



Katalysatoren und Liganden zur Entwicklung von C-C- und C-Heteroatom-Bindungsknüpfungen

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Meiner Familie und meinen Freunden

„Chemie ist nicht wie Boxen, eher wie Jiu-Jitsu.“

Prof. Dr. Lukas J. Goßen

Die vorliegende Arbeit wurde im Zeitraum von Juli 2015 bis Juli 2019 im Arbeitskreis von Prof. Dr. Lukas J. Goößen im Fachbereich Chemie der Technischen Universität Kaiserslautern und an der Fakultät für Chemie und Biochemie an der Ruhr-Universität Bochum angefertigt.

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Eidesstattliche Erklärung

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

Bochum, den _____

Philip M. Weber

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Abkürzungsverzeichnis

Ac	Acetyl	ESI	Elektronensprayionisierung
Ac-Ile-OH	<i>N</i> -Acetyl-L-Isoleucin	Et	Ethyl
acac	Acetylacetonat	<i>et al.</i>	et alii
Ad	Adamantyl	EWG	Elektronenziehende Gruppe
aq.	Wässrig	FG	Funktionelle Gruppe
Ar	Aryl	FT	Fourier-Transformation
BPhen	4,7-Diphenyl-1,10-phenanthrolin	GC	Gaschromatographie
bdppmapy	<i>N,N</i> -Bis(diphenylphosphanyl-methyl)-3-aminopyridin	h	Stunden
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl	Het	Hetero
Bn	Benzyl	HFIP	Hexafluorisopropanol
Bu	Butyl	HRMS	Hochauflösende Massenspektrometrie
BQ	Benzochinon	IMes·HCl	1,3-Dimesitylimidazolium Chlorid
C ₆ H ₆	Benzol	^t Pr	Isopropyl
calcd.	Kalkuliert	IR	Infrarot
CDC	Cross-dehydrogenative coupling	JohnPhos	(2-Biphenyl)di- <i>tert</i> -butylphosphan
CMD	Concerted Metallation-Deprotonation	<i>J</i>	Kopplungskonstante
COD	1,5-Cyclooctadien	KHMDS	Kaliumhexamethyldisilazid
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl	L	Ligand
Cy	Cyclohexyl	LM	Lösungsmittel
CyJohnPhos	2-(Dicyclohexylphosphino)biphenyl	M	Metall
Δ	Erhöhte/r Temperatur / Druck	MAS	Festkörperspektroskopie
δ	Chemische Verschiebung	Me	Methyl
DavePhos	(2-(Dicyclohexylphosphino)-2'- <i>(N,N</i> -dimethylamino))biphenyl	Me ₄ Phen	3,4,7,8-Tetramethyl-1,10-phenanthrolin
dba	Dibenzylidenaceton	MeCN	Acetonitril
DC	Dünnschichtchromatographie	MePhos	2-Methyl-2'-dicyclohexylphosphinobiphenyl
DCE	1,2-Dichlorethan	Me-Dalpos	2-(Di-1-adamantylphosphino)- <i>N,N</i> -dimethylanilin
DCM	Dichlormethan	Mor-Dalpos	<i>N</i> -[2-(Di-1-adamantylphosphino)phenyl]morpholin
DFT	Dichtefunktionaltheorie	Mes	Mesitylen
DG	Dirigierende Gruppe	m.p.	Schmelzpunkt
diglyme	Diglycoldimethylether	MPLC	Mitteldruckflüssigkeitschromatographie
DMAc	Dimethylacetamid	MS	Massenspektrometrie Molekularsieb
DMF	Dimethylformamid	μW	Mikrowelle
DMI	1,3-Dimethyl-2-imidazolidin	<i>n</i>	unverzweigt
DMSO	Dimethylsulfoxid	<i>n</i> -Bu	<i>n</i> -Butyl
dppe	1,2-Bis(diphenylphosphino)ethan	n.d.	Nicht detektiert
EI	Elektronenstoßionisation	NMP	<i>N</i> -Methyl-2-pyrrolidon
EDX	Energiedispersive Röntgenspektroskopie	NMR	Nuklearmagnetische Resonanz
equiv	Äquivalente		

ABKÜRZUNGSVERZEICHNIS

<i>p</i> -cym	<i>para</i> -Cymol
Ph	Phenyl
PhMe	Toluol
Phen	Phenanthrolin
ppm	Parts per Million
Py	Pyridin
quin	Chinolin
R	Organischer Rest
reflux	Unter Rückfluss
rt	Raumtemperatur
SEAr	Elektrophile aromatische Substitution
SEM	Rasterelektronenmikroskopie
SPhos	2-Dicyclohexylphosphino-2',6'- dimethoxybiphenyl
T	Temperatur
^t AmOH	<i>tert</i> -Amylalkohol
^t Bu	<i>tert</i> -Butyl
TCE	2,2,2-Trichlorethanol
TEMPO	2,2,6,6-Tetramethylpiperidinyloxyl
Tf	Trifluormethansulfonyl
TFA	Trifluoressigsäure
TFE	2,2,2-Trifluorethanol
THF	Tetrahydrofuran
TM	Übergangsmetall
TMEDA	Tetramethylethylendiamin
Tol	Tolyl
Ts	<i>p</i> -Toluolsulfonyl
X	(Pseudo)Halogen
XPhos	2-dicyclohexylphosphino-2',4',6'- triisopropylbiphenyl
XRD	Röntgendiffraktion

Nummerierung der Verbindungen

Da ein Großteil dieser Arbeit aus eigenen wissenschaftlichen Veröffentlichungen besteht, wurden die Nummerierungen der Verbindungen aus den jeweiligen Originaltexten übernommen und in den jeweiligen Unterkapiteln getrennt voneinander dargestellt. Verbindungen, die nicht Teil einer Veröffentlichung sind, werden im entsprechenden Unterkapitel neu nummeriert.

Zur besseren Übersicht wurde auf eine Nummerierung von Verbindungen in der Einleitung verzichtet, jedoch wurden Intermediate in Mechanismen mit römischen Ziffern (**I, II, III, ...**) versehen.

Veröffentlichungen

Die meisten Resultate dieser Arbeit wurden in naturwissenschaftlichen Fachjournalen veröffentlicht:

- 1) D. Hackenberger, P. Weber, D. C. Blakemore, L. J. Goossen, *J. Org. Chem.* **2017**, 82, 3917-3925: *Synthesis of 3-Substituted 2-Arylpyridines via Cu/Pd-Catalyzed Decarboxylative Cross-Coupling of Picolinic Acids with (Hetero)Aryl Halides*. DOI: 10.1021/acs.joc.7b00046.
- 2) A. S. Trita, A. Biafora, M. Pichette-Drapeau, P. Weber, L. J. Goossen, *Angew. Chem.* **2018**, 130, 14788-14792: *Regiospecific ortho-C-H Allylation of Benzoic Acids*. DOI: 10.1002/ange.201712520. *Angew. Chem. Int. Ed.* **2018**, 57, 14580-14584: *Regiospecific ortho-C-H Allylation of Benzoic Acids*. DOI: 10.1002/anie.201712520.
- 3) P. Weber, T. Scherpf, I. Rodstein, D. Lichte, L. T. Scharf, L. J. Gooßen, V. H. Gessner, *Angew. Chem.* **2019**, 131, 3235-3293: *Ein hochaktives, Ylid-funktionalisiertes Phosphan für die palladiumkatalysierte Aminierung von Arylchloriden*. DOI: 10.1002/ange.201810696. *Angew. Chem. Int. Ed.* **2019**, 58, 3203-3207: *A Highly Active Ylide-Functionalized Phosphine for Palladium-Catalyzed Aminations of Aryl Chlorides*. DOI: 10.1002/anie.201810696.
- 4) P. Weber, C. K. Rank, E. Yalcinkaya, M. Dyga, T. van Lingen, R. Schmid, F. W. Patureau, L. J. Gooßen, *Adv. Synth. Catal.* **2019**: *Rhodium-catalyzed ortho-Arylation of (Hetero)aromatic Acids*. DOI: 10.1002/adsc.201900596.
- 5) P. Weber, A. Biafora, A. Doppiu, H.-J. Bongard, H. Kelm, L. J. Gooßen, *Org. Process Res. Dev.* **2019**: *A comparative study of dibenzylideneacetone palladium complexes in catalysis*. DOI: 10.1021/acs.oprd.9b00214.
- 6) X.Q. Hu, D. Lichte, I. Rodstein, P. Weber, A.-K. Seitz, T. Scherpf, V. H. Gessner, L. J. Gooßen: *Ylide-Functionalised Phosphine (YPhos)-Palladium Catalysts: Selective Monoarylation of Alkyl Ketones with Aryl Chlorides*.

Dieses Manuskript soll bei „Organic Letters“ eingereicht werden.

Inhaltsverzeichnis

Danksagung	I
Abkürzungsverzeichnis	II
Nummerierung der Verbindungen	IV
Veröffentlichungen	V
Inhaltsverzeichnis	VI
1. Kurzzusammenfassung	1
2. Struktur der Arbeit	3
3. Einleitung	4
3.1 Palladium-katalysierte Kreuzkupplungsreaktionen	4
3.1.1 Der allgemeine Mechanismus.....	5
3.1.2 Pd-dba – Ein populärer Katalysatorvorläufer mit Schönheitsfehler	7
3.1.3 Die Weiterentwicklung von Liganden	8
3.2 Darstellung von (Hetero)Biarylen	10
3.2.1 Vorkommen und Anwendungen	10
3.2.2 Darstellung.....	11
3.2.4 Arylierung von Azinen.....	12
3.3 (Hetero)Aromatische Carbonsäuren	18
3.3.1 Vorkommen und Anwendung.....	18
3.3.2 Darstellung.....	19
3.3.3 Allgemeine Reaktivität.....	20
3.3.4 Übergangsmetall-vermittelte Transformationen	20
3.3.5 Protodecarboxylierung	21
3.3.6 Decarboxylierende Kreuzkupplungen zur Biarylsynthese	23
3.3.7 Carbonsäuren als <i>ortho</i> -dirigierende Gruppe	27
4. Aufgabenstellung	34
5. Ergebnisse und Diskussion	36
5.1 A comparative study of dibenzylideneacetone palladium complexes in catalysis	36
5.2 A highly active Ylide-Functionalized Phosphine for Palladium-Catalyzed Aminations for Aryl Chlorides	47
5.3 Ylide-Functionalised Phosphine (YPhos)-Palladium Catalysts: Selective Monoarylation of Alkyl Ketones with Aryl Chlorides.....	54
5.4 Cu/Pd-Katalysierte Decarboxylierende Kreuzkupplung von Pyridinsäurederivaten	61

5.4.1 Studien zur decarboxylierenden Kreuzkupplung von 2-Picolin- und 2-Pyrimidincarbonsäure	62
5.4.2 Synthesis of 3-Substituted 2-Arylpyridines via Cu/Pd-Catalyzed Decarboxylative Cross-Coupling of Picolinic Acids with (Hetero)Aryl Halides.....	82
5.5 Rhodium-catalyzed <i>ortho</i> -Arylation of (hetero)aromatic Acids	93
5.6 Regiospecific <i>ortho</i> -C-H Alkylation of Benzoic Acids.....	101
6. Zusammenfassung und Ausblick.....	108
7. Experimenteller Teil.....	113
7.1 Struktur und Inhalt des Experimentellen Teils	113
7.2 Allgemeine Methoden.....	113
7.2.1 Chemikalien und Lösungsmittel	113
7.2.2 Durchführung von Parallelreaktionen	113
7.2.3 Analytische Methoden.....	114
7.3 A comparative study of dibenzylideneacetone palladium complexes in catalysis	117
7.3.1 Allgemeine Informationen.....	117
7.3.2 Properties of crystals and Pd nanoparticles	117
7.3.3 Catalytic test reactions	118
7.3.4 X-ray analysis	120
7.4 A Highly Active Ylide-Functionalized Phosphine for Palladium-Catalyzed Aminations of Aryl Chlorides	122
7.4.1 Preparation of the catalyst stock solution	122
7.4.2 General procedure for the amination.....	122
7.4.3 Synthesis and characterization of products	122
7.5 A Highly Electron-Rich Ylide Functionalized Phosphine for Selective Monoarylation of Alkyl Ketones with Aryl Chlorides	133
7.5.1 General Methods.....	133
7.5.2 Preparation of catalyst stock solution	133
7.5.3 General procedure for the arylation	133
7.5.4 Synthesis and characterization of products	135
7.6 Cu/Pd-Katalysierte decarboxylierende Kreuzkupplung von Pyridinsäurederivaten	157
7.6.1 Studien zur decarboxylierenden Kreuzkupplung von 2-Picolin- und 2-Pyrimidincarbonsäure	157
7.6.2 Synthesis of 3-Substituted 2-Arylpyridines via Cu/Pd-Catalyzed Decarboxylative Cross-Coupling of Picolinic Acids with (Hetero)Aryl Halides.....	158
7.7 Rhodium-catalyzed <i>ortho</i> -Arylation of (Hetero)aromatic Acids	161
7.7.1 General procedure for the <i>ortho</i> -arylation.....	161
7.7.2 Screening of the reaction conditions	161
7.7.3 General procedure for the one-pot <i>ortho</i> -arylation and protodecarboxylation.....	164
7.7.4 Protodecarboxylation Experiment	165

INHALTSVERZEICHNIS

7.7.5 Mechanistic investigations	166
7.7.6 Additional Experiments demonstrating the Scope.....	189
7.7.7 Synthesis and characterization of products	190
7.8 Regiospecific <i>ortho</i> -C-H Allylation of Benzoic Acids.....	222
7.8.1 General procedure for the <i>ortho</i> -allylation.....	222
7.8.2 General procedure for the <i>ortho</i> -propenylation.....	222
7.8.3 Procedure for the one-pot <i>ortho</i> -propenylation and protodecarboxylation.....	222
7.8.4 Synthesis and characterization of products	223
7.8.8 Unreactive substrates.....	236
8. Literaturverzeichnis	237
Lebenslauf.....	264

1. Kurzzusammenfassung

Im Rahmen dieser Arbeit wurden neue Katalysatorsysteme und Liganden für nachhaltige C-C- und C-Heteroatom-Bindungsknüpfungen entwickelt und angewendet.

Im ersten Teil dieser Arbeit wurden Palladium-katalysierte Kreuzkupplungsreaktionen behandelt. Der Fokus lag dabei auf Reproduzierbarkeit und der Einführung neuer Liganden. In vorherigen Arbeiten in der Gruppe von Prof. Dr. Gooßen¹ konnte die katalytische Aktivität kommerziell erhältlicher Pd-dba-Proben durch eine Testreaktion bestimmt werden. Daraufhin wurden diese mit physikalischen und spektroskopischen Methoden untersucht, um weitere Indikatoren für die katalytische Aktivität zu identifizieren. Katalytisch weniger aktive Proben konnten zu einem Toluol-Addukt kristallisiert werden, welches seine exzellente Aktivität selbst nach zwei Jahren Lagerung unter Luft und Sonnenlicht beibehält.

Mit den gewonnenen Erkenntnissen aus dem Pd-dba-Projekt konnte die Überlegenheit zweier neuer Ylid-haltiger Liganden (YPhos) aus der Gruppe von Prof. Dr. Däschlein-Gessner gegenüber anderen Katalysatorsystem demonstriert werden (Abbildung 1).

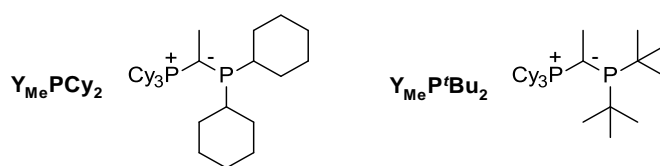


Abbildung 1. Zwei neue YPhos-Liganden aus der Gruppe von Prof. Dr. Däschlein-Gessner.

Mit $Y_{Me}PCy_2$ reicht schon eine geringe Katalysatorbeladung (0.5 mol%) und kurze Reaktionszeit zur effizienten Aminierung von Arylchloriden bei Raumtemperatur. Zudem wurden Ketone mit Arylchloriden α -aryliert. Dabei konnte wenig reaktives Cyclohexanon mit $Y_{Me}P'Bu_2$ schon bei Raumtemperatur in guten Ausbeuten selektiv monoaryliert werden.

Im zweiten Teil dieser Arbeit wurden aromatische Carbonsäuren funktionalisiert, der Fokus lag dabei auf Arylierungen schwer umsetzbarer Pyridincarbonsäuren. Im ersten Teilprojekt konnten elektronenziehende Substituenten in 3-Position die Palladium- und Kupfer-katalysierte decarboxylierende Kreuzkupplung von Picolinsäuren mit Arylhalogeniden deutlich erleichtern.

Im zweiten Teilprojekt wurde eine neue Rhodium-katalysierte Methode zur *ortho*-Arylierung von aromatischen Carbonsäuren entwickelt, wobei erstmals Nicotinsäurederivate wie 2-Methoxy- oder 2-Morpholinnicotinsäure effizient umgesetzt werden konnten. Anders als bei oxidativen Varianten ist die Verwendung überstöchiometrischer Mengen an Silber sowie

KURZZUSAMMENFASSUNG

teurem $[\text{RhCp}^*\text{Cl}_2]_2$ nicht von Nöten und es kann auf günstigere Salze wie $\text{Rh}_2(\text{OAc})_4$ zurückgegriffen werden.

Im dritten Teilprojekt wurde ein Protokoll entwickelt, welches mit $[\text{Ru}(p\text{-cym})\text{Cl}_2]_2$ aromatische Carbonsäuren mit Allylcarbonaten allyliert. Ebenfalls konnte gezeigt werden, dass eine nachfolgende Lactonisierung oder Protodecarboxylierung im selben Reaktionsgefäß möglich ist.

2. Struktur der Arbeit

Diese Arbeit wurde in kumulativer Form verfasst. Der Hauptteil besteht fast ausschließlich aus sechs wissenschaftlichen Veröffentlichungen, bei denen ich als Coautor mitgewirkt habe. Aufgrund ihrer kumulativen Form enthält diese Arbeit die englischen (oder deutschen) Originaltexte. Diese werden mit einer deutschsprachigen Einführung in die Thematik eingeleitet.

Kapitel drei erläutert die grundlegenden Aufgabenstellungen und Zielsetzungen, welche in den darauffolgenden Kapiteln detaillierter beschrieben werden. Auf dem Gebiet der Übergangsmetall-katalysierten Kreuzkupplungsreaktionen werden drei Hauptthemen behandelt. Zuerst wird auf die jüngere Geschichte und Bedeutung von Palladium-katalysierten Reaktionen eingegangen. Hierbei soll der Fokus auf das Zusammenspiel von Palladiumquelle und den eingesetzten Liganden gelegt werden. Dabei wird vor allem auf die Entwicklung von neuen phosphorhaltigen Liganden eingegangen, da diese im Laufe meiner Arbeit von großer Bedeutung waren. Des Weiteren wird auf die Synthese von (Hetero)Biarylen eingegangen. Aufgrund ihrer Struktur und der Anwesenheit von Stickstoffatomen im aromatischen Ring sind Azine dabei zum einen wichtige Untereinheiten in biologisch aktiven Stoffen oder Liganden, zum anderen aber auch schwieriger zu funktionalisieren als Aromaten ohne Heteroatome im Ring. Im dritten Unterkapitel wird auf Funktionalisierungen von aromatischen Carbonsäuren eingegangen. Neben Allylierungen soll auch hier der Fokus auf die Synthese von Heterobiarylen gelegt werden, da diese ein großer Teil meiner Arbeit waren.

Kapitel vier beschreibt die Aufgaben, welche in den einzelnen Teilprojekten meiner Arbeit gestellt wurden. Kapitel fünf beinhaltet, neben einigen unveröffentlichten Resultaten, Kopien der Manuskripte bereits veröffentlichter Ergebnisse sowie Manuskriptentwürfe, welche zur Veröffentlichung eingereicht worden sind. Mein Anteil an den gemeinsam bearbeiteten Projekten ist in der jeweiligen Einleitung in Kapitel fünf erläutert. In Kapitel sechs werden die Ergebnisse kurz zusammengefasst und ein Ausblick auf nachfolgende Arbeiten und noch ausstehende Herausforderungen auf dem Feld der Palladium-katalysierten Chemie, der Heterobiarylsynthese und Funktionalisierung (hetero)aromatischer Carbonsäuren gegeben. In Kapitel sieben finden sich die experimentellen und analytischen Daten, welche die generellen Arbeitsmethoden auf Deutsch sowie die Daten aus der jeweiligen „Supporting Information“ der einzelnen Projekte in englischer Originalsprache enthalten. Kapitel acht enthält die Literaturverweise aus den Kapiteln drei und sieben. Der größte Teil der Literaturverweise aus Kapitel fünf sind in den jeweiligen Originalmanuskripten enthalten.

3. Einleitung

Kohlenstoff ist die Basis allen Lebens und (definitionsgemäß) in gebundener Form in allen organischen Molekülen vertreten.² Übergangsmetall-katalysierte Kreuzkupplungen haben es ermöglicht C-C- und C-Heteroatombindungen effizient, selektiv und unter vergleichsweise milden Bedingungen zu knüpfen.^{2,3} Besonders Palladium hat sich dabei als Katalysator etabliert und ist in der Lage eine Vielzahl an Transformationen zu ermöglichen.⁴

Als Nachteil solcher Reaktionen hat sich vor allem die Entstehung großer Mengen an giftigen Metallabfällen herausgestellt.³ Aus ökologischer Sicht ist es dabei von großem Interesse nachhaltige Verfahren zu entwickeln, welche ein Minimum an Abfall generieren und mit gut verfügbaren sowie ungiftigen Substraten arbeiten. Besonders Carbonsäuren erfüllen diese Kriterien und konnten in den letzten Jahren immer mehr an Bedeutung gewinnen.⁵ In unserer Gruppe werden (hetero)aromatische Carbonsäuren traditionell bei Biarylsynthesen geschätzt.⁶ Biaryle sind eine häufige Unterstruktur in Medikamenten, Liganden oder Agrochemikalien,⁷ weshalb deren Synthese von großem Interesse ist.

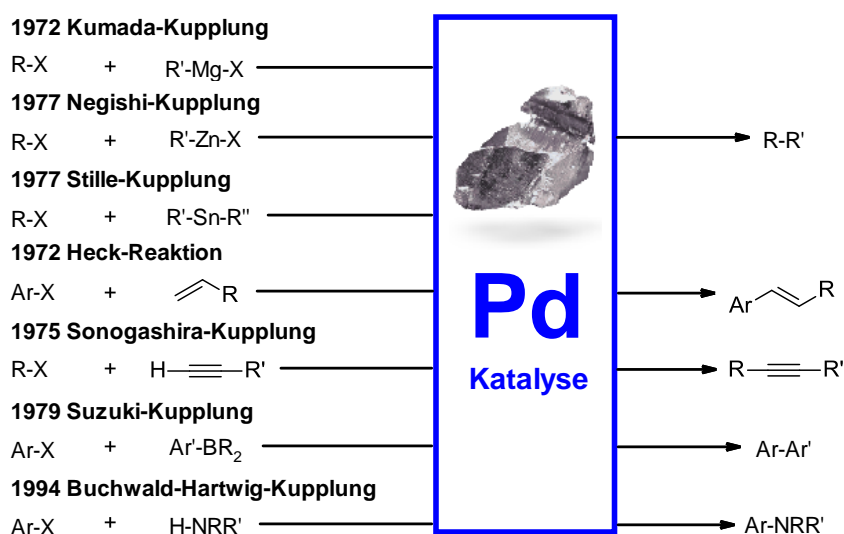
3.1 Palladium-katalysierte Kreuzkupplungsreaktionen

Palladium-katalysierte Kreuzkupplungsreaktionen sind heutzutage ein fester Bestandteil in der homogenen Katalyse.³ Seit ihrer Entwicklung in den 1970er bis 90er Jahren werden diese zur Synthese von Spezialchemikalien, Feinchemikalien, Arzneimitteln und anderen anspruchsvollen organischen Molekülen eingesetzt. Im Jahre 2010 wurden Heck, Negishi und Suzuki für die Entwicklung Palladium-katalysierter Kreuzkupplungen mit dem Nobelpreis für Chemie ausgezeichnet (Abbildung 2).⁸



Abbildung 2. Richard F. Heck, Ei-ichi Negishi und Akira Suzuki. © Holger Motzkau, Wikipedia/Wikimedia Commons. Lizenz: cc-by-sa-3.0.

Palladium ist ein Edelmetall, welches in der 10. Gruppe des Periodensystems mit Nickel und Platin steht. Am häufigsten nimmt es die Oxidationsstufen +II und +IV an, andere zwischen 0 und +V sind allerdings ebenfalls möglich.³ In der Katalyse kann Palladium die oxidative Addition und reduktive Eliminierung, genauer den Wechsel zwischen den Oxidationszahlen 0 und +II, sehr einfach eingehen.⁹ Dadurch gehört es zu den am meisten verwendeten Übergangsmetall-Katalysatoren in metallorganischen Reaktionen, diverse C-C- und C-Heteroatom-Bindungsknüpfungen wurden bis heute realisiert. Die Kumada-,^{10,11} Negishi-,¹² Stille-,^{13,14} Heck-,¹⁵ Sonogashira-,¹⁶ Suzuki-^{17,18} oder Buchwald-Hartwig-Reaktion^{19,20} gehören zu den populärsten Vertretern ihrer Art (Schema 1).



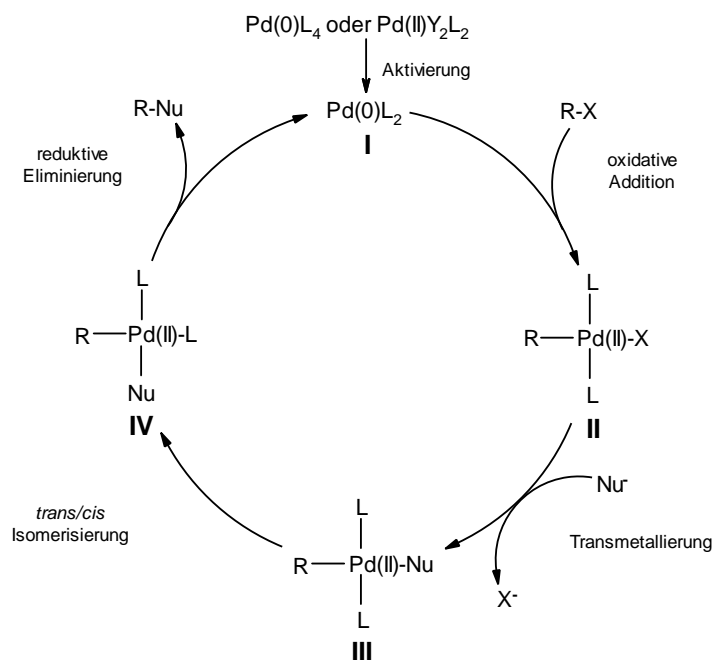
Schema 1. Ausgewählte Pd-katalysierte Kreuzkupplungs-Reaktionen. © Quelle der Abbildung von Palladium: Umicore.

3.1.1 Der allgemeine Mechanismus

Diverse Kreuzkupplungsreaktionen mit unterschiedlichen Übergangsmetall-Katalysatoren basieren auf einem ähnlichen Mechanismus, der in Schema 2 am Beispiel von Palladium dargestellt wird.²¹ Vor allem in der homogenen Katalyse ist es wichtig Liganden zu verwenden um die Metallzentren zu stabilisieren, in Lösung zu halten und somit eine Agglomeration zu inaktiven Nanopartikeln zu unterbinden. Falls die katalytisch aktive Spezies **I** nicht direkt eingesetzt wird, muss diese *in situ* aus einem Katalysatorvorläufer generiert werden. Je nach Oxidationsstufe des Vorläufers, meistens 0 oder +II, erfolgt eine Aktivierung durch den Austausch von Liganden oder einer Reduktion. Durch die oxidative Addition eines Elektrophils bildet sich der Organometallkomplex **II**, welcher im nachfolgenden Schritt eine Transmetallierung eingeht, dabei ein Nukleophil übertragen bekommt und zu Komplex **III** wird. Je nach Reaktion kommt es zu einer *trans-cis*-Isomerisierung zu Komplex **IV** um die

EINLEITUNG

nachfolgende reduktive Eliminierung zu ermöglichen, wobei das Produkt gebildet und der Katalysator **I** regeneriert wird.



Schema 2. Allgemeiner Reaktionsmechanismus für Pd-katalysierte Kreuzkupplungen.

Je nach geschwindigkeitsbestimmendem Schritt der Reaktion werden Liganden gemäß ihren elektronischen oder sterischen Eigenschaften ausgewählt (Kapitel 3.1.3). Werden beispielsweise Arylchloride, welche eine hohe C-Cl-Bindungsstärke ($\Delta H = 339 \text{ kJ/mol}$)²² aufweisen, als Elektrophil eingesetzt erschwert dies die oxidative Addition. In diesem Fall werden elektronenreiche Liganden (z.B. starke σ -Donoren) benötigt, um die Oxidationsstufe am Metall zu erhöhen. Eine Erhöhung der Anzahl der Liganden ist ebenfalls vorteilhaft. Diese wird durch einen niedrigen sterischen Anspruch begünstigt. Die Richtung der Transmetallierung wird über die relative Position der Metalle in der elektrochemischen Spannungsreihe vorgegeben. Dieser Schritt kann durch polare Lösungsmittel und die Wahl geeigneter Metalle beeinflusst werden. Starke π -Akzeptorliganden erleichtern die kinetisch unbeständige Transmetallierung ebenfalls. Der organische Rest R ist ebenfalls in der Lage an das Metallzentrum zu koordinieren. Alkenyl- und Arylreste sind deshalb meist reaktiver als Alkylreste. Bei der reduktiven Eliminierung wird die Erniedrigung der Oxidationsstufe am Metall durch sterisch anspruchsvolle und elektronenarme Liganden (z.B. schwache σ -Donoren, starke π -Akzeptoren) begünstigt. Da eine *cis*-Geometrie der Liganden erforderlich ist, kann dieser Schritt durch den Einsatz von Chelatliganden beschleunigt werden.

Zur besseren Übersicht fokussieren sich die folgenden Kapitel auf den Katalysatorvorläufer Pd-dba und Liganden, welche im Laufe dieser Doktorarbeit intensiv studiert wurden.

3.1.2 Pd-dba – Ein populärer Katalysatorvorläufer mit Schönheitsfehler

Neben diversen Pd(II)-Halogeniden, Allylpalladiumchlorid-Dimeren oder Pd(OAc)₂ gehört auch Pd-dba in seinen diversen Spezies zu den beliebtesten palladiumhaltigen Katalysatorvorläufern. Der Vorteil des Einsatzes von Katalysatorvorläufern gegenüber dem direkten Einsatz der aktiven Spezies besteht meist darin, dass sie lagerungsfähiger und robuster unter normaler Atmosphäre sind. Zudem besteht bei Reaktionsoptimierungen die Möglichkeit diese mit diversen anderen Liganden zu kombinieren und sie so den jeweiligen Reaktionsbedingungen anzupassen.

Nach der Entdeckung von Dibenzylidenaceton (dba) als Ligand für Pd(0) Komplexe von Takahashi²³ wurden diverse Konformationen und Addukte von Pd-dba postuliert (Abbildung 3b). Die Struktur von Pd₂(dba)₃ ist bestätigt (Abbildung 3a), doch obwohl die Strukturformel von Pd(dba)₂ eine feste Stöchiometrie vorgibt besteht keine Einigkeit über dessen Struktur. Man geht davon aus, dass es sich um eine komplexe Mischung von Pd₂(dba)₃·dba_x mit einem erhöhten dba-Wert handelt.^{1,24–26}

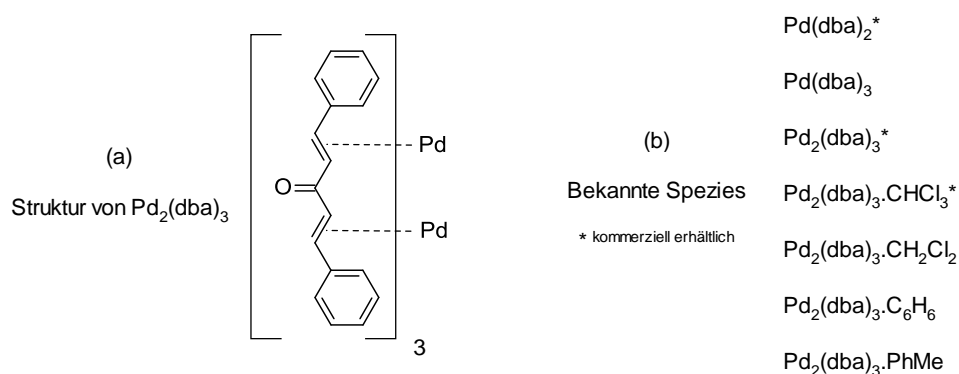


Abbildung 3. (a) Bekannte Pd-dba Spezies. (b) Struktur von Pd₂(dba)₃.

Aufgrund seiner hohen Reaktivität und einfachen Herstellung ist Pd-dba ein beliebter Katalysatorvorläufer für allerart Palladium-katalysierter Reaktionen. Früher nahm man an, dass dba mit seiner olefinischen Doppelbindung vergleichsweise schwach an das Palladium koordiniert und somit leicht durch andere Liganden (wie z.B. Phosphane) auszutauschen ist. Mittlerweile ist allerdings bekannt, dass dba teilweise noch an das Palladium gebunden bleiben kann und die katalytische Aktivität beeinflusst.²⁴

Trotz der hohen Popularität von Pd-dba zeigt die Erfahrung, dass Reaktionen aus der Literatur oftmals nicht reproduziert werden können.¹ Dies liegt meistens daran, dass einige Gruppen ihre Katalysatoren selbst herstellen und andere auf kommerzielle Quellen zurückgreifen. Je nach Beschaffenheit des eingesetzten Pd-dba und der Sensitivität der Reaktion können die erzielten Ausbeuten stark voneinander abweichen. Ananikov und Zalesskiy hatten bereits festgestellt,

EINLEITUNG

dass kommerziell erhältliche Proben bis zu 40% an Pd-Nanopartikeln enthalten können.^{27,28} Das bedeutet, dass Reaktionen eher heterogen als (wie postuliert) homogen katalysiert werden könnten. Zudem kann eine hohe Anzahl an Pd-Nanopartikeln die Bildung von unreaktivem „Pd-Black“ beschleunigen.

3.1.3 Die Weiterentwicklung von Liganden

Liganden tragen maßgeblich zur Entwicklung neuer Katalysatorsysteme bei. Sie bestimmen über Aktivitätsbereiche, Selektivität oder Effizienz einer Reaktion. Neben Allylen oder Cyclopentadienylen (meist anionisch) sowie Aminen oder Carbenen,^{29–31} gelten Phosphane als die dominierende Ligandenklasse, welche in aller Art Kupplungsreaktionen und industriellen Prozessen beteiligt sind.^{32–34} Triarylphosphane gehören dabei zu den früheren Beispielen gebräuchlicher Phosphanliganden (Abbildung 4).¹⁶ Im Gegensatz zu NHC-Liganden, welche auch bei höheren Temperaturen stabil sind, kann deren P-C-Bindung vergleichsweise leicht brechen.³⁵

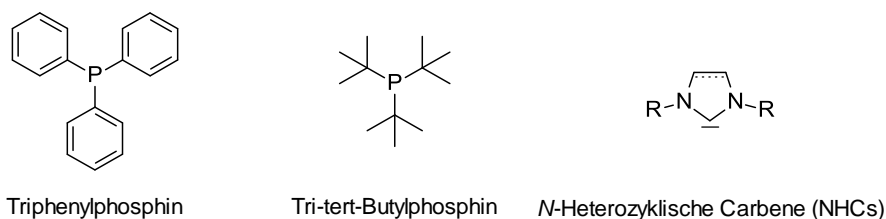
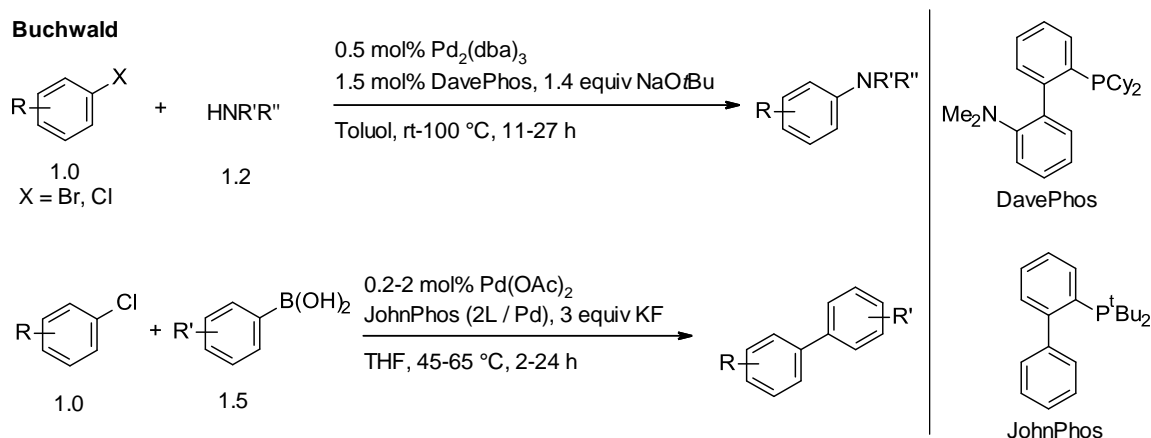


Abbildung 4. Gebräuchliche Liganden in Übergangsmetall-katalysierten Reaktionen.

Triarylphosphane stoßen bei schwierigeren Substraten wie Arylchloriden allerdings schnell an ihre Grenzen, weshalb elektronenreichere und sterisch anspruchsvollere Liganden benötigt werden,³⁶ deshalb wurden in den 1990er Jahren Trialkylphosphane entwickelt und verwendet.^{37,38} Ein sehr potentes Beispiel ist P^tBu_3 aus der Gruppe von Fu (Abbildung 4).³⁹ Durch den hohen sterischen Anspruch der *tert*-Butylgruppe werden reduktive Eliminierungen begünstigt.^{40,41}

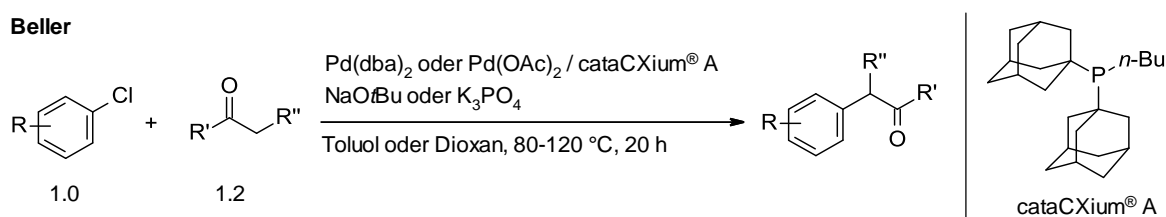
Daraufhin wurden viele weitere elektronenreiche Ligandenklassen entdeckt und eine Auswahl der prominentesten Beispiele soll hier behandelt werden. Da Phosphorliganden in Palladium-katalysierten Reaktionen eine sehr dominante Rolle einnehmen, soll der Fokus darauf liegen. Seit 1998 untersucht die Gruppe von Buchwald sterisch anspruchsvolle und elektronenreiche Dialkylbiarylphosphane, welche in vielen C-C- und C-Heteroatom-Bindungsknüpfungen eingesetzt werden. Als erste Beispiele wurden Palladium-katalysierte Suzuki-Miyaura-Kupplungen und Buchwald-Hartwig-Aminierungen bei niedrigeren Reaktionstemperaturen präsentiert (Schema 3).^{42,43} Die hohe Aktivität wurde neben dem

Elektronenreichtum und dem erhöhten sterischen Anspruch auch mit einer koordinativen Stabilisierung des Palladiums durch die Phenylyringe oder sich daran befindenden koordinierenden Gruppen erklärt.



Schema 3. Erste Beispiele zum Einsatz von Buchwald-Liganden in Pd-katalysierten Reaktionen.

2000 wurden in der Gruppe von Beller erstmals sterisch anspruchsvolle Liganden entwickelt, welche auf Diadamantylalkylphophanen basieren (cataCXium®).^{44,45} Mit diesem Liganden war es ebenfalls möglich günstige aber relativ unreaktive Arylchloride in diversen Palladium-katalysierten Kupplungen mit einer niedrigen Katalysatorbeladung, milden Reaktionsbedingungen und kurzen Reaktionszeiten in hohen Ausbeuten umzusetzen. Beispielsweise bei der α -Arylierung von Ketonen mit Arylchloriden zählen sie bis heute zu den besten Liganden (Schema 4). Durch die Wahl geeigneter Basen und dem richtigen Verhältnis von Arylchloriden und Ketonen kann die Selektivität von Mono- und Diarylierung beeinflusst werden.

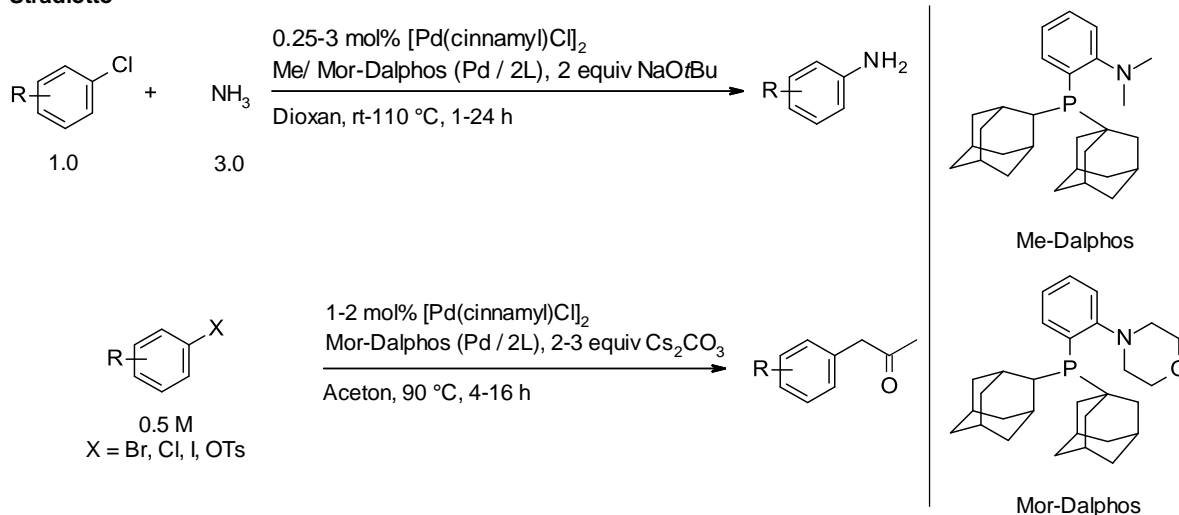


Schema 4. cataCXium® bei der Arylierung von Ketonen mit Arylchloriden.

Die Klasse der DalPhos Liganden, welche von Stradiotto entwickelt wurde, gehört zu den *P,N*-Chelatliganden. Sie basieren auf einem Diadamantylphophangerüst und einer zusätzlichen 2-Aminophenyleinheit. Selektive Monoarylierungen von kleinen Molekülen konnten mit Mor-DalPhos anhand der Kupplungen von Ammoniak mit Arylchloriden und der α -Arylierung von Aceton mit Arylhalogeniden und -tosylaten realisiert werden (Schema 5).^{46,47}

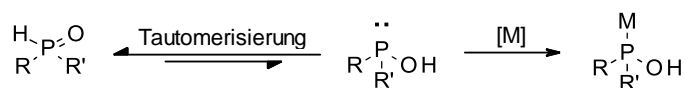
EINLEITUNG

Stradiotto



Schema 5. DalPhos-Liganden bei der monoselektiven Arylierung von Ammoniak und Aceton.

2001 konnte Li einen der ersten Phosphanoxid-Liganden präsentieren, welcher in Kreuzkupplungsreaktionen eingesetzt werden kann.⁴⁸ Phosphanoxide (RR'P(O)H) können in Gegenwart von Übergangsmetallen zu phosphoriger Säure tautomerisieren (RR'POH), welche anschließend mit dem Phosphoratom an das Metallzentrum koordiniert (Schema 6).⁴⁹ Durch die Zugabe einer Base kann dadurch eine deprotonierte elektronenreiche anionische Verbindung erzeugt werden. Wie bereits in Kapitel 3.1.1 erwähnt sind diese bei Reaktionen mit einer schwierigen oxidativen Addition von Vorteil. Ackermann konnte dies bei der erfolgreichen Umsetzung von Arylchloriden in Aminierungen, Suzuki-Kupplungen oder auch intramolekularen α -Arylierungen demonstrieren.^{50,51}



Schema 6. Tautomerisierung von Phosphanoxiden mit anschließender Koordination an ein Metall.

3.2 Darstellung von (Hetero)Biarylen

3.2.1 Vorkommen und Anwendungen

Biaryle kommen in vielen Agrochemikalien, Liganden und Medikamenten als Unterstruktur vor, weshalb sie als bedeutsam gelten.⁷ Simple Biphennyl wurde früher als Schädlingsbekämpfungsmittel sowie Konservierungsmittel für Citrusfrüchte verwendet, ist in der Europäischen Union allerdings als solches nicht mehr zugelassen.² Es dient zudem als Grundkörper für diverse Diazofarbstoffe, wobei *ortho*-Tolidin und -Dianisidin als Ausgangsstoffe bei deren Herstellung fungieren (Abbildung 5).² Als Werkstoffe sind Biphenyle

beispielsweise in Flüssigkristallen vertreten, welche in LCD-Bildschirmen („Liquid Crystal Displays“) eingesetzt werden.^{52,53}

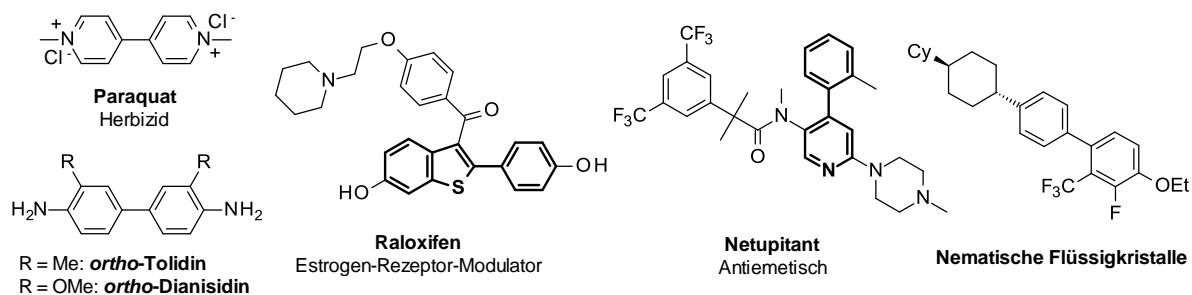


Abbildung 5. Vorkommen von Biarylen als Untereinheit von Farb- oder Wirkstoffen.

Besonders heteroaromatische Biphenyle sind oft vertretene Leitmotive in biologisch aktiven Wirkstoffen. Beispielsweise gilt 4,4'-Bipyridin als Muttersubstanz diverser Herbizide.² Durch die Umsetzung von Pyridin mit Natrium und anschließender Oxidation erhält man Paraquat (Abbildung 5), welches in den 1960er Jahren unter dem Namen Gramoxone® auf den Markt kam und als äußerst wirksam und toxisch gilt.⁵⁴ In der Medizin wird Raloxifen (Evista®) zur Prävention von Osteoporose bei postmenstrualen Frauen sowie bei Schizophrenie eingesetzt und Netupitant (Akynzeo®) zur Vorbeugung von Übelkeit und Erbrechen während Chemotherapien (Abbildung 5).⁵⁵⁻⁵⁷

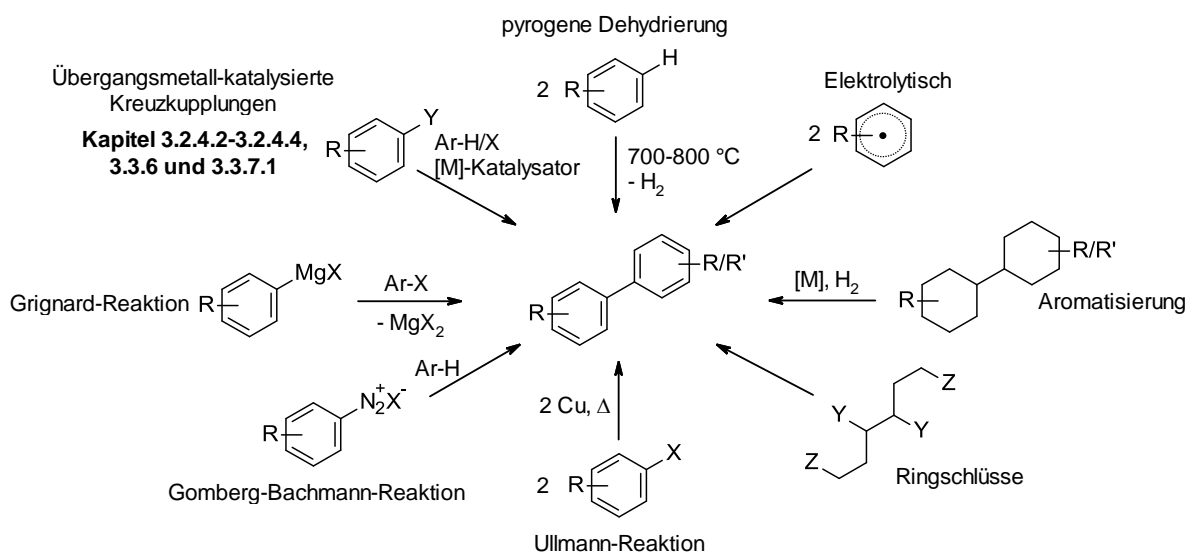
Chemisch verhalten sich Biphenyle wie die entsprechenden monozyklischen Aromaten.² Als Substituent betrachtet ist Phenyl ein elektronenziehender Rest, welcher auch über einen +M-Effekt verfügt und daher elektrophile aromatische Substitutionen überwiegend in *ortho*- und *para*-Position dirigiert.

3.2.2 Darstellung

Zu einem geringen Anteil ist Biphenyl in Erdgas und Rohöl enthalten und kann durch fraktionierte Destillation daraus gewonnen werden.² Im nachfolgenden Schema werden einige synthetische Methoden präsentiert, welche zur Herstellung komplexerer Biphenyle angewendet werden können (Schema 7). Technisch können Biphenyle durch pyrogene Dehydrierung von Benzolen in mit Bimsstein gefüllten Eisenröhren dargestellt werden, wobei Temperaturen zwischen 700-800 °C benötigt werden.² Durch Elektrolyse können Benzolderivate, bei der anodisch ein Radikalkation generiert wird, mit weiteren Äquivalenten zum Biphenyl reagieren.² In den letzten Jahren haben elektrochemische Biarylsynthesen stark an Bedeutung gewonnen, da oftmals auf Metallkatalysatoren, Oxidationsmittel oder spezielle Abgangsgruppen verzichtet werden kann.^{58,59} Aromatisierungen⁶⁰ oder Ringschlüsse⁶¹ können zwar auch zur Biarylsynthese genutzt werden, allerdings werden diese Methoden weniger oft und nur in

EINLEITUNG

spezielleren Fällen verwendet. Bei der Ullmann-Kupplung werden zwei Arylhalogenide in Anwesenheit überstöchiometrischer Mengen Kupfer unter Abspaltung der jeweiligen Kupferhalogenide miteinander gekuppelt. Man erhält dabei meist symmetrische Biaryle.⁶² In frühen Beispielen wurden teils extreme Temperaturen von 360 °C benötigt. In der Gomberg-Bachmann-Reaktion können Aryldiazoniumsalze in der Anwesenheit einer Base mit Aromaten zu Biarylen gekuppelt werden.⁶³ Aryl-Magnesiumhalogenide (Grignard-Reagenzien) können zudem als Nukleophil mit Elektrophilen (wie Arylhalogenide) zu den entsprechenden Biarylen umgesetzt werden.²



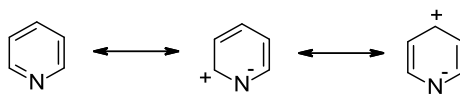
Schema 7. Klassische Ullmann-Reaktion zur Synthese von Biarylen.

Seit den 1970er Jahren werden Biaryle hauptsächlich durch Übergangsmetall-katalysierte Reaktionen wie Suzuki-, Negishi- oder der Stille-Kupplungen hergestellt. Diese Reaktionen wurden in Kapitel 3.1 vorgestellt und sollen in den folgenden Kapiteln anhand der Arylierung von Azinen genauer beleuchtet werden.

3.2.4 Arylierung von Azinen

Azine sind sechsgliedrige, aromatische Ringe, welche mindestens ein Stickstoffatom beinhalten. Diese haben bis zu fünf C-H-Bindungen mit unterschiedlichen Reaktivitäten, was die Tür für regioselektive Funktionalisierungen öffnet. Das elektronegative Stickstoffatom im Ring führt dazu, dass Azine elektronenarm und Lewis-basisch sind. Metalle wie Kupfer können leicht daran koordinieren und stabile Komplexe bilden, welche weitere Reaktionen unterbinden.⁶⁴ Aromatische elektrophile Substitutionen (S_EAr) sind dadurch schwer zu realisieren, Lewis-Säuren werden inaktiviert und dadurch Friedel-Crafts-Reaktionen verhindert. Allerdings können dadurch nukleophile aromatische Substitutionen (S_NAr)

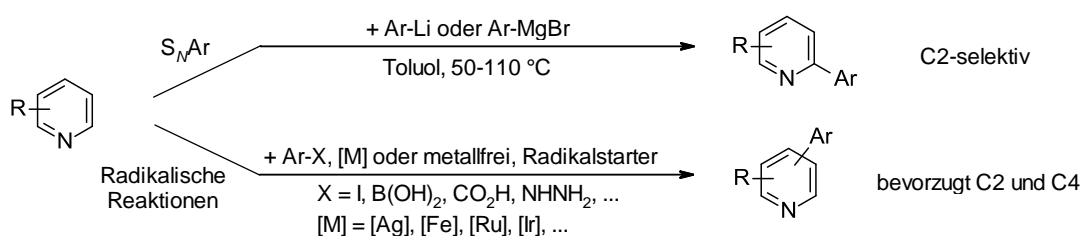
einfacher ablaufen. Ein Blick auf die mesomeren Grenzstrukturen des Pyridins verdeutlicht die Elektrophilie der C2- und C4-Position (Schema 8).



Schema 8. Die Mesomerie von Pyridin.

3.2.4.1 Klassische Arylierungen

Bereits 1938 nutzten Evans und Allan die elektronische Struktur von Pyridin aus und phenylierten es selektiv mit Phenyllithium in C2-Position,⁶⁵ während Zhuo *et al.* aromatische Grignard Reagenzien mit TMEDA kombinierten, um elektronenarme *N*-Heterozyklen selektiv zu arylieren (Schema 9).⁶⁶ Eine klassische radikalische Substitution von Pyridinen ist die 1971 entdeckte Minisci-Reaktion.⁶⁷ In frühen Beispielen wurden Alkylradikale mit katalytischen Mengen an Silber(I)-Salzen aus den entsprechenden Carbonsäuren generiert. Der Angriff erfolgt dabei an den elektrophilen Positionen (C2 und C4) des Pyridins. Minisci entdeckte, dass aus Diazoniumsalzen generierte Arylradikale zur Arylierung von Pyridinen verwendet werden können, diese erfolgt allerdings nur in seltenen Fällen selektiv.^{68,69} In der Gruppe von Baran wurde daraufhin ein Protokoll entwickelt, welches Arylboronsäuren verwendet.^{70,71} Dabei bildet Ag(I) mit $K_2S_2O_8$ ein $SO_4^{\cdot-}$ -Radikal, welches wiederum ein Arylradikal aus der Boronsäure generiert. Daraufhin wurden diverse Protokolle entwickelt, welche durch Eisen-Katalyse,^{72,73} mit Ruthenium-Komplexen,^{74,75} metallfrei⁷⁶ oder als redoxneutrale radikalische Arylierung mit Aryliodiden in Gegenwart von KO^tBu ablaufen können.⁷⁷



Schema 9. Klassische Arylierungsreaktionen von Azinen.

Alle radikalischen Methoden haben gemeinsam, dass Arylierungen selten regioselektiv an einer Position des Pyridins stattfinden.

3.2.4.2 Übergangsmetall-katalysierte C-H-Arylierungen ohne dirigierende Gruppen

Die elektronische Struktur von Pyridinen und die Lewis-Basizität dessen Stickstoffatoms erlauben es den meisten Übergangsmetall-Katalysatoren, diese auch ohne dirigierende Gruppe regioselektiv zu funktionalisieren. Dabei haben viele Metalle spezifische Affinitäten gegenüber

EINLEITUNG

bestimmten Positionen.⁷⁸ Die Regioselektivität der Metalle in Gruppe 10 (Nickel und Palladium) ist besonders von der Wahl des Katalysators und den Reaktionsbedingungen abhängig. Im speziellen Fall von Arylierungen wird mit den meisten Metallen die C2-Position angegriffen (Abbildung 6). Mit Palladiumkatalysatoren sind Protokolle bekannt welche auch in C3-Position arylieren können.

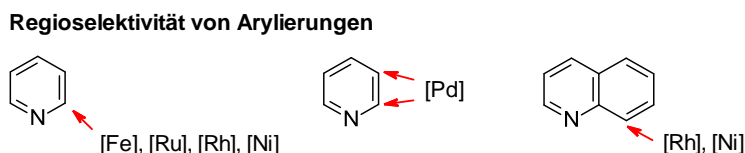
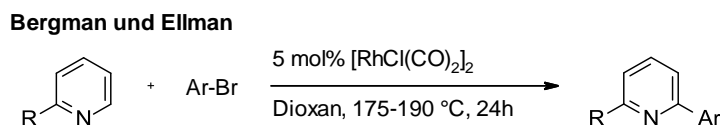


Abbildung 6. Regioselektivität von Arylierungen an Pyridinderivaten.

Durch Eisen(III)-Chlorid in Kombination mit Cyclen kann Pyridin mit Arylboronsäuren in C2-Position aryliert werden, der Mechanismus wurde bislang nicht geklärt.⁷⁹ Mit Dirutheniumkomplexen waren Suzuki *et al.* in der Lage dehydrierende Dimerisierungen von Pyridinen in C2-Position durchzuführen.^{80,81} Mit der Voraussetzung, dass diese in C5-Position substituiert sind, konnten Bergman und Ellman Pyridine mit $[\text{RhCl}(\text{CO})_2]_2$ als Katalysator und Arylbromide als Kupplungspartner in C2-Position verknüpfen (Schema 10).⁸²

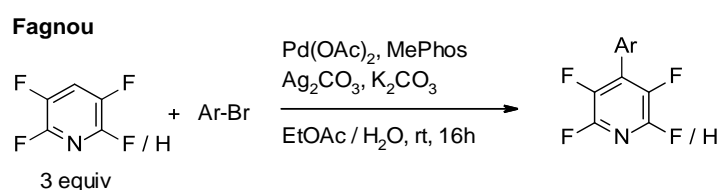


Schema 10. Rhodium-katalysierte Arylierung von Pyridinen mit Arylbromiden.

Chang *et al.* arylierten Chinoline mit $\text{Rh}_2(\text{OAc})_4$ und Carbenliganden selektiv in C8-Position (Abbildung 6).⁸³ Der exakte Mechanismus wurde nicht untersucht. Stattdessen wurde postuliert, dass entweder eine monomere oder dimere Rh-Spezies beteiligt ist. Tobisu und Chatani behandelten Pyridin mit Diarylzink-Reagenzien in Gegenwart katalytischer Mengen an $\text{Ni}(\text{COD})_2$ und Tricyclohexylphosphin, um diese in C2-Position zu arylieren.^{84,85} Dieser Ansatz ist auch bei der C4-Arylierung von Acridin erfolgreich.⁸⁶ Bei $\text{Pd}(\text{OAc})_2$ -katalysierten dehydrogenierenden Kreuzkupplungen (CDCs) werden Pyridine und Chinoline ausschließlich in C2-Position gekuppelt.⁸⁷ In einer ähnlichen Reaktion verwendeten Itami *et al.* organische Halogenide als Oxidationsmittel, welche zusätzlich die Regioselektivität beeinflussen.⁸⁸ Bei der Wahl von Benzylbromid wird Pyridin überwiegend in C2- und mit 2-Brommesitylen in C3-Position aryliert. Bei der Verwendung von Arylhalogeniden und dem Zusatz von Phenanthrolin konnte Pyridin in der Gruppe von Yu fast ausschließlich in C3-Position aryliert werden.⁸⁹ Die Selektivität wird durch den *trans*-Effekt erklärt, wobei Pyridin mit seinen π -Elektronen zwischenzeitlich an das Palladiumzentrum koordiniert.

3.2.4.3 Übergangsmetall-katalysierte C-H-Arylierungen mit aktivierenden Gruppen

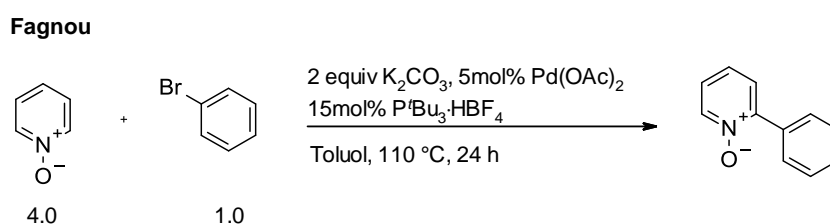
Bei der Arylierung von Pyridinen wird oftmals auch auf aktivierende oder dirigierende Gruppen zurückgegriffen. Zwei beliebte Möglichkeiten sind die Verwendung von elektronenziehenden Gruppen (EWGs) oder *N*-Oxiden. Ein frühes Beispiel für die Arylierung von Azinen mit elektronenziehenden Gruppen ist die direkte, Palladium-katalysierte C-H-Arylierung tetrafluorierter Pyridine mit Arylbromiden aus der Gruppe von Fagnou.⁹⁰ Schon bei Raumtemperatur kann ein Proton des fluorierten Pyridins von einem Carbonat durch einen konzertierten Metallierungs-Deprotonierungs-Mechanismus (CMD) abstrahiert werden (Schema 11).



Schema 11. Arylierung von tetrafluorierten Pyridinen mit Arylbromiden.

Sames präsentierte ein Palladium-katalysiertes Protokoll, welches Pyridine mit diversen elektronenziehenden Gruppen (Nitro, Fluor, Chlor, Cyano, ...) unter Verwendung von Arylbromiden und *P*-*n*-BuAd₂ als Ligand aryliert.⁹¹ Die Reaktion fand entweder in C3- (mit einer EWG in C4-Position) oder C4-Position (mit einer EWG in C3-Position) statt. Mit Palladium als Katalysator wurden daraufhin auch oxidative Arylierungen von Tetrafluorpyridin mit Heteroarenen⁹² und Arylborsäuren⁹³ entwickelt. Do und Daugulis entwickelten Kupfer-katalysierte Systeme zur direkten Arylierung (poly)fluorierter Pyridine.^{94,95}

Durch zusätzliche Gruppen am Stickstoffatom können Pyridine in C2 und C5-Position für C-H-Funktionalisierungen weiter aktiviert werden. Ein prominentes Beispiel dafür ist die Oxidation zum *N*-Oxid. Fagnou nutzte die aktivierende Eigenschaft und konnte die C2-Position über *N*-Oxide mit Arylbromiden arylieren (Schema 12).⁹⁶ Von Nachteil ist, dass das *N*-Oxid im Überschuss (4 Äquivalente) verwendet werden muss um gute Ausbeuten zu erhalten. Zudem führt eine Rückreduktion zum Pyridin in der Regel zu einem Ausbeuteverlust.



Schema 12. Arylierung von Pyridin-*N*-oxiden mit Arylbromiden.

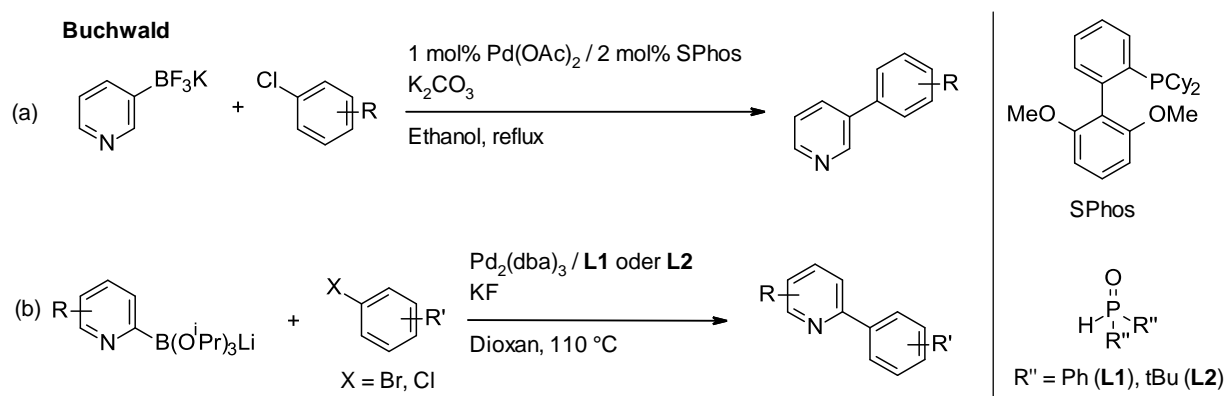
EINLEITUNG

In Kapitel 3.3.7.1 werden Carbonsäuren als dirigierende Gruppen für Biarylsynthesen behandelt.

3.2.4.4 Übergangsmetall-katalysierte Kreuzkupplungsreaktionen

Halogenierte Azine finden bei Übergangsmetall-katalysierten Kreuzkupplungen oft Verwendung. Strebt man allerdings Biaryle mit zwei heteroaromatischen Einheiten an, werden auch organometallische Heteroaromaten benötigt. π -Elektronenarme, organometallische Azine sind instabiler als simple Benzolderivate, weniger nukleophil und durchgehen eine langsame Transmetallierung, welche dadurch oftmals auch geschwindigkeitsbestimmend sein kann.^{97,98} Aufgrund der geringen Stabilität organometallischer 2-Azine neigen diese zum Zerfall und sind in Reaktionen besonders selten vertreten.^{99,100}

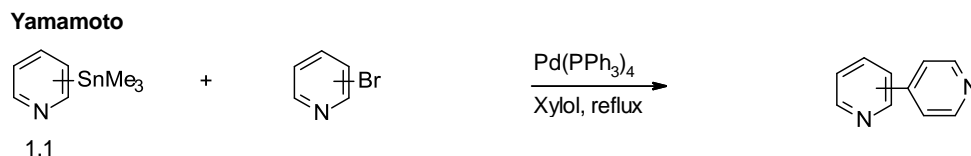
In der Industrie werden noch häufig Suzuki-Kupplungen von Pyridinboraten verwendet.¹⁰¹ Ein gutes Beispiel ist die Kupplung von (Hetero)arylchloriden mit Kalium-3-pyridyltrifluorborat unter Verwendung eines Katalysatorsystems aus $\text{Pd}(\text{OAc})_2$ und SPhos von Buchwald (Schema 13a).¹⁰² Bei organometallischen 2-Azinen ist es wichtig stabilisierte Borverbindungen zu verwenden, da diese ansonsten einfach protodeborieren können.¹⁰³ Buchwald stellte eine Methode vor, in der Lithiumtriisopropyl-2-pyridinborate mit einem Katalysatorsystem aus $\text{Pd}_2(\text{dba})_3$ und Phosphanoxiden in guten Ausbeuten aryliert werden konnten (Schema 13b).¹⁰⁴



Schema 13. Suzuki-Miyaura-Kupplungen von Pyridinboraten mit Arylhalogeniden.

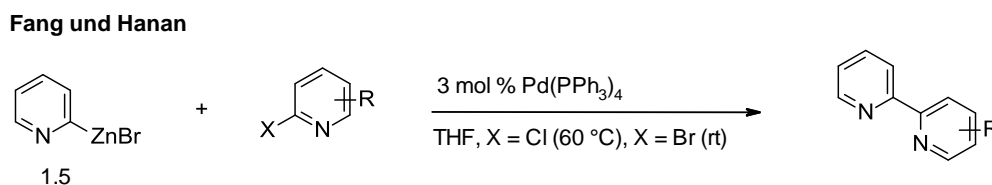
1986 konnten Yamamoto *et al.* eine der ersten Stille-Kupplungen von Trimethylstannylpyridinen und -chinolinen präsentieren.¹⁰⁵ Alle drei Stannylpyridinderivate (C1-C3) konnten mit Arylbromiden in moderaten bis guten Ausbeuten gekuppelt werden (Schema 14). Littke, Schwarz und Fu konnten ein Protokoll präsentieren, welches Arylchloride mit 2-Tributylstannylpyridinen kuppelt, allerdings meist in moderaten Ausbeuten.¹⁰⁶ Zwar gelten Pyridinstannane als stabilere organometallische Verbindungen, allerdings werden Stille-

Reaktionen aufgrund der schwierigen Entsorgung der toxischen Zinnabfälle kaum noch durchgeführt.^{107,108}



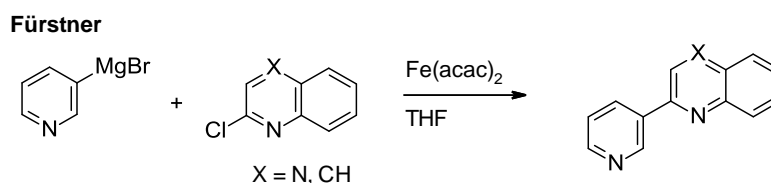
Schema 14. Stille-Kupplungen von Pyridinstannanen mit Arylhalogeniden.

Negishi- und Kumada-Kupplungen werden weniger benutzt, dennoch gibt es ein paar Beispiele. Stanetty kuppelte 4-(2-Fluorpyridyl)zinkiodid mit 2,4-Dichlorpyrimidin unter Verwendung von $\text{Pd}(\text{PPh}_3)_4$.¹⁰⁹ Gallagher *et al.* benutzten den gleichen Katalysator bei der Kupplung organometallierter Brompyridine mit Aryliodiden.¹¹⁰ Fang und Hanan konnten 2003 2-Pyridinzinkbromide mit diversen 2-Chlor- und 2-Bromazinen umsetzen (Schema 15).¹¹¹



Schema 15. Negishi-Kupplung von 2-Pyridinzinkbromid mit Arylhalogeniden.

Bezüglich der Kumada-Kupplung von heteroaromatischen Grignardreagenzien konnten Mongin und Knochel Arylierungen von 3-Pyridylmagnesiumchloriden präsentieren.¹¹² Palladium dient bei der Kupplung mit Aryliodiden als Katalysator, während Arylbromide und -chloride besser mit $\text{Ni}(\text{acac})_2(\text{dppe})$ als Katalysator funktionieren. In der Gruppe von Fürstner konnten Kumada-Kupplungen von 3-Pyridingrignardreagenzien mit hetherozyklischen Arylchloriden unter Eisenkatalyse realisiert werden (Schema 16).¹¹³ Es gibt nur wenige Beispiele für Kupplungen mit 2-Pyridingrignardreagenzien, da diese sehr instabil sind. Normalerweise funktionieren solche Reaktionen nur bei sehr niedrigen Temperaturen und unter Ausschluss von Wasser.¹¹⁴



Schema 16. Eisenkatalysierte Kumada-Kupplung von 3-Pyridingrignard Reagenzien mit Arylhalogeniden.

Für die Hiyama Kupplung von 3- oder 4-Silylpyridinen gibt es kaum Beispiele. Seganish und DeShong konnten ein Protokoll präsentieren, welches mit Aryliodiden und -triflaten sowie

EINLEITUNG

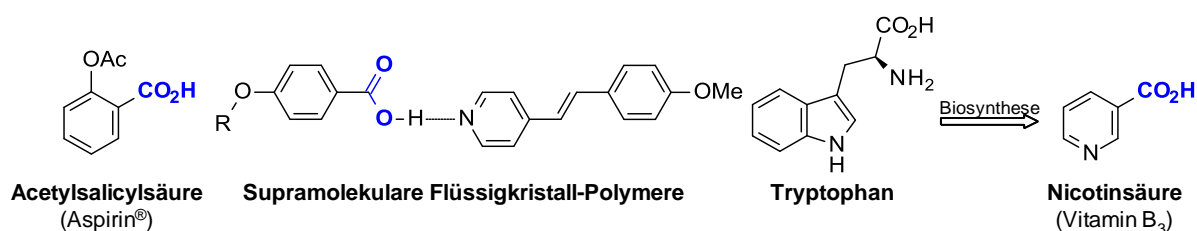
Pd(dba)₂ und CyJohnPhos als Katalysator gute Ausbeuten erzielen konnte.¹¹⁵ Gros *et al.* konnten zeigen, dass Chlorpyridintrimethylsilane stabil genug sind, um sie mit Aryliodiden und -bromiden umzusetzen.¹¹⁶

Obwohl es für die meisten Umsetzungen mit organometallischen Azinen mittlerweile spezialisierte Methoden mit teils speziell designten Liganden gibt welche die Probleme der Instabilität umgehen können, müssen diese vorher immer noch präformiert werden.^{117–122} In Kapitel 3.3.6.1 werden deshalb decarboxylierende Kreuzkupplungen mit leicht zugänglichen (hetero)aromatischen Carbonsäuren ausgiebig behandelt.

3.3 (Hetero)Aromatische Carbonsäuren

3.3.1 Vorkommen und Anwendung

Aromatische Carbonsäuren sind in der Natur und Pharmazie weitverbreitete Teilstrukturen (Schema 17). Die simple Benzoesäure wurde erstmals im 16. Jahrhundert bei der Destillation des Harzes von Benzoebäumen gewonnen,² kommt in der Natur in zahlreichen Beeren vor und entsteht bei der bakteriellen Zersetzung von Milchprodukten.^{123,124} Durch ihre antifungalen Eigenschaften wird sie auch als Konservierungsmittel in Nahrungsmitteln und Tabak verwendet.^{125,126} Eines der bekanntesten bioaktiven Beispiele aus der Medizin ist Acetylsalicylsäure, diese wird durch Acetylierung von Salicylsäure gewonnen.¹²⁷ Aufgrund ihrer Fähigkeit Wasserstoffbrückenbindungen zu bilden, befinden sich aromatische Carbonsäuren ebenfalls in Flüssigkristallen. Als selbstorganisierende Moleküle können sie in diversen sensorischen, optischen, bioaktiven oder ionentransportierenden Funktionsmaterialien vorkommen.^{128,129}



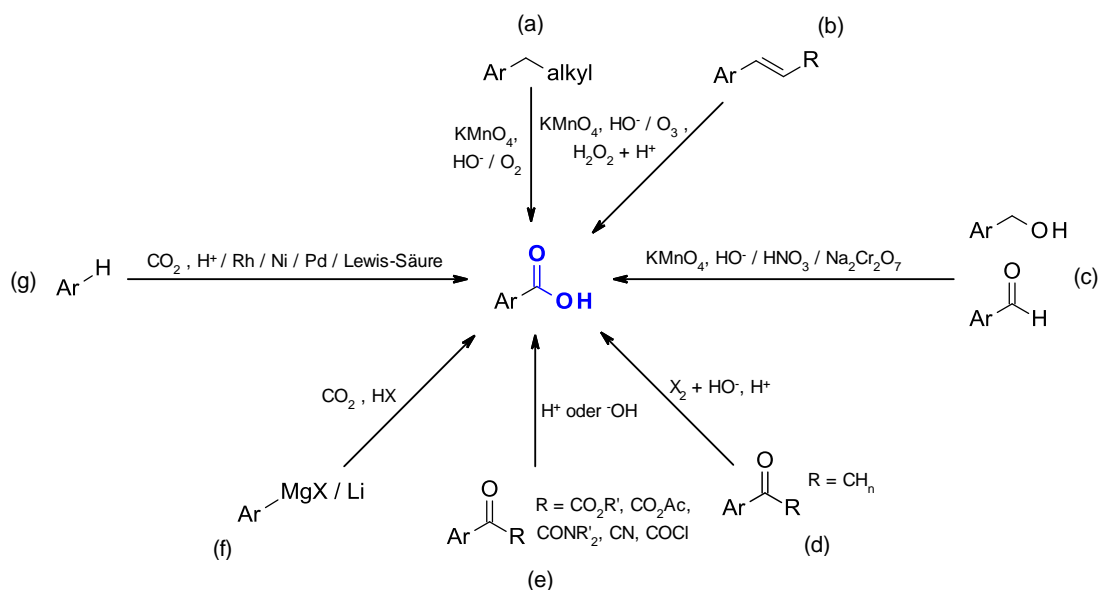
Schema 17. Aromatische Carbonsäuren als Teilstrukturen in Natur-, Wirk- und Wertstoffen.

Die heteroaromatische Nicotinsäure, welche auch als Vitamin B₃ oder Niacin bekannt ist, wurde 1867 bei der Oxidation von Nicotin entdeckt.¹³⁰ Im frühen 20. Jahrhundert wurde die Beteiligung am Vitaminsystem und deren Verbindung zur Krankheit Pellagra, welche durch Nicotinsäuremangel ausgelöst wird, nachgewiesen.¹³¹ In der Medizin wird Niacin heutzutage hauptsächlich als Lipidsenker bei Durchblutungsstörungen verwendet.¹³² Nicotinsäure befindet

sich in allen lebenden Zellen und ist als bedeutsamer Baustein von Coenzymen (NAD, NADP) Teil des Stoffwechsels von Fetten, Eiweißen und Kohlenhydraten.¹³³ Über die Biosynthese der Nicotinsäure in Pilzen und Pflanzen ist wenig bekannt, man geht allerdings davon aus, dass Tryptophan über Kynurenin oxidativ zu dieser abgebaut werden.¹³⁴

3.3.2 Darstellung

Im nachfolgenden Schema soll ein kurzer Überblick über einige gängige Methoden zur Herstellung aromatischer Carbonsäuren gewährt werden (Schema 18). Die gängigste Methode ist die Oxidation gesättigter Seitenketten von Aromaten im Basischen mit Kaliumpermanganat (a).¹³⁵ Vor allem im großtechnischen Maßstab werden Toluol oder Xylol mit Luftsauerstoff in Gegenwart von Cobalt, Mangan oder Vanadium zur entsprechenden Carbonsäure oxidiert.^{135–142} Nicotinsäure wird beispielsweise durch Oxidation von Nicotin mit Salpetersäure oder von 3-Picolin bzw. Chinolin (über das Zwischenprodukt Chinolinsäure) mit Kaliumpermanganat erhalten.^{143,144} Heutzutage ist die Oxidation von 5-Ethyl-2-methylpyridin (MEP) mit Salpetersäure von Bedeutung.¹⁴⁵



Schema 18. Darstellungen aromatischer Carbonsäuren.

Auch ungesättigte Seitenketten können mit Kaliumpermanganat über eine oxidative Spaltung zu Carbonsäuren oxidiert werden (b). Eine Ozonolyse ist ebenfalls möglich.^{135,146} Primäre Alkohole oder Aldehyde werden in basischem Medium mit Kaliumpermanganat, im Säuren mit Natriumdichromat oder Salpetersäure zu Carbonsäuren oxidiert (c). Sekundäre Alkohole benötigen Salpetersäure in Gegenwart von Vanadiumpentoxid.^{135,146} Carbonylverbindungen mit Protonen in α -Position können unter basischen Bedingungen mit Halogenen unter Abspaltung des entsprechenden Haloforms zu Carbonsäuren reagieren (d).^{135,147,148} Nitrile,

EINLEITUNG

Amide und Carbonsäurederivate wie Ester, Anhydride oder Säurechloride können unter sauren und basischen Bedingungen zu Carbonsäuren hydrolysiert werden (e).^{2,135,146} Grignard-Reagenzien und Organolithiumverbindungen können durch Insertion von CO₂ und nachfolgender Hydrolyse in Carbonsäuren umgewandelt werden (f).^{2,135,149} CO₂ kann auch direkt in aromatische C-H-Bindungen implementiert werden. Ein bekanntes Beispiel ist die Kolbe-Schmitt-Reaktion, wobei Natriumphenolat durch eine elektrophile Substitution zu Salicylsäure umgesetzt wird (g).^{135,146} Heutzutage sind allerdings noch weitere Methoden bekannt welche starke Lewis-Säuren oder Übergangsmetalle wie zum Beispiel Rhodium verwenden.^{150,151}

3.3.3 Allgemeine Reaktivität

Generell kann die saure CO₂H-Gruppe (pK_s Benzoesäure = 4.2) Säure-Base-Reaktionen eingehen. Im Basischen kommt es zur Deprotonierung zum Carboxylat, im Sauren wird das Carbonylsauerstoffatom protoniert, danach können nukleophile Substitutionen mit der Hydroxygruppe durchgeführt werden.^{135,146} Beispielsweise kann dann mit Alkoholen eine Veresterung unter Abspaltung von Wasser erfolgen.¹⁵² In diesem dynamischen Gleichgewicht kann es auch zur Verseifung (Rückreaktion) kommen.¹⁴⁶ Die ausgeprägte Polarität der Säuregruppe führt dazu, dass das Carbonylkohlenstoffatom von Nucleophilen und der Sauerstoff von Elektrophilen angegriffen werden kann (Abbildung 7a).¹³⁵

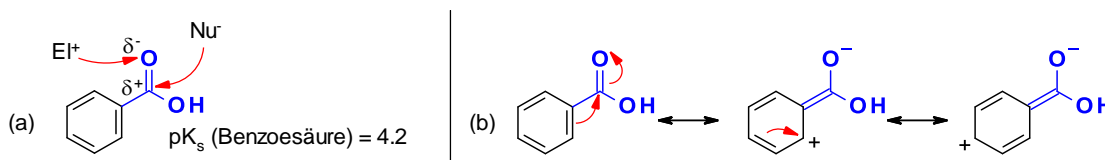


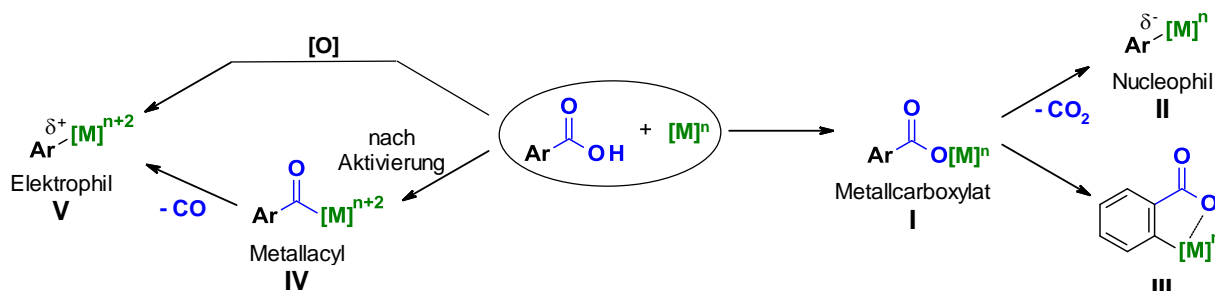
Abbildung 7. Reaktivität von aromatischen Carbonsäuren.

Dies führt dazu, dass die Carboxylgruppe auf vielerlei Art und Weise transformiert werden und somit als Ausgangsmaterial für andere aromatische Substanzen dienen kann. Die Carboxylgruppe übt ebenfalls einen negativen mesomeren Effekt auf den aromatischen Ring aus. Dies führt dazu, dass die *ortho*- und *para*-Position für elektrophile aromatische Substitutionen ($S_{\text{E}}\text{Ar}$) deaktiviert werden und Elektrophile hauptsächlich in *meta*-Position eingefügt werden (Abbildung 7b).

3.3.4 Übergangsmetall-vermittelte Transformationen

Aromatische Carbonsäuren haben sich in den letzten Dekaden als sehr beliebte Substrate in der homogenen Katalyse etabliert. Dabei ist eine Aktivierung der O-H-Gruppe auf verschiedene Weise möglich (Schema 19).^{5,153} An der Säure kann eine Metallcarboxylatspezies **I** gebildet

werden, welche bereits mit anderen Substraten Kupplungsreaktionen am Carboxylsauerstoff eingehen kann (z.B. Hydroacyloxylierungen).¹⁵⁴ Folgt daraufhin eine Decarboxylierung, entsteht eine Organometallspezies **II**, die als Kohlenstoffnucleophil weiterreagieren kann (Protodecarboxylierungen oder decarboxylierende Kupplungen).^{155–157} Ausgehend von **I** besteht ebenfalls die Möglichkeit das Metall in *ortho*-Position zur Säuregruppe zu installieren (**III**). Auf diese Weise wird der *meta*-dirigierende Effekt überwunden und *ortho*-Funktionalisierungen realisiert.¹⁵⁸ Die Carboxylgruppe kann daraufhin weiterfunktionalisiert werden. Wurde die Säure vorher aktiviert (etwa durch Reaktion zum Anhydrid oder Säurechlorid), kann das Metall auch in die Acyl-C-Bindung eingefügt werden, wobei eine Acyl-Metall-Spezies **IV** entsteht. Diese kann entweder in Acylierungsreaktionen^{159,160} genutzt oder mit nachfolgender Decarbonylierung zum Kohlenstoffelektrophil **V** werden. **V** fungiert in Kupplungsreaktionen analog zu (Pseudo)Arylhalogeniden.¹⁶¹ Unter oxidativen Bedingungen kann das Elektrophil ebenfalls aus der Säure und dem Metall erhalten werden.¹⁶²



Schema 19. Reaktionsmodi von aromatischen Carbonsäuren in der homogenen Katalyse.

Im Rahmen dieser Doktorarbeit werden neben Protodecarboxylierungen hauptsächlich decarboxylierende Kreuzkupplungen und *ortho*-Funktionalisierungen zur Biaryl- und Allylsynthese behandelt.

3.3.5 Protodecarboxylierung

3.3.5.6 Metallfreie Protodecarboxylierung

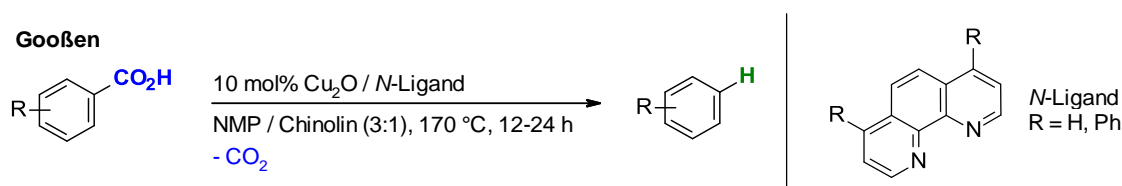
Metallfreie Methoden zur Protodecarboxylierung aromatischer Carbonsäuren beschränken sich meist auf aktivierte Substrate. Bei Zugabe von starken Brønsted-Säuren können beispielsweise Azulene, polyfluorierte, eine Reihe heterozyklischer oder *ortho,ortho*-disubstituierte Carbonsäurederivate bereits bei moderaten Temperaturen decarboxylieren.^{147,161,163–165} Ohne den Einsatz von Metallen können allerdings keine weiterführenden Funktionalisierungen eingeleitet werden.

3.3.5.7 Metall-vermittelte Protodecarboxylierung

1930 konnte Shepard beobachten, dass halogenierte Furancarbonsäuren mit stöchiometrischen Mengen an Kupfer besser decarboxyliert werden als ohne Zusatz von Metallen.¹⁶⁶ Diese Methode wurde daraufhin verfeinert und für weitere aktivierte Carbonsäuren wie Benzoessäurederivate mit elektronenziehenden *ortho*-Substituenten, Phenyl- oder Diphenylessigsäuren und 2-Thiophensäure zugänglich gemacht.¹⁶⁷⁻¹⁶⁹ Zur Stabilisierung des Komplexes koordinieren dabei oft stickstoffhaltige Bipyridyl- oder Phenanthrolin-Liganden an das Kupfer. Silber und Palladium konnten ebenfalls verwendet werden, diese sind aber teurer als Kupfer. Eine Decarboxylierung nicht aktivierter Carbonsäuren blieb weiterhin kritisch. Mit stöchiometrischen Mengen an Quecksilbersalzen kann eine Protodecarboxylierung auch milder verlaufen, allerdings sind die intermediär gebildeten Organoquecksilber(II)verbindungen sehr toxisch.¹⁷⁰

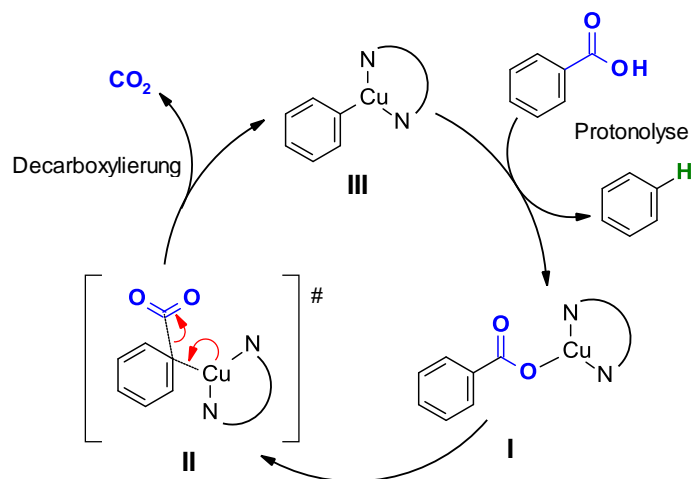
3.3.5.8 Metall-katalysierte Protodecarboxylierung

In frühen Zeiten hab es nur wenige Protokolle, mit denen katalytische Mengen an Metall ausreichen um aktivierte Substrate zu protodecarboxylieren.^{171,172} In der Gruppe von Gooßen wurden DFT-Studien durchgeführt, welche zu einem stark verbesserten Katalysatorsystem führten.¹⁵⁵ Dabei wurden bei 170 °C mit Kupfer(I)-Oxid und (4,7-Diphenyl)-1,10-phenanthrolin zum ersten Mal Benzoessäuren katalytisch protodecarboxyliert, welche nicht zwingend aktivierende *ortho*-Substituenten besitzen (Schema 21).



Schema 20. Kupfer-katalysierte Protodecarboxylierung nicht aktivierter Benzoessäurederivate.

Darauf basierend wurde ein Mechanismus postuliert (Schema 21).¹⁷³ Der Komplex aus Kupfer und dem *N*-Chelatliganden koordiniert an den Carboxylsauerstoff der Carbonsäure (**I**) und decarboxyliert diese indem es in die Aryl-CO₂-Bindung eingefügt wird (**II**). Nach der Abspaltung von CO₂ wird eine Arