prepared starting from 2–ethylbenzoic acid (75.1 mg, 0.5 mmol) and diphenylacetylene (89.1 mg, 0.5 mmol). The title compound was isolated as colorless liquid (119 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.34 (m, 3H), 7.26–7.21 (m, 4H), 7.17–7.12 (m, 5H), 7.06–7.04 (m, 2H), 6.99 (s, 1H), 2.65 (q, J = 7.6 Hz, 2H), 1.25 ppm (t, J = 7.6 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.1 (s), 143.4 (s), 142.8 (s), 140.4 (s), 137.5 (s), 130.4 (s), 129.5 (s), 128.6 (s), 128.1 (s), 128.0 (s), 127.9 (s), 127.3 (s), 127.1 (s), 126.6 (s), 125.2 (s), 28.9 (s), 15.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2964, 1599, 1492, 1444, 1075, 793, 753, 691 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 284 (64) [M^+], 269 (88), 154 (100); **HRMS** (EI–TOF) calcd. for $C_{22}H_{20}$: 284.1565; found: 284.1570.

7.4.6.7. Synthesis of (E)–3–(1,2–diphenylvinyl)–phenol



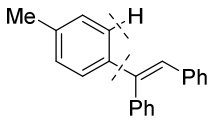
[CAS: 1892558-46-1]

The title compound was prepared starting from 2–hydroxybenzoic acid (64.7 mg, 0.5 mmol) and diphenylacetylene (89.1 mg, 0.5 mmol). The title compound was isolated as colorless liquid (83 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 3H), 7.22–7.19 (m, 3H), 7.17–7.11 (m, 3H), 7.03–7.01 (m, 2H), 6.98 (s, 1H), 6.97–6.94 (m, 1H), 6.79–6.76 (m, 2H), 4.66 ppm (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.3 (s), 145.2 (s), 142.0 (s), 140.1 (s), 137.2 (s), 130.3 (s), 129.6 (s), 129.4 (s), 128.7 (s), 128.4 (s), 128.0 (s), 127. 5 (s), 126.8 (s), 120.2 (s), 114.4 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1596, 1578, 1492, 1444, 1271,1191, 695 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%):

255 (100) [M^+-OH], 178 (55); **HRMS** (EI–TOF) calcd. for $C_{20}H_{16}O$: 270.1201; found: 270.1202.

7.4.6.8. Synthesis of (E)–(1–p–tolylethene–1,2–diyl)–dibenzene

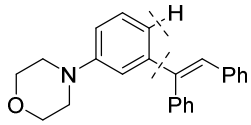


[CAS: 84224-86-2]

The title compound was prepared starting from 3–methylbenzoic acid (68.8 mg, 0.5 mmol) and diphenylacetylene (89.1 mg, 0.5 mmol). The title compound was isolated as colorless solid (83.6 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 3H), 7.24–7.20 (m, 4H), 7.16–7.10 (m, 5H), 7.04–7.02 (m, 2H), 6.95 (s, 1H), 2.37 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.4 (s), 140.6 (s), 140.5 (s), 137.5 (s), 137.4 (s), 130.4 (s), 129.5 (s), 128.9 (s), 128.6 (s), 127.9 (s), 127.5 (s), 127.3 (s), 126.6 (s), 21.1 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1597, 1491, 1442, 1072, 807, 754, 693 cm^{-1}; **HRMS** (EI–TOF) calcd. for $C_{21}H_{18}$: 270.1409; found: 270.1406; **m.p.**: 69–70 °C. The analytical data matched those reported in the literature.[353]

7.4.6.9. Synthesis of (E)–4–(3–(1,2–diphenylvinyl)–phenyl)–morpholine

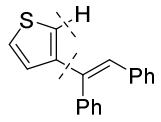


[CAS: 1914997-24-2]

The title compound was prepared starting from 4–morpholinobenzoic acid (107 mg, 0.5 mmol) and diphenylacetylene (89.1 mg, 0.5 mmol). The title compound was isolated as yellow liquid (112 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.32 (m, 3H), 7.23–7.20 (m, 3H), 7.16–7.11 (m, 3H), 7.04–7. 02 (m, 2H), 6.96 (s, 1H), 6.91–6.83 (m, 3H), 3.85 (t, J = 4.8 Hz, 4H), 3.14 ppm (t, J = 4.8 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.2 (s), 144.6 (s), 143.0 (s), 140.3 (s), 137.4 (s), 130.4 (s), 129.5 (s), 128.9 (s), 128.5 (s), 128.1 (s), 127.9 (s), 127.4 (s), 126.7 (s), 119.9 (s), 115.2 (s), 114.9 (s), 66.9 (s), 49.4 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1592, 1488, 1444, 1254, 1119, 930, 779, 692 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 341 (25) [M^+], 313 (55), 269 (42), 255 (100); **HRMS** (EI–TOF) calcd. for $C_{24}H_{23}NO$: 341.1780; found: 341.1781.

7.4.6.10. Synthesis of (E)–3–(1,2–diphenylethenyl)–thiophene



[CAS: 93080-10-5]

The title compound was prepared starting from 2–thiophenecarboxylic acid (64.7 mg, 0.5 mmol) and diphenylacetylene (89.1 mg, 0.5 mmol). The title compound was isolated as colorless liquid (83 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.36 (m, 3H), 7.34–7.31 (m, 2H), 7.29–7.28 (m, 2H), 7.16–7.11 (m, 3H), 7.06 (s, 1H), 7.00 (dd, J = 8.0 Hz, 2 Hz, 2H), 6.92 ppm (q, J = 2.4 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 145.1 (s), 140.2 (s), 137.3 (s), 137.0 (s), 129.8 (s), 129.4 (s), 128.7 (s), 127.9 (s), 127.5 (s), 126.6 (s), 126.6 (s), 125.9 (s), 125.6 (s), 123.0 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 1597, 1493, 1444, 1072, 864, 779, 752, 691 cm^{-1}. The analytical data matched those reported in the literature.[355]

7.5. Doubly Regioselective C–H Hydroarylation of Unsymmetrical Alkynes Using Carboxylates as Deciduous Directing Groups

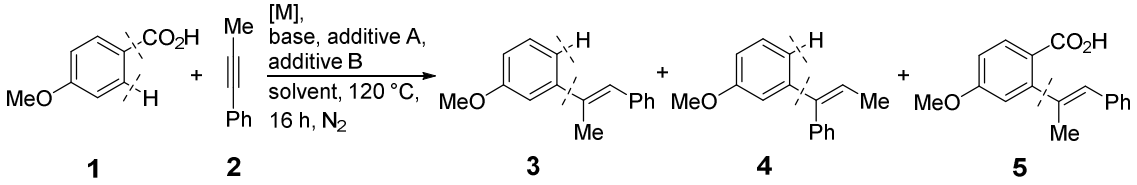
7.5.1. General Methods

Chemicals and solvents were either purchased (puriss p.A.) from commercial supplier or purified by standard techniques.[343] All reactions, if not stated otherwise, were performed in oven-dried glassware under a nitrogen atmosphere containing a Teflon-coated stirrer bar and dry septum. All reactions were monitored by GC using tetradecane as an internal standard. Response factors of the products with regard to *n*-tetradecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP–5 capillary column (Phenyl methyl siloxane, 30 m × 320 × 0.25, 100/2.3-30-300/3, 2 min at 60 °C, heating rate 30 °C/min, 3 or 10 min at 300 °C). Column chromatography was performed using a Combi Flash Companion-Chromatography-System (*Isco-Systems*) and *Reveleris* packed columns (12 g). NMR spectra were recorded on *Bruker Avance 400* at ambient temperature using $CDCl_3$ as solvent, with proton, carbon, and fluorine resonances at 400, 101, and 376 MHz respectively.

7.5.2. Catalyst development

7.5.2.1. Optimization of the regioselective decarboxylative C–H hydroarylation with unsymmetrical alkynes and conventional heating

Table 16: Screening experiments for the regioselective decarboxylative C–H hydroarylation with 1–phenyl–1–propyne.



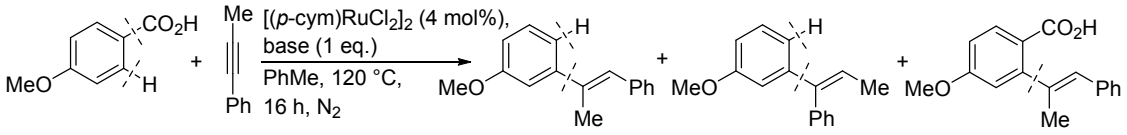
1 **2** **3** **4** **5**

#	[M]/4 mol%	solvent	base/eq.	add. A/eq.	add. B/eq.	1:2	Yield/%/[a]		
							3	**4**	**5**
1	$[(p\text{–cym})RuCl_2]_2$	PhMe	$GuanCO_3$/0.2	AcOH/1	2–picoline/0.2	1:1	25	n.d.	21
2	$[(p\text{–cym})RuI_2]_2$	"	"	"	"	"	29	"	19
3	$[(C_6Me_6)RuCl_2]_2$	"	"	"	"	"	16	"	32
4	$[(C_6Me_3)RuCl_2]_2$	"	"	"	"	"	13	"	29
5	$[(C_6H_6)RuCl_2]_2$	"	"	"	"	"	8	"	23
6	$[(p\text{–cym})RuCl_2]_2$	NMP	"	"	"	"	22	trace	27
7	$[(p\text{–cym})RuI_2]_2$	"	"	"	"	"	22	"	23
8	$[(C_6Me_6)RuCl_2]_2$	"	"	"	"	"	38	"	20
9	$[C_6Me_3)RuCl_2]_2$	"	"	"	"	"	15	"	16
10	$[(C_6H_6)RuCl_2]_2$	"	"	"	"	"	9	"	16
11	$[(C_6Me_6)RuCl_2]_2$	C_6Me_3	"	"	"	"	15	"	30
12	"	DMF	"	"	"	"	n.d.	"	n.d.
13	"	DMAc	"	"	"	"	21	"	23
14	"	NCyP	"	"	"	"	18	"	23
15	"	PC	"	"	"	"	18	"	trace
16	"	NMP	"	"	"	1:1.5	53	3	23
17	"	"	"	PivOH/1	"	"	42	"	33
18	"	"	"	$AdCO_2H$/1	"	"	44	"	36
19	"	"	"	TFA/1	"	"	n.d.	n.d.	n.d.
20	"	"	"	$MesCO_2H$/1	"	"	62	trace	27
21	"	"	"	AcOH/1	-	"	64	``	32
22	"	"	-	"	-	"	n.d.	n.d.	n.d.
23	"	"	$GuanCO_3$/0.2	-	-	"	"	"	"
24	"	"	Li_2CO_3/0.2	AcOH/1	-	"	16	14	13

25	"	"	K_2CO_3/0.2	"	-	"	31	16	18
26	"	"	Cs_2CO_3/0.2	"	-	"	23	9	8
27	"	"	K_2CO_3/0.05	"	-	"	16	9	9
28	"	"	K_2CO_3/0.1	"	-	"	39	3	5
29	"	"	K_2CO_3/0.3	"	-	"	23	25	6
30	"	"	K_2CO_3/0.5	"	-	"	21	22	4
31	"	"	K_2CO_3/1	"	-	"	24	17	3
32	"	"	K_2CO_3/0.1	"	$GuanCO_3$/0.2	"	43	7	25
33	"	"	"	"	$GuanCO_3$/0.05	"	60	9	13
34	"	"	"	$MesCO_2H$/0.5	-	"	80	13	4
35	"	"	"	$MesCO_2H$/1	-	"	59	11	5
36	"	"	"	$MesCO_2H$/0.5	$GuanCO_3$/0.05	"	63	12	8
37	"	"	"	$MesCO_2H$/1	"	"	71	2	n.d.
38	"	"	DABCO/1	"	"	"	12	trace	45
39	"	"	NEt_3/1	"	"	"	15	"	18
40	"	"	Quinuclidine/1	"	"	"	11	"	40

*Reaction conditions: **1** (0.5 mmol), **2**, [M] (4 mol%), base, solvent, 120 °C, 16 h under N_2-atmosphere. [a] Yields of corresponding methyl esters determined by GC after esterification with K_2CO_3 (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard.*

Table 17: Evaluation of organic bases for the decarboxylative hydroarylation with 1–phenyl–1–propyne.



1 **2** **3** **4** **5**

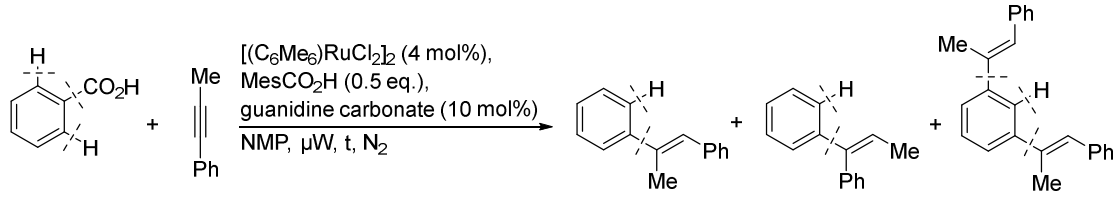
#	base /1 eq.	Yield/%[a]		
		3	**4**	**5**
1	triethylamine	13	n.d.	47
2	TMEDA	9	"	14
3	diisopropylethylamin	15	"	26
4	*N*–Me–tetramethylpiperidine	16	"	38
5	Quinuclidine	11	"	54
6	DBU	5	"	10
7	*N*–Me–pyrrolidine	10	"	10
8	$TBAOH{\cdot}30H_2O$	41	3	24

9	TBAOAc	40	11	8

*Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), [(p−cym)RuCl$_2$]$_2$ (4 mol%), base, PhMe (2 mL), 120 °C, 16 h under N_2-atmosphere. [a] Yields of corresponding methyl esters determined by GC after esterification with K_2CO_3 (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard.*

7.5.2.2. Optimization of the microwave conditions for the regioselective decarboxylative C–H hydroarylation with unsymmetrical alkynes

Table 18: Screening of microwave conditions for simple benzoic acid.



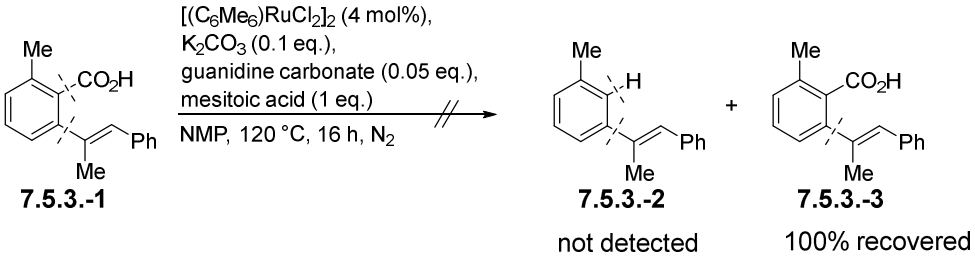
7.5.2.2.-1 **7.5.2.2.-2** **7.5.2.2.-3** **7.5.2.2.-4** **7.5.2.2.-5**

#	t /min	µW T /°C	Yield/%[a]		
			7.5.2.2.-3	**7.5.2.2.-4**	**7.5.2.2.-5**
1	0.5	200	53	18	trace
		180	44	13	"
		170	45	15	"
		160	44	9	"
2	1	200	52	14	8
		180	51	11	trace
		170	48	11	"
3	3	200	56	13	7
		180	51	12	7
		170	50	12	7
4	5	200	56	14	trace
		180	60	8	n.d.
		180[b]	40	16	12
		170	50	11	trace
		160	47	10	"
		150	51	10	"
		140	29	trace	"
		130	15	``	n.d.

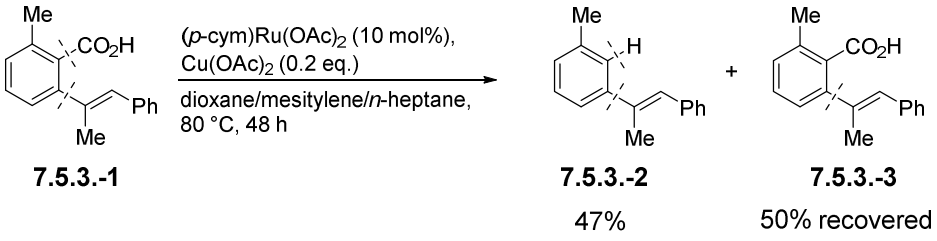
		120	10	15	trace
5	10	180	55	11	"
		170	27	7	"
		160	50	12	"
		150	45	8	"
		140	18	trace	"
6	15	180	25	7	"
		150	43	9	"
		120	20	22	"
7	30	180	29	6	"

Reaction conditions: ***7.5.2.2.-1*** *(0.5 mmol),* ***7.5.2.2.-2*** *(0.75 mmol), $[(C_6Me_6)RuCl_2]_2$ (4 mol%), K_2CO_3 (10 mol%), NMP (1 mL), µW-irradiation, t, under N_2-atmosphere. [a] Yields of corresponding methyl esters determined by GC after esterification with K_2CO_3 (2 eq.) and MeI (5 eq.) in NMP using n-tetradecane as the internal standard. [c] conventional heating after 16 h.*

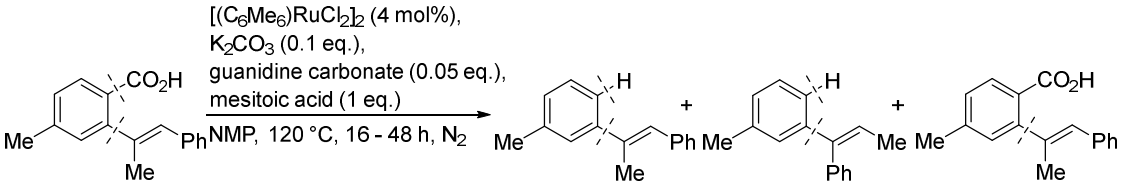
7.5.3. Mechanistic control experiments for the deciduous character of the CO_2H group



Scheme 52: Standard decarboxylative hydroarylation reaction set-up.



Scheme 53: Decarboxylative reaction set-up reported by Hartwig and Zhao.[338]

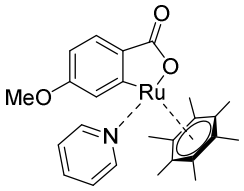


7.5.3.-4

reaction time	**7.5.3.-5**	**7.5.3.-6**	**7.5.3.-7**
16 h	62%	4%	30%
48 h	62%	4%	30%

Scheme 54: Standard reaction condition vs prolonged reaction time.

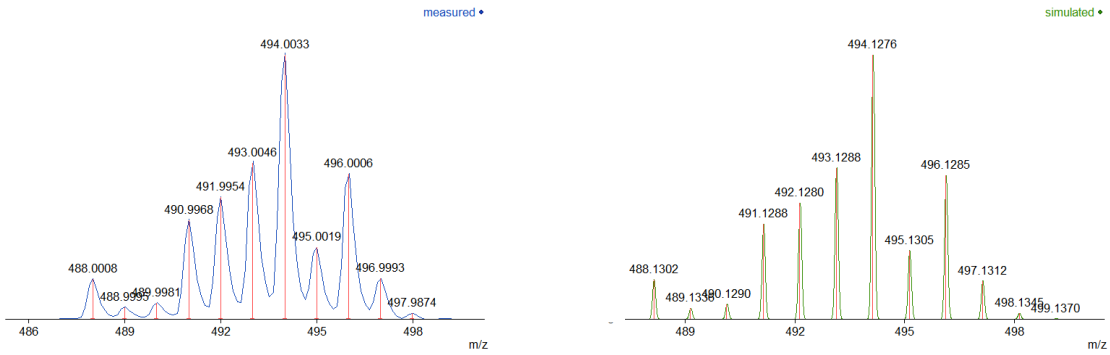
7.5.4. Synthesis of [Ru(4–OMe-benzoato^{2}–C^{6},O^{1})(hexamethylbenzene)(pyridine)]



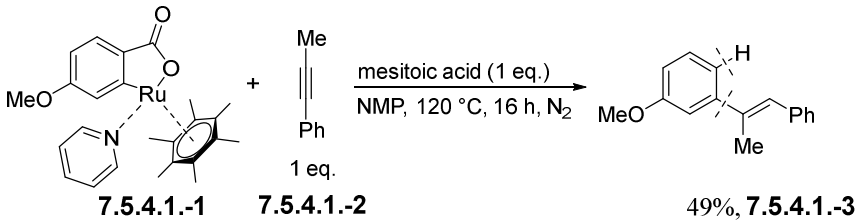
[CAS: 2079114-43-3]

The title compound was synthesized following the literature reported procedure,[284] starting from potassium 4–methoxy benzoate (285 mg, 1.5 mmol), [Ru(*hexamethylbenzene*)Cl_2]$_2$ (334 mg, 0.5 mmol), pyridine (79 mg, 8.1 µL, 1 mmol) and trimethylamine (715 mg, 983 µL, 7 mmol). The title compound was isolated as a yellow solid (148 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29–8.42 (m, 2H), 7.46 (tt, *J* = 7.7, 1.6 Hz, 1H), 7.38 (d, *J* = 2.5 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 6.98–7.09 (m, 2H), 6.44 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.86 (s, 3H), 1.94 ppm (s, 18H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 181.3 (s), 160.6 (s), 153.2 (s), 136.4 (s), 131.0 (s), 129.1 (s), 124.4 (s), 120.0 (s), 112.7 (s), 106.1 (s), 93.4 (s), 54.9 (s), 15.2 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2917, 1600, 1573, 1445, 1430, 1385, 1308, 1242, 1222, 1207, 1167, 1144, 1067, 1026, 855, 777, 761, 696 cm^{-1}; **HRMS** (ESI): *m/z* = calcd. for $C_{25}H_{29}O_3NRu+H^+$: 494.1276; found 494.0033; **m.p.**: 144 °C, decomposition.

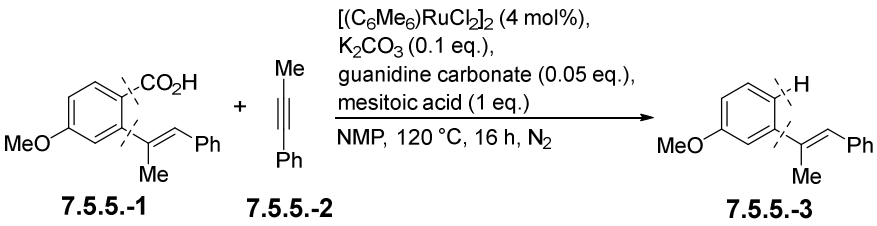


7.5.4.1. Mechanistic control experiments

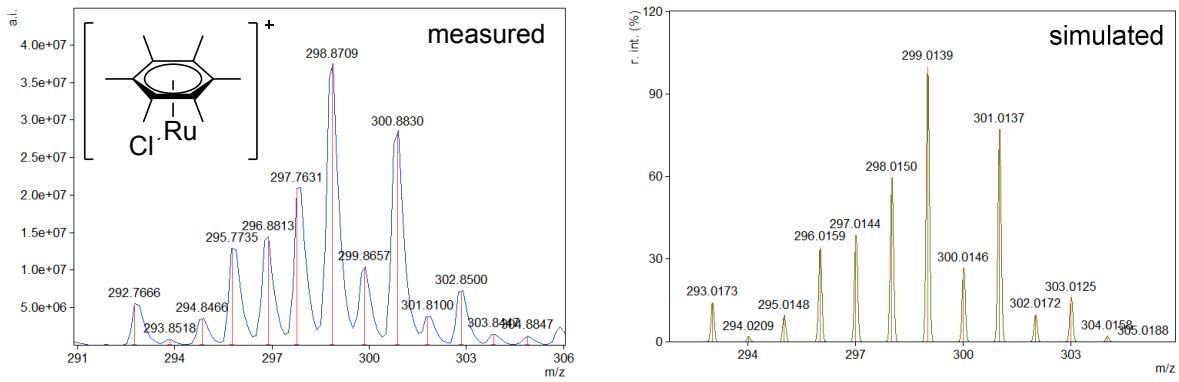


Scheme 55: Reaction starting from a preformed ruthenacycle.

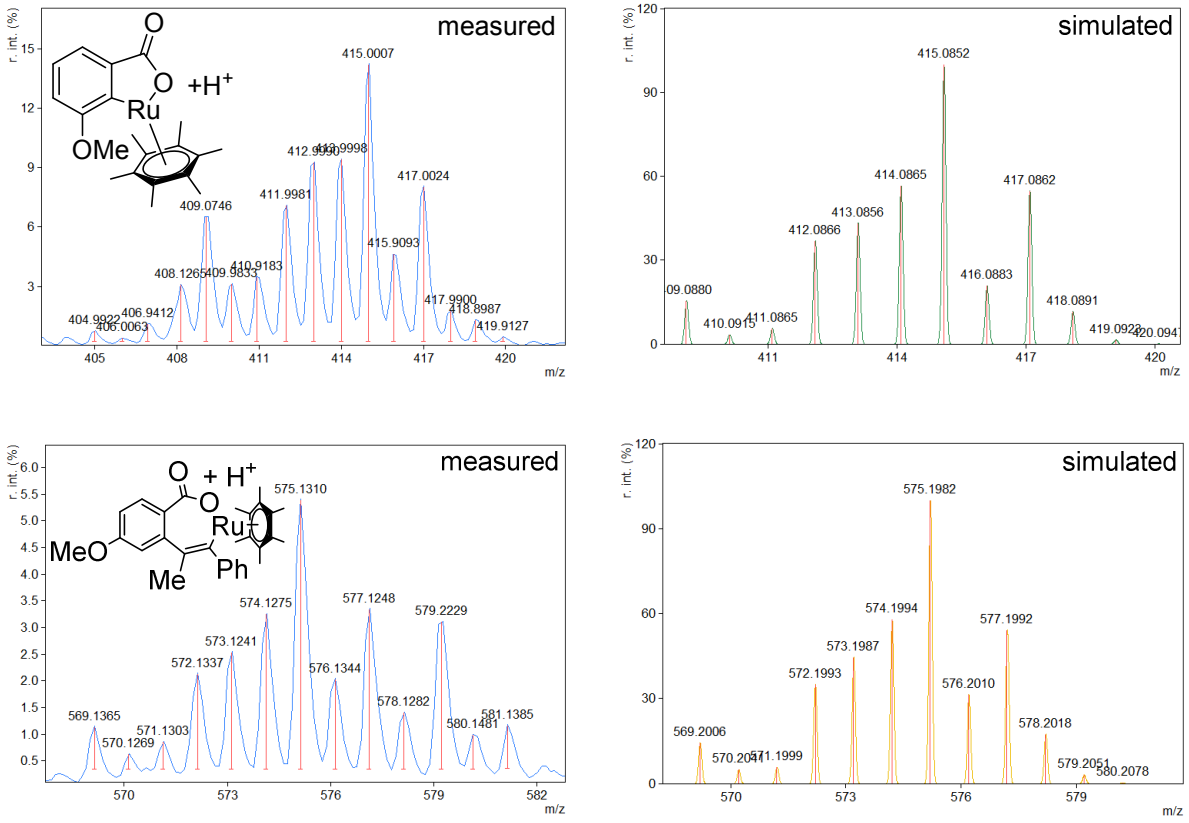
7.5.5. ESI-MS measurements



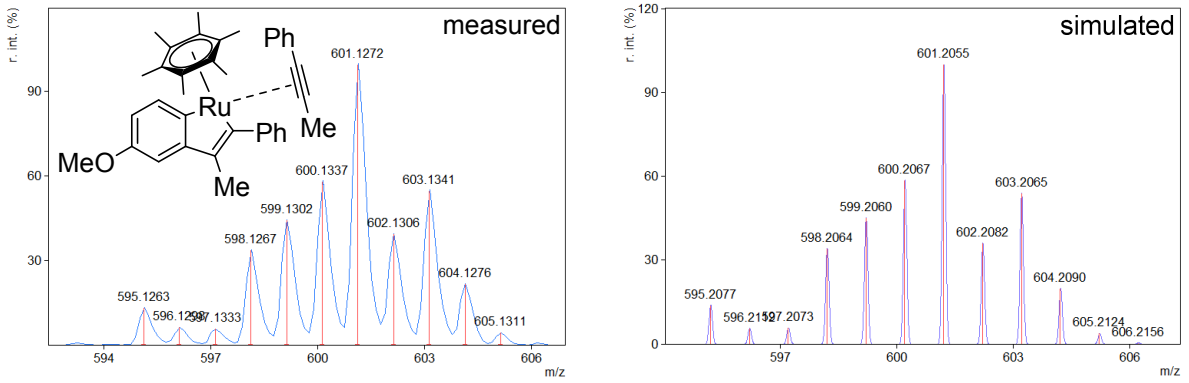
Scheme 56: Standard decarboxylative hydroarylation reaction set-up for ESI-MS experiments.



Scheme 57: ESI-MS measurement of the reaction mixture (t = 0, room temperature).

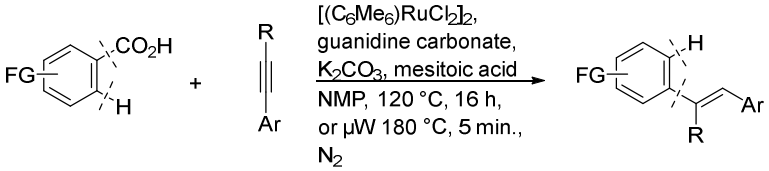


Scheme 58: ESI–MS measurement of the reaction mixture (t = 0, 120°C).



Scheme 59: ESI-MS measurement of the reaction mixture (t = 3h, 120°C).

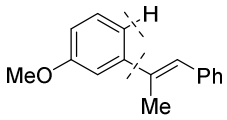
7.5.6. Synthesis of the corresponding vinylarenes via decarboxylative ortho-C-H hydroarylation of unsymmetrical alkynes



Standard procedure A – conventional hating: An oven-dried 20 mL vessel was charged with [(*hexamethylbenzene*)$RuCl_2$]$_2$ (13.4 mg, 0.02 mmol, 4 mol%), guanidine carbonate (4.6 mg, 0.025 mmol, 5 mol%), 2,4,6-trimethylbenzoic acid (82.9 mg, 0.5 mmol, 1 eq.), potassium carbonate (6.98 mg, 0.05 mmol, 10 mol%) and the benzoic acid (0.5 mmol). After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, degassed NMP (1 mL) and the internal alkyne (0.75 mmol) were added *via* syringe. The resulting mixture was stirred at 120 °C for 16 h. After the reaction was complete, the mixture was allowed to cool to room temperature. Lithium chloride (20%) was added and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The organic layers were washed with brine (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate/pentane or cyclohexane gradient) yielding the corresponding vinylarenes.

Standard procedure B – microwave conditions: An oven-dried 2 mL microwave vial was charged with [(*hexamethylbenzene*)$RuCl_2$]$_2$ (13.4 mg, 0.02 mmol, 4 mol%), guanidine carbonate (9 mg, 0.05 mmol, 10 mol%), 2,4,6-trimethylbenzoic acid (41 mg, 0.25 mmol, 0.5 eq.), and the benzoic acid (1 mmol). After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, degassed NMP (2 mL) and the internal alkyne (0.5 mmol) were added *via* syringe. The resulting mixture was first stirred in a water bath at 50 °C for 10 minutes then irradiated in the microwave at 180 °C for 5 minutes at a maximum power of 50 W, the air-jet cooled. Lithium chloride (20%) was added and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The organic layers were washed with brine (20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2, ethyl acetate/pentane or cyclohexane gradient) yielding the corresponding vinylarenes.

7.5.6.1. Synthesis of 1–((E)–2–(3–methoxyphenyl)–prop–1–enyl)–benzene



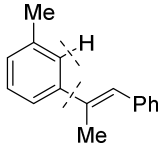
[CAS: 721428-17-7]

The title compound was prepared following general procedure A, starting from 4–methoxybenzoic acid (90 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (80 mg, 71%).

The title compound was prepared following general procedure B, starting from 4–methoxybenzoic acid (180 mg, 1 mmol) and 1–phenyl–1–propyne (59 mg, 64 µL, 0.5 mmol). The title compound was isolated as colorless liquid (85 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.39 (m, 4H), 7.19–7.30 (m, 2H), 7.08–7.13 (m, 1H), 7.03–7.06 (m, 1H), 6.79–6.85 (m, 2H), 3.83 (s, 3H), 2.25 ppm (d, J = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.6 (s), 145.5 (s), 138.2 (s), 137.3 (s), 129.2 (s), 129.1 (s), 128.2 (s), 127.8 (s), 126.5 (s), 118.6 (s), 112.4 (s), 112.0 (s), 77.3 (s), 76.7 (s), 55.3 (s), 17.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3022, 2996, 2941, 2834, 1597, 1576, 1485 ,1427, 1284, 1219, 1170, 852, 775 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 225 (19), 224 (100) [M^+], 223 (13), 209 (63), 208 (15), 194 (24), 193 (14); **HRMS** (EI–TOF) calcd. for $C_{16}H_{16}O$: 224.1201; found: 224.1209.

7.5.6.2. Synthesis of 1–methyl–3–((E)–1–phenylprop–1–en–2–yl)–benzene



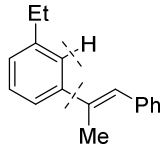
[CAS: 58662-09-2]

The title compound was prepared following general procedure A, starting from 2–methylbenzoic acid (69.5 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (75 mg, 72%).

The title compound was prepared following general procedure B, starting from 2–methylbenzoic acid (140 mg, 1 mmol) and 1–phenyl–1–propyne (59 mg, 64 µL, 0.5 mmol). The title compound was isolated as colorless liquid (73 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.42 (m, 6H), 7.24–7.31 (m, 2H), 7.13 (d, *J* = 7.0 Hz, 1H), 6.84 (d, *J* = 1.3 Hz, 1H), 2.42 (s, 3H), 2.30 ppm (d, *J* = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.0 (s), 138.4 (s), 137.8 (s), 137.5 (s), 129.1 (s), 128.2 (s), 128.1 (s), 127.9 (s), 127.5 (s), 126.8 (s), 126.4 (s), 123.1 (s), 77.3 (s), 76.7 (s), 21.6 (s), 17.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3023, 2958, 2927, 2871, 1601, 1493, 1455 ,1377, 781, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 209 (16), 208 (100) [M^+], 194 (13), 193 (85), 178 (27), 115 (21), 89 (12); **HRMS** (EI–TOF) calcd. for $C_{16}H_{16}$: 208.1243; found: 208.1252.

7.5.6.3. Synthesis of 1–ethyl–3–((E)–1–phenylprop–1–en–2–yl)–benzene

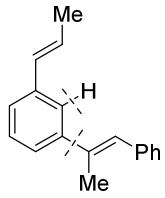


[CAS: 2079113-53-2]

The title compound was prepared following general procedure A, starting from 2–ethylbenzoic acid (75.1 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (89 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.33 (m, 6H) 7.21 (d, *J* = 8.0 Hz, 1H) 7.15 (s, 1H) 7.05 (s, 1H) 6.74 (d, *J* = 1.3 Hz, 1H) 2.60 (d, *J* = 7.5 Hz, 2H) 2.19 (d, *J* = 1.5 Hz, 3H) 1.18 ppm (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.2 (s), 144.0 (s), 138.4 (s), 137.6 (s), 129.1 (s), 128.3 (s), 128.1 (s), 127.5 (s), 126.8 (s), 126.4 (s), 125.6 (s), 123.4 (s), 77.3 (s), 76.7 (s), 29.0 (s), 17.6 (s), 15.7 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3023, 2958, 2927, 2871, 1601, 1493, 1455 ,1377, 781, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 223 (21), 222 (100) [M^+], 208 (9), 207 (44), 193 (14), 129 (10), 115 (26), 89 (12); **HRMS** (EI–TOF) calcd. for $C_{17}H_{18}$: 222.1400; found 222.1409.

7.5.6.4. Synthesis of 1–((Z)–1–phenylprop–1–en–2–yl)–3–(E)–prop–1–enyl)–benzene

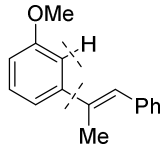


[CAS: 2079113-54-3]

The title compound was prepared following general procedure A, starting from 2–allylbenzoic acid (83 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (75 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (t, J = 2.0 Hz, 1H), 7.34–7.41 (m, 5H), 7.22–7.34 (m, 4H), 6.84 (d, J = 1.5 Hz, 1H), 6.42–6.51 (m, 1H), 6.30 (dd, J = 15.7, 6.7 Hz, 1H), 2.29 (d, J = 1.5 Hz, 3H), 1.92 ppm (dd, J = 6.5, 1.8 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 143.9 (s), 138.0 (s), 137.6 (s), 137.2 (s), 130.7 (s), 128.8 (s), 128.1 (s), 127.8 (s), 127.3 (s), 126.1 (s), 125.6 (s), 124.3 (s), 124.2 (s), 123.4 (s), 76.9 (s), 76.7 (s), 76.4 (s), 18.2 (s), 17.2 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3021, 2913, 1700, 1597, 1576, 1491 ,1443, 1377, 961, 771 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 235 (19), 234 (100) [M^{+}], 220 (8), 219 (45), 204 (9), 191 (10), 115 (13); **HRMS** (EI–TOF) calcd. for $C_{18}H_{18}$: 234.1407; found 234.1409.

7.5.6.5. Synthesis of 1–methoxy–3–((Z)–1–phenylprop–1–en–2–yl)–benzene



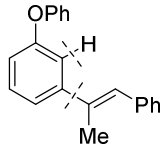
[CAS: 721428-17-7]

The title compound was prepared following general procedure A, starting from 2–methoxybenzoic acid (77 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (88 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, J = 2.3 Hz, 4H), 7.12–7.23 (m, 2H), 7.01–7.06 (m, 1H), 6.95 –6.99 (m, 1H), 6.72–6.78 (m, 2H), 3.75 (s, 3H), 2.18 ppm (d, J = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.6 (s), 145.5 (s), 138.2 (s), 137.3 (s), 129.2 (s), 129.1 (s), 128.2 (s), 127.8 (s), 126.5 (s), 118.6 (s), 112.4 (s), 112.0 (s), 77.3 (s), 76.7 (s), 55.3 (s), 17.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3022, 2996, 2941, 2834, 1597, 1576, 1485 ,1427, 1284, 1219, 1170, 852, 775 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 225 (19), 224 (100) [M^{+}], 223 (13), 209 (63),

208 (15), 194 (24), 193 (14); **HRMS** (EI–TOF) calcd. for $C_{16}H_{16}O$: 224.1201; found 224.1208.

7.5.6.6. Synthesis of 1–phenoxy–3–((Z)–1–phenylprop–1–en–2–yl)–benzene



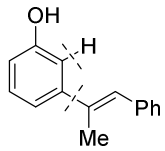
[CAS: 2079113-55-4]

The title compound was prepared following general procedure A, starting from 2–phenoxybenzoic acid (109 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (130 mg, 99%).

The title compound was prepared following general procedure B, starting from 2–phenoxybenzoic acid (218 mg, 1 mmol) and 1–phenyl–1–propyne (59 mg, 64 µL, 0.5 mmol). The title compound was isolated as colorless liquid (110 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.42 (m, 8H), 7.27–7.30 (m, 1H), 7.22 (s, 1H) 7.10–7.15 (m, 1H), 7.06 (d, J = 8.3 Hz, 2H), 6.88–7.00 (m, 1H), 6.86 (s, 1H), 2.27 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.3 (s), 157.1 (s), 145.9 (s), 138.1 (s), 136.7 (s), 129.7 (s), 129.5 (s), 129.1 (s), 128.2 (s), 128.2 (s), 128.1 (s), 126.6 (s), 125.3 (s), 123.1 (s), 121.0 (s), 118.7 (s), 117.6 (s), 116.8 (s), 77.3 (s), 77.2 (s), 76.7 (s), 17.4 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3052, 3021, 2915, 1591, 1572, 1485, 1431, 127, 1218, 1163,1071, 1086, 916, 749 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 287 (19), 286 (100) [M^+], 271 (40), 193 (20), 178 (20), 77 (15); **HRMS** (EI–TOF) calcd. for $C_{21}H_{18}O$: 286.1358; found 286.1358.

7.5.6.7. Synthesis of 1–hydroxy–3–((Z)–1–phenylprop–1–en–2–yl)–benzene



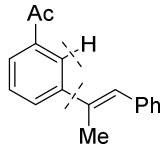
[CAS: 2079113-56-5]

The title compound was prepared following general procedure A, starting from 2–hydroxybenzoic acid (90 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid as the corresponding

methylether after treatment with MeI (5 eq.) and K_2CO_3 (2 eq.) at 60 °C in NMP (93 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.39 (m, 4H), 7.19–7.30 (m, 2H), 7.08–7.13 (m, 1H), 7.03–7.06 (m, 1H), 6.79–6.85 (m, 2H), 3.83 (s, 3H), 2.25 ppm (d, *J* = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.6 (s), 145.5 (s), 138.2 (s), 137.3 (s), 129.2 (s), 129.1 (s), 128.2 (s), 127.8 (s), 126.5 (s), 118.6 (s), 112.4 (s), 112.0 (s), 77.3 (s), 76.7 (s), 55.3 (s), 17.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3022, 2996, 2941, 2834, 1597, 1576, 1485 ,1427, 1284, 1219, 1170, 852, 775 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 225 (19), 224 (100) [M^+], 223 (13), 209 (63), 208 (15), 194 (24), 193 (14); **HRMS** (EI–TOF) calcd. for $C_{16}H_{16}O$: 224.1201; found 224.1209.

7.5.6.8. Synthesis of 1–(3–((E)–1–phenylprop–1–en–2–yl)–phenyl)–ethanone

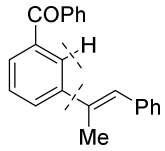


[CAS: 568572-33-8]

The title compound was prepared following general procedure A, starting from 2–acetylbenzoic acid (83 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (91 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.18 (m, 1H), 7.89 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.74 (dt, *J* = 8.1, 1.5 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.37–7.43 (m, 4H), 7.29 (dt, *J* = 6.0, 2.9 Hz, 1H), 6.88–6.92 (m, 1H), 2.66 (s, 3H), 2.33 ppm (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 198.3 (s), 144.5 (s), 137.9 (s), 137.2 (s), 136.5 (s), 130.6 (s), 129.1 (s), 128.7 (s), 128.6 (s), 128.2 (s), 128.2 (s), 127.1 (s), 126.7 (s), 125.7 (s), 77.3 (s), 77.0 (s), 76.7 (s), 26.8 (s), 17.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3061, 3022, 1681, 1596, 1577, 1491, 1423, 1355, 1283, 1259, 1228, 792, 750, 692 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 237 (26), 236 (100) [M^+], 221 (64), 193 (54), 178 (39), 50 (13), 43 (57); **HRMS** (EI–TOF) calcd. for $C_{17}H_{16}O$: 236.1200; found 236.1201.

7.5.6.9. Synthesis of phenyl–(3–((E)–1–phenylprop–1–en–2–yl)–phenyl)–methanone

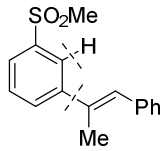


[CAS: 2079113-61-2]

The title compound was prepared following general procedure A, starting from 2–benzoylbenzoic acid (83 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless solid (131 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (t, *J* = 1.9 Hz, 1H), 7.86 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.76 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.70 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.59–7.65 (m, 1H) 7.47–7.54 (m, 3H), 7.35–7.41 (m, 4H), 7.24–7.30 (m, 2H), 6.90 (d, *J* = 1.5 Hz, 1H), 2.32 ppm (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 196.9 (s), 144.2 (s), 137.9 (s), 137.7 (s), 137.6 (s), 136.5 (s), 132.5 (s), 130.1 (s), 129.9 (s), 129.9 (s), 129.1 (s), 128.9 (s), 128.7 (s), 128.3 (s), 128.2 (s), 128.2 (s), 127.4 (s), 126.7 (s), 77.3 (s), 77.2 (s), 76.7 (s), 17.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3059, 3024, 1656, 1595, 1576, 1491, 1446, 1337, 1317, 1284, 1239, 1177, 1144, 1074, 948, 912 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 299 (22), 298 (100) [M^+], 280 (23), 221 (10), 178 (72), 105 (67), 77 (48); **HRMS** (EI–TOF) calcd. for $C_{22}H_{18}O$: 298.1351; found 298.1358; **m.p.**: 64–67 °C.

7.5.6.10. Synthesis of 1–(methylsulfonyl)–3–((E)–1–phenylprop–1–en–2yl)–benzene



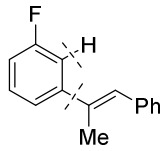
[CAS: 2079113-62-3]

The title compound was prepared following general procedure A, starting from 2–methylsulfonylbenzoic acid (83.2 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (130 mg, 95%).

The title compound was prepared following general procedure B, starting from 2–methylsulfonylbenzoic acid (168 mg, 1 mmol) and 1–phenyl–1–propyne (59 mg, 64 µL, 0.5 mmol). The title compound was isolated as colorless liquid (90 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (t, *J* = 1.9 Hz, 1H), 7.87 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.81 (dt, *J* = 8.1, 1.5 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.34–7.44 (m, 4H), 7.30 (d, *J* = 6.8 Hz, 1H), 6.90–6.96 (m, 1H), 3.11 (s, 3H), 2.32 ppm (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 145.4 (s), 140.7 (s), 137.4 (s), 135.5 (s), 131.1 (s), 129.8 (s), 129.4 (s), 129.1 (s), 128.3 (s), 127.0 (s), 125.7 (s), 124.7 (s), 77.3 (s), 76.7 (s), 44.5 (s), 17.4 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3059, 3021, 2927, 1297, 1142,1097, 1086, 955, 760, 744 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 272 (100) [M^+], 85 (63), 68 (47), 57 (46), 54 (68), 43 (61), 41 (72); **HRMS** (EI–TOF) calcd. for $C_{16}H_{16}O_2S$: 272.0871; found 272.0861.

7.5.6.11. Synthesis of 1–fluoro–3–((Z)–1–phenylprop–1–en–2–yl)–benzene

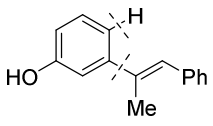


[CAS: 2079113-63-4]

The title compound was prepared following general procedure A, starting from 2–fluorobenzoic acid (71 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless solid (86 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.43 (m, 6H), 7.27–7.31 (m, 1H), 7.20–7.26 (m, 1H), 6.95–7.03 (m, 1H), 6.87 (s, 1H), 2.28 ppm (d, *J* = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.9 (d, *J* = 244.3 Hz), 146.2 (d, *J* = 7.3 Hz), 137.9 (s), 136.2 (d, *J* = 2.7 Hz), 129.7 (d, *J* = 8.2 Hz), 129.1 (s), 128.5 (s), 128.2 (s), 126.7 (s), 121.6 (d, *J* = 2.7 Hz), 113.9 (d, *J* = 20.89 Hz), 112.9 (d, *J* = 21.8 Hz), 17.4 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -113.55 ppm; **IR** (ATR): $\tilde{\nu}$ = 2980, 1718, 1371, 1207, 1157 ,1029, 781 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 213 (15), 212 (100) [M^+], 197 (62), 196 (19), 177 (16), 115 (13), 50 (12); **HRMS** (EI–TOF) calcd. for $C_{15}H_{13}F$: 212.1005; found 212.1005.

7.5.6.12. Synthesis of 1–((E)–2–(3–hydroxyphenyl)–prop–1–enyl)–benzene



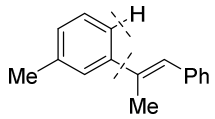
[CAS: 2079113-56-5]

The title compound was prepared following general procedure A, starting from 4–hydroxybenzoic acid (70 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL,

0.75 mmol). The title compound was isolated as colorless liquid as the corresponding methylether after treatment with MeI (5 eq.) and K_2CO_3 (2 eq.) at 60 °C in NMP (79 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.42 (m, 4H), 7.21–7.34 (m, 2H), 7.11–7.16 (m, 1H), 7.05–7.09 (m, 1H), 6.82–6.90 (m, 2H), 3.86 (s, 3H), 2.28 ppm (d, J = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.6 (s), 145.5 (s), 138.2 (s), 137.3 (s), 129.2 (s), 129.1 (s), 128.2 (s), 127.8 (s), 126.5 (s), 118.6 (s), 112.4 (s), 112.0 (s), 77.3 (s), 76.7 (s), 55.3 (s), 17.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3022, 2996, 2941, 2834, 1597, 1576, 1485 ,1427, 1284, 1219, 1170, 852, 775 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 225 (19), 224 (100) [M$^+$], 223 (13), 209 (63), 208 (15), 194 (24), 193 (14); **HRMS** (EI–TOF) calcd. for $C_{16}H_{16}O$: 224.1201; found 224.1208.

7.5.6.13. Synthesis of 1–((E)–2–m–tolylprop–1–enyl)–benzene



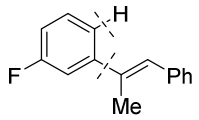
[CAS: 58662-09-2]

The title compound was prepared following general procedure A, starting from 4–methylbenzoic acid (75.1 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (65 mg, 62%).

The title compound was prepared following general procedure B, starting from 4–methylbenzoic acid (150.2 mg, 1 mmol) and 1–phenyl–1–propyne (59 mg, 64 µL, 0.5 mmol). The title compound was isolated as colorless liquid (68 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.32 (m, 6H), 7.13–7.20 (m, 2H), 7.02 (d, J = 7.0 Hz, 1H), 6.73 (d, J = 1.3 Hz, 1H), 2.30 (s, 3H), 2.18 ppm (d, J = 1.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.0 (s), 138.4 (s), 137.8 (s), 137.5 (s), 129.1 (s), 128.2 (s), 128.1 (s), 127.9 (s), 127.5 (s), 126.8 (s), 126.4 (s), 123.1 (s), 77.3 (s), 76.7 (s), 21.5 (s), 17.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3021, 2917, 1600, 1582, 1499, 1442, 1376, 859, 779, 754, 694 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 209 (16), 208 (100) [M$^+$], 194 (13), 193 (85), 178 (27), 115 (21), 89 (12); **HRMS** (EI–TOF) calcd. for $C_{16}H_{16}$: 208.1243; found 208.1250.

7.5.6.14. Synthesis of 1–((E)–2–(3–fluorophenyl)–prop–1–enyl)–benzene



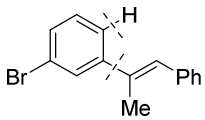
[CAS: 2079113-63-4]

The title compound was prepared following general procedure A, starting from 4–fluorobenzoic acid (71 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (60 mg, 56%).

The title compound was prepared following general procedure B, starting from 4–fluorobenzoic acid (142 mg, 1 mmol) and 1–phenyl–1–propyne (59 mg, 64 µL, 0.5 mmol). The title compound was isolated as colorless liquid (75 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 77.39–7.43 (m, 1H), 7.35–7.39 (m, 3H), 7.30–7.34 (m, 2H), 7.20–7.30 (m, 3H), 6.95–7.04 (m, 1H), 6.88 (s, 1H), 2.28 ppm (d, J = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 162.9 (d, J = 244.3 Hz), 146.2 (d, J = 7.3 Hz), 137.9 (s), 136.2 (d, J = 2.7 Hz), 129.7 (d, J = 8.2 Hz), 129.1 (s), 128.5 (s), 128.2 (s), 126.7 (s), 121.6 (d, J = 2.7 Hz), 113.9 (d, J = 20.89 Hz), 112.9 (d, J = 21.8 Hz), 17.4 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -113.55 ppm; **IR** (ATR): $\tilde{\nu}$ = 2980, 1718, 1371, 1207, 1157 ,1029, 781 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 213 (15), 212 (100) [M^+], 197 (62), 196 (19), 177 (16), 115 (13), 50 (12); **HRMS** (EI–TOF) calcd. for $C_{15}H_{13}F$: 212.1005; found 212.1000.

7.5.6.15. Synthesis of 1–((E)–2–(3–bromophenyl)–prop–1–enyl)–benzene



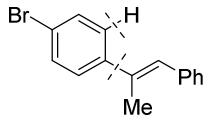
[CAS: 1361147-98-9]

The title compound was prepared following general procedure A, starting from 4–bromobenzoic acid (103 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (78 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (t, J = 1.9 Hz, 1H), 7.41–7.47 (m, 2H), 7.34–7.41 (m, 4H), 7.22–7.31 (m, 2H), 6.84 (s, 1H), 2.27 ppm (d, J = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 146.1 (s), 137.8 (s), 136.1 (s), 130.0 (s), 129.8 (s), 129.1 (s), 128.8 (s), 128.2 (s), 126.8 (s), 124.6 (s), 122.5 (s), 77.3 (s), 76.7 (s), 17.4 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3060, 3021,

1589, 1558, 1474 ,1441, 1247, 1062, 863, 777, 742, 692 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 275 (18), 274 (100) [M^+], 273 (18), 272 (96), 259 (18), 193 (33), 178 (60); **HRMS** (EI–TOF) calcd. for $C_{15}H_{13}{}^{79}Br$: 272.0201; found 272.0189. calcd. for $C_{15}H_{13}{}^{81}Br$: 274.0180; found 274.0163.

7.5.6.16. Synthesis of 1–((E)–2–(4–bromophenyl)–prop–1–enyl)–benzene

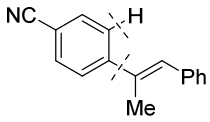


[CAS: 580002-13-7]

The title compound was prepared following general procedure A, starting from 3–bromobenzoic acid (103 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless solid (58 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.51 (m, 2H), 7.31–7.40 (m, 5H), 7.22–7.28 (m, 1H), 6.81 (s, 1H), 2.24 ppm (d, *J* = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 142.8 (s), 137.9 (s), 136.2 (s), 131.3 (s), 129.1 (s), 128.2 (s), 128.1 (s), 127.6 (s), 126.7 (s), 121.0 (s), 17.3 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3060, 3021, 1589, 1558, 1474 ,1441, 1247, 1062, 863, 777, 742, 692 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 275 (18), 274 (100) [M^+], 273 (18), 272 (96), 259 (18), 193 (33), 178 (60); **HRMS** (EI–TOF) calcd. for $C_{15}H_{13}{}^{79}Br$: 272.0201; found 272.0201. calcd. for $C_{15}H_{13}{}^{81}Br$: 274.0180; found 274.0200; **m.p.**: 79–80 °C.

7.5.6.17. Synthesis of 4–((E)–1–phenylprop–1–en–2–yl)–benzonitrile



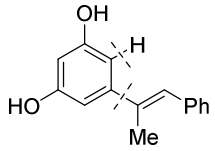
[CAS: 2079113-70-3]

The title compound was prepared following general procedure A, starting from 3–cyanobenzoic acid (75.1 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless solid (46 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.69 (m, 4H), 7.36–7.44 (m, 4H), 7.27–7.33 (m, 1H), 6.93 (s, 1H), 2.30 ppm (d, *J* = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.4 (s), 137.4 (s), 135.7 (s), 132.2 (s), 130.4 (s), 129.1 (s), 128.3 (s), 127.1 (s), 126.6 (s), 119.0 (s), 110.5 (s), 17.1 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2950, 2226, 1598, 1501, 1444, 1407, 1377, 1180, 1117,

1080, 1062, 842, 827, 758, 711, 696 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 220 (25), 219.(100) [M^+], 218 (15), 204 (78), 203 (14), 115 (14), 50 (14); **HRMS** (EI–TOF) calcd. for $C_{15}H_{13}{}^{79}Br$: 272.0201; found 272.0201. calcd. for $C_{16}H_{13}N$: 219.1048; found 298.1053; **m.p.**: 35–36 °C.

7.5.6.18. Synthesis of 1,2–dihydroxy–5–((E)–1–phenylprop–1–enyl)–benzene

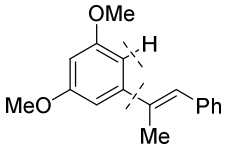


[CAS: 2079113-73-6]

The title compound was prepared following general procedure A, starting from 2,4–dihydroxybenzoic acid (103 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid as the corresponding methylether after treatment with MeI (5 eq.) and K_2CO_3 (2 eq.) at 60 °C in NMP (104 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.50 (m, 4H), 7.22–7.30 (m, 1H), 6.79–6.99 (m, 1H), 6.69 (d, *J* = 2.3 Hz, 2H), 6.37–6.50 (m, 1H), 3.85 (s, 6H), 2.27 ppm (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 161.0 (s), 146.6 (s), 138.4 (s), 137.7 (s), 129.5 (s), 128.5 (s), 128.2 (s), 126.8 (s), 104.8 (s), 99.4 (s), 77.6 (s), 77.5 (s), 77.3 (s), 55.7 (s), 17.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2997, 2943, 2837, 1588, 1454 ,1421, 1348, 1329, 1203, 1152, 1067, 1048, 833, 751, 699 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 255 (19), 254 (100) [M^+], 253 (32), 239 (56), 224 (14), 223 (12), 208 (14); **HRMS** (EI–TOF) calcd. for $C_{17}H_{18}O_2$: 254.1307; found 254.1319.

7.5.6.19. Synthesis of 1,2–dimethoxy–5–((E)–1–phenylprop–1–enyl)–benzene



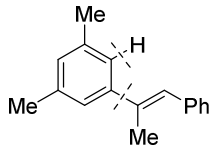
[CAS: 2079113-76-9]

The title compound was prepared following general procedure A, starting from 2,4–dimethoxybenzoic acid (93 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (78 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.50 (m, 4H), 7.22–7.30 (m, 1H), 6.79–6.99 (m, 1H), 6.69 (d, *J* = 2.3 Hz, 2H), 6.37–6.50 (m, 1H), 3.85 (s, 6H), 2.27 ppm (d, *J* = 1.5 Hz, 3H); **^{13}C**

NMR (101 MHz, $CDCl_3$): δ = 161.0 (s), 146.6 (s), 138.4 (s), 137.7 (s), 129.5 (s), 128.5 (s), 128.2 (s), 126.8 (s), 104.8 (s), 99.4 (s), 77.6 (s), 77.5 (s), 77.3 (s), 55.7 (s), 17.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2997, 2943, 2837, 1588, 1454 ,1421, 1348, 1329, 1203, 1152, 1067, 1048, 833, 751, 699 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 255 (19), 254 (100) [M^+], 253 (32), 239 (56), 224 (14), 223 (12), 208 (14); **HRMS** (EI–TOF) calcd. for $C_{17}H_{18}O_2$: 254.1307; found 254.1316.

7.5.6.20. Synthesis of 1,3–dimethyl–5–((Z)–1–phenylprop–1–en–2–yl)–benzene

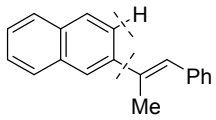


[CAS: 2079113-76-2]

The title compound was prepared following general procedure A, starting from 2,4–dimethylbenzoic acid (76 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (93 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 1.8 Hz, 4H), 7.14 (s, 1H), 7.06 (s, 2H), 6.86 (s, 1H), 6.72 (d, *J* = 1.3 Hz, 1H), 2.27 (s, 6H), 2.18 ppm (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.1 (s), 138.4 (s), 137.7 (s), 137.6 (s), 129.1 (s), 128.8 (s), 128.8 (s), 128.5 (s), 128.1 (s), 127.8 (s), 127.4 (s), 126.3 (s), 126.0 (s), 125.7 (s), 123.9 (s), 77.3 (s), 76.7 (s), 21.4 (s), 21.3 (s), 17.6 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3021, 2916, 2861, 1599, 1493, 1443, 1375, 841, 749, 696 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 223 (19), 222 (100) [M^+], 208 (9), 207 (52), 192 (17), 115 (14), 91 (9); **HRMS** (EI–TOF) calcd. for $C_{17}H_{18}$: 222.1409; found 222.1413.

7.5.6.21. Synthesis of 2–((E)–1–phenylprop–1–en–2–yl)–naphthalene

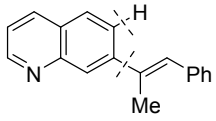


[CAS: 52520-45-3]

The title compound was prepared following general procedure A, starting from 2–naphthoic acid (88 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless solid (50 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 1.3 Hz, 1H), 7.83–7.92 (m, 3H), 7.71–7.78 (m, 1H), 7.40–7.54 (m, 6H), 7.30 (td, *J* = 6.0, 2.9 Hz, 1H), 7.04 (d, *J* = 1.0 Hz, 1H), 2.42 ppm (d, *J* = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.1 (s), 138.4 (s), 137.2 (s), 133.5 (s), 132.7 (s), 129.3 (s), 128.3 (s), 128.2 (s), 128.2 (s), 127.8 (s), 127.6 (s), 126.6 (s), 126.2 (s), 125.8 (s), 124.7 (s), 124.4 (s), 17.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3055, 1595, 1571, 1486, 1444, 1386, 1275, 1130, 1072, 853, 810, 742, 716, 695 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 245 (24), 244 (100) [M^+], 243 (11), 230 (11), 229 (61), 228 (20), 115 (9); **HRMS** (EI–TOF) calcd. for $C_{19}H_{16}$: 244.1252; found 244.1244; **m.p.**: 137–139 °C.

7.5.6.22. Synthesis of 7–((E)–1–phenylprop–1–en–2–yl)–quinoline

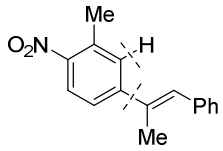


[CAS: 2079113-84-9]

The title compound was prepared following general procedure A, starting from 6–quinolinecarboxylic acid (89.3 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as orange solid (44 mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.24 (d, *J* = 1.0 Hz, 1H), 8.16 (ddd, *J* = 8.3, 1.5, 0.8 Hz, 1H), 7.82 (d, *J* = 1.3 Hz, 2H), 7.36–7.45 (m, 5H), 7.30 (td, *J* = 5.8, 2.8 Hz, 1H), 7.10 (d, *J* = 1.3 Hz, 1H), 2.43 ppm (d, *J* = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 150.7 (s), 148.4 (s), 144.7 (s), 138.0 (s), 136.5 (s), 135.7 (s), 129.3 (s), 129.2 (s), 128.2 (s), 127.5 (s), 127.4 (s), 126.8 (s), 126.0 (s), 125.1 (s), 120.8 (s), 17.3 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3021, 2917, 2340, 1740, 1614, 1593, 1495, 1441, 1383, 1320, 835, 826, 753, 714, 693 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 245 (25), 244 (100) [M^+], 229 (12), 202 (3), 115 (4); **HRMS** (EI–TOF) calcd. for $C_{18}H_{15}N$: 245.1204; found 245.1175; **m.p.**: 50–51 °C.

7.5.6.23. Synthesis of 1–((E)–1–(3–methyl–4–nitrophenyl)–prop–1–enyl)–benzene

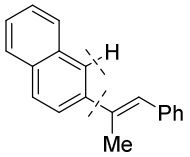


[CAS: 2079113-87-2]

The title compound was prepared following general procedure A, starting from 2–methyl-3-nitrobenzoic acid (91 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as orange solid (69 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–8.08 (m, 1H), 7.46–7.50 (m, 2H), 7.36–7.45 (m, 4H), 7.31 (d, *J* = 6.8 Hz, 1H), 6.91–6.97 (m, 1H), 2.68 (s, 3H), 2.31 ppm (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.9 (s), 147.6 (s), 137.4 (s), 135.5 (s), 134.0 (s), 130.6 (s), 130.2 (s), 129.1 (s), 128.3 (s), 127.1 (s), 125.0 (s), 124.3 (s), 77.3 (s), 76.7 (s), 21.0 (s), 17.3 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3025, 2997, 2915, 2858, 1599, 1578, 1510, 1488, 1445, 1337, 1813, 1207, 1184, 1069, 870, 827, 760, 753, 701 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 254 (19), 253 (100) [M^+], 238 (9), 236 (15), 206 (8), 192 (18), 191 (11); **HRMS** (EI–TOF) calcd. for $C_{16}H_{15}NO_2$: 253.1103; found 253.1110; **m.p.**: 61–62 °C.

7.5.6.24. Synthesis of 2–((E)–1–phenylprop–1–en–2–yl)–naphthalene



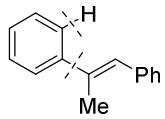
[CAS: 52520-45-3]

The title compound was prepared following general procedure A, starting from 1–naphthoic acid (88 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless solid (109 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.99 (m, 1H), 7.82–7.91 (m, 3H), 7.74 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.49 (ddd, *J* = 7.6, 5.5, 1.8 Hz, 2H), 7.39–7.45 (m, 4H), 7.29 (d, *J* = 2.8 Hz, 1H), 7.03 (d, *J* = 1.3 Hz, 1H), 2.42 ppm (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.1 (s), 138.3 (s), 137.2 (s), 133.4 (s), 132.7 (s), 129.2 (s), 128.2 (s), 128.2 (s), 128.1 (s), 127.8 (s), 127.5 (s), 126.5 (s), 126.2 (s), 125.8 (s), 124.7 (s), 124.4 (s), 77.3 (s), 76.7 (s), 17.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3055, 1595, 1571, 1486, 1444, 1386, 1275, 1130, 1072, 853,

810, 742, 716, 695 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 245 (24), 244 (100) [M^+], 243 (11), 230 (11), 229 (61), 228 (20), 115 (9); **HRMS** (EI–TOF) calcd. for $C_{19}H_{16}$: 244.1252; found 244.1246; **m.p.**: 137–138 °C.

7.5.6.25. Synthesis of (E)–1,2–diphenylprop–1–ene



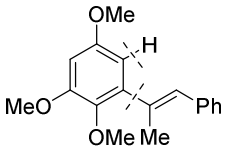
[CAS: 833-81-8]

The title compound was prepared following general procedure A, starting from benzoic acid (61 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless liquid (39 mg, 40%).

The title compound was prepared following general procedure B, starting from 4–fluorobenzoic acid (150.2 mg, 1 mmol) and 1–phenyl–1–propyne (59 mg, 64 µL, 0.5 mmol). The title compound was isolated as colorless liquid (58 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.60 (m, 2H), 7.20–7.45 (m, 8H), 6.85 (d, *J* = 1.0 Hz, 1H), 2.30 ppm (d, *J* = 1.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.0 (s), 138.4 (s), 137.4 (s), 129.1 (s), 128.3 (s), 128.1 (s), 127.7 (s), 127.2 (s), 126.4 (s), 126.0 (s), 17.5 ppm (s). The analytical data matched those reported in the literature.[356],[357],[358]

7.5.6.26. Synthesis of 1,2,5–trimethoxy–3–((E)–1–phenylprop–1–en–2–yl)–benzene



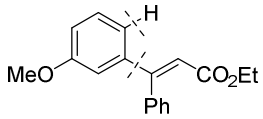
[CAS: 2079113-93-0]

The title compound was prepared following general procedure A, starting from 2,4,5–trimethoxybenzoic acid (107 mg, 0.5 mmol) and 1–phenyl–1–propyne (88 mg, 95.7 µL, 0.75 mmol). The title compound was isolated as colorless solid (86 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.45 (m, 4H), 7.21–7.31 (m, 2H), 6.59 (d, *J* = 1.5 Hz, 1H), 6.48 (d, *J* = 3.0 Hz, 1H), 6.40 (d, *J* = 3.0 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 2.28 ppm (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.1 (s), 153.7 (s), 140.5 (s), 138.3 (s), 137.5 (s), 129.7 (s), 129.3 (s), 128.5 (s), 126.8 (s), 104.8 (s), 99.3 (s), 77.6 (s),

77.3 (s), 61.2 (s), 56.2 (s), 55.9 (s), 19.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2939, 2837, 1588, 1482, 1463, 1419, 1338, 1274, 1224, 1199, 1174, 1157,1135, 1100, 1006, 830, 773, 749, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 285 (20), 284 (100) [M^+], 269 (48), 253 (15), 241 (10), 103 (9), 91 (14); **HRMS** (EI–TOF) calcd. for $C_{18}H_{20}O_3$: 284.1412; found 284.1410; **m.p.**: 71–73 °C.

7.5.6.27. Synthesis of ethyl–(2E)–3–(3–methoxyphenyl)–3–phenylprop–2–enoate



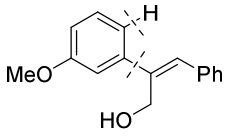
[CAS: 329968-30-1]

The title compound was prepared following general procedure A, starting from 4–methoxybenzoic acid (90 mg, 0.5 mmol) and ethyl–3–phenylpropiolate (133 mg, 127 µL, 0.75 mmol). The title compound was isolated as colorless liquid (102 mg, 72%).

The title compound was prepared following general procedure B, starting from 4–methoxybenzoic acid (180 mg, 1 mmol) and ethyl–3–phenylpropiolate (88.7 mg, 84.7 µL, 0.5 mmol). The title compound was isolated as colorless liquid (58 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.46 (m, 6H), 7.01–7.12 (m, 3H), 6.90 (dd, *J* = 8.2, 2.6 Hz, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 3H), 1.22 ppm (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.5 (s), 159.7 (s), 138.3 (s), 135.6 (s), 135.1 (s), 131.3 (s), 129.7 (s), 128.4 (s), 128.3 (s), 128.2 (s), 118.9 (s), 113.8 (s), 112.0 (s), 61.3 (s), 55.3 (s), 13.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2967, 2836, 1603, 1718, 1596, 1578, 1488, 1371, 1287, 1215, 1184, 1156, 1023, 691 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 283 (19), 282 (100) [M^+], 237 (11), 209 (30), 194 (10), 135 (12), 107 (11); **HRMS** (EI–TOF) calcd. for $C_{18}H_{18}O_2$: 282.1256; found 282.1249.

7.5.6.28. Synthesis of (Z)–2–(3–Methoxyphenyl)–3–phenylprop–2–en–1–ol



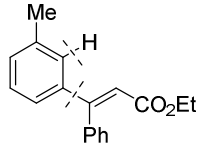
[CAS: 1694650-56-0]

The title compound was prepared following general procedure A, starting from 4–methoxybenzoic acid (90 mg, 0.5 mmol) and 1–(3–hydroxyprop–1–ynyl)–benzene (105 mg, 110 µL, 0.75 mmol). The title compound was isolated as colorless liquid (96 mg, 80%).

The title compound was prepared following general procedure B, starting from 4–methoxybenzoic acid (180 mg, 1 mmol) and 1–(3–hydroxyprop–1–ynyl)–benzene (70 mg, 73.3 µL, 0.5 mmol). The title compound was isolated as colorless liquid (63 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.49 (m, 7H), 7.17–7.21 (m, 1H), 7.13–7.16 (m, 1H), 6.99 (s, 1H), 6.90 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 4.71 (s, 2H), 3.87 (s, 3H), 1.62 ppm (br. s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 159.9 (s), 142.1 (s), 140.0 (s), 136.8 (s), 131.4 (s), 129.7 (s), 128.9 (s), 128.4 (s), 127.4 (s), 119.0 (s), 113.1 (s), 112.5 (s), 60.4 (s), 55.3 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3392, 3023, 2938, 2834, 1713, 1597, 1576, 1487, 1447, 1286, 1266, 1228, 1169, 1033, 1010, 862, 777, 755, 694 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 241 (16), 240 (100) [M^+], 223 (30), 135 (19), 121 (7); **HRMS** (EI–TOF) calcd. for $C_{16}H_{16}O_2$: 240.1150; found 240.1156.

7.5.6.29. Synthesis of ethyl–(2E)–3–(3–methylphenyl)–3–phenylprop–2–enoate

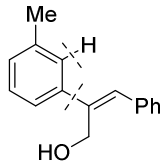


[CAS: 329968-28-7]

The title compound was prepared following general procedure A, starting from 2–methoxybenzoic acid (69 mg, 0.5 mmol) and ethyl–3–phenylpropiolate (133 mg, 127 µL, 0.75 mmol). The title compound was isolated as colorless liquid (59 mg, 44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.43 (m, 4H), 7.28–7.34 (m, 4H), 7.18 (ddd, *J* = 4.6, 3.5, 1.5 Hz, 1H), 7.05 (s, 1H), 4.30 (q, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 1.22 ppm (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.7 (s), 138.3 (s), 136.8 (s), 135.8 (s), 135.4 (s), 130.9 (s), 129.1 (s), 128.6 (s), 128.4 (s), 128.2 (s), 128.2 (s), 127.0 (s), 123.5 (s), 61.3 (s), 21.5 (s), 13.9 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 2981, 1717, 1602, 1495, 1446, 1371, 1286,, 1208, 1157, 1094, 1029, 782, 752, 692 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 267 (19), 266 (100) [M^+], 219 (11), 193 (43), 178 (12), 135 (21), 107 (18); **HRMS** (EI–TOF) calcd. for $C_{18}H_{18}O_2$: 266.1307; found 266.1294.

7.5.6.30. Synthesis of 1–((E)–3–hydroxy–1–phenylprop–1–en–2–yl)–3-methylbenzene

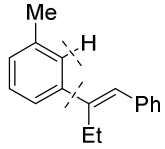


[CAS: 335267-58-8]

The title compound was prepared following general procedure A, starting from 2–methylbenzoic acid (69 mg, 0.5 mmol) and 1–(3–hydroxyprop–1–ynyl)–benzene (105 mg, 110 µL, 0.75 mmol). The title compound was isolated as colorless liquid (79 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.47 (m, 6H), 7.29–7.36 (m, 2H), 7.17 (d, J = 7.5 Hz, 1H), 6.97 (s, 1H), 4.72 (s, 2H), 2.42 (s, 3H), 1.63 ppm (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.3 (s), 138.3 (s), 137.0 (s), 131.1 (s), 128.9 (s), 128.6 (s), 128.5 (s), 128.4 (s), 127.4 (s), 127.3 (s), 123.7 (s), 120.0 (s), 60.4 (s), 21.6 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3360, 3052, 3021, 2921, 1601, 1493, 1445, 1010, 999, 966, 782, 754, 692 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 225 (12), 224 (100) [M^+], 209 (15), 195 (13), 178 (11), 119 (70), 105 (40), 91 (36), 77 (20); **HRMS** (EI–TOF) calcd. for $C_{16}H_{16}O$: 224.1201; found 224.1212.

7.5.6.31. Synthesis of 1–methyl–3–((Z)–1–phenylbut–1–en–2–yl)–benzene

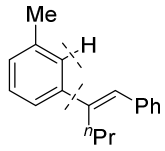


[CAS: 2079114-98-8]

The title compound was prepared following general procedure A, starting from 2–methylbenzoic acid (69 mg, 0.5 mmol) and 1–(but–1–ynyl)–benzene (97 mg, 109 µL, 0.75 mmol). The title compound was isolated as colorless solid (80 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.41 (m, 4H), 7.29–7.31 (m, 1H), 7.25–7.29 (m, 3H), 7.09–7.15 (m, 1H), 6.69 (s, 1H), 2.75 (q, J = 7.4 Hz, 2H), 2.40 (s, 3H), 1.07 ppm (t, J = 7.5 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 144.6 (s), 142.7 (s), 138.3 (s), 137.9 (s), 128.9 (s), 128.7 (s), 128.2 (s), 127.9 (s), 127.8 (s), 127.4 (s), 126.5 (s), 123.7 (s), 23.3 (s), 21.6 (s), 13.5 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3020, 2965, 1601, 1494, 1445, 1376, 864, 780, 753, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 223 (21), 222 (100) [M^+], 208 (9), 207 (44), 193 (14), 129 (10), 115 (26); **HRMS** (EI–TOF) calcd. for $C_{17}H_{18}$: 222.1409; found 298.1401; **m.p.**: 46–47 °C.

7.5.6.32. Synthesis of 1–methyl–3–((Z)–1–phenylpent–1–en–2–yl)–benzene

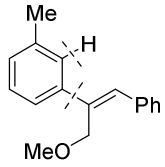


[CAS: 2079115-31-2]

The title compound was prepared following general procedure A, starting from 2–methylbenzoic acid (69 mg, 0.5 mmol) and 1–phenyl–1–pentyne (110 mg, 115 µL, 0.75 mmol). The title compound was isolated as colorless liquid (95 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.40 (m, 4H), 7.22–7.30 (m, 4H), 7.09–7.15 (m, 1H), 6.69 (s, 1H), 2.63–2.72 (m, 2H), 2.40 (s, 3H), 1.40–1.52 (m, 2H), 0.91 ppm (t, J = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 143.4 (s), 143.2 (s), 138.4 (s), 137.8 (s), 128.8 (s), 128.2 (s), 128.2 (s), 128.1 (s), 127.9 (s), 127.4 (s), 126.4 (s), 123.7 (s), 77.3 (s), 76.7 (s), 32.2 (s), 22.0 (s), 21.6 (s), 14.1 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3023, 2958, 2927, 1601, 1493, 1455, 1377, 1088, 781, 698 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 237 (21), 236 (100) [M^+], 208 (9), 207 (44), 193 (14), 129 (10), 115 (26); **HRMS** (EI–TOF) calcd. for $C_{18}H_{20}$: 236.1565; found 236.1576.

7.5.6.33. Synthesis of 1–((E)–3–methoxy–1–phenylprop–1–en–2–yl)–3-methylbenzene

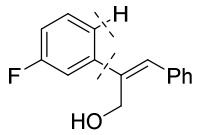


[CAS: 2079115-01-6]

The title compound was prepared following general procedure A, starting from 2–methylbenzoic acid (69 mg, 0.5 mmol) and 1–(3–methoxyprop–1–ynyl)–benzene (110 mg, 115 µL, 0.75 mmol). The title compound was isolated as colorless liquid (66 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.45 (m, 6H), 7.28–7.35 (m, 2H), 7.12–7.15 (m, 1H), 7.05 (s, 1H), 4.39 (s, 2H), 3.40 (s, 3H), 2.41 ppm (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 141.5 (s), 138.0 (s), 138.0 (s), 137.2 (s), 132.4 (s), 129.0 (s), 128.3 (s), 128.3 (s), 128.2 (s), 127.2 (s), 127.1 (s), 123.4 (s), 70.1 (s), 58.1 (s), 21.6 ppm (s); **IR** (ATR): $\tilde{\nu}$ = 3022, 2922, 1603, 1493, 1446, 1193, 1094, 952, 785, 692 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 238 (100) [M^+], 237 (59), 223 (75), 207 (21), 206 (21), 115 (34), 91 (22); **HRMS** (EI–TOF) calcd. for $C_{17}H_{18}O$: 238.1358; found 238.1363.

7.5.6.34. Synthesis of (Z)–2–(3–fluorophenyl–3–phenylprop–1–en–1–ol)



[CAS: 2079115-04-9]

The title compound was prepared following general procedure A, starting from 4–fluorobenzoic acid (71.5 mg, 0.5 mmol) and 1–(3–hydroxyprop–1–ynyl)–benzene (105 mg, 110 µL, 0.75 mmol). The title compound was isolated as colorless liquid (83 mg, 73%).

The title compound was prepared following general procedure B, starting from 4–fluorobenzoic acid (143 mg, 1 mmol) and 1–(3–hydroxyprop–1–ynyl)–benzene (70 mg, 73.3 µL, 0.5 mmol). The title compound was isolated as colorless liquid (75 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.50 (m, 8H), 6.97–7.10 (m, 2H), 4.70 ppm (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 163.1 (d, J = 246.1 Hz), 143.0 (d, J = 7.3 Hz), 138.9 (d, J = 2.7 Hz), 136.5 (s), 132.2 (s), 130.1 (d, J = 8.2 Hz), 128.9 (s), 128.5 (s), 127.7 (s), 122.2 (d, J = 2.7 Hz), 114.5 (d, J = 21.8 Hz), 113.5 (d, J = 22.7 Hz), 60.3 ppm (s); **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -112.95 ppm; **IR** (ATR): $\tilde{\nu}$ = 3333, 3024, 2338, 1741, 1609, 1580, 1484, 1443, 1263, 1229, 1174, 1158, 1011, 968, 902, 864, 780, 756, 694 cm^{-1}; **MS** (EI, 70 eV) *m/z* (%): 228 (15), 227 (100) [M^+], 211 (32), 123 (10), 105 (33), 91 (13); **HRMS** (EI–TOF) calcd. for $C_{15}H_{13}OF$: 228.0950; found 228.0964.

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9. Curriculum vitae

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04/2014 – 08/2017	Promotion im Arbeitskreis von Prof. Dr. Lukas J. Gooßen (TU Kaiserslautern)
22.02.2014	Abschluss zum Diplom Chemiker, Gesamtnote: sehr gut (1,2)
03/2013 – 12/2013	Diplomarbeit im Arbeitskreis von Prof. Dr. F. W. Patureau (TU Kaiserslautern): „Ru-catalyzed cross-dehydrogenative *ortho-N*-carbazolation of diarylamines: Versatile access to unsymmetrical diarylamines; Lauternamines“, Note: sehr gut (1,0)
11/2012 – 2/2013	dreimonatiges Auslandspraktikum im Arbeitskreis von Prof. Dr. S. Otto (Stratingh Institute, Centre for Systems Chemistry, University of Groningen, Niederlande): “Self-Replication Driven by Self-Assembly in Dynamic Combinatorial Libraries” (ERASMUS-Stipendium)
04/2008 – 03/2013	Studium der Chemie an der TU Kaiserslautern, Schwerpunkt Organische Chemie
08/2003 – 03/2007	Abitur am Werner-Heisenberg-Gymnasium, Bad Dürkheim
12/1999 – 04/2003	Mittlere Reife an der Carl-Orff-Realschule, Bad Dürkheim
06.12.1999	Umzug nach Deutschland
10/1997 – 12/1999	Scuola Media Statale di S.Severina (Italien)

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04/2014 – 08/2017	Wissenschaftlicher Mitarbeiter (TU Kaiserslautern) im Arbeitskreis von Prof. Dr. L. J. Gooßen
06/2007 – 07/2012	Rettungssanitäter beim DRK in Bad Dürkheim (monatlich 2-3 Schichten)
Seit 10/2016	Geprüfter Projektmanager Wirtschaftschemie (GDCh)

Zivildienst und Extracurriculäres Engagement

06/2016 – 03/2017	Sprecher des Jungchemiker-Forums (JCF) in Kaiserslautern
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Sprachen

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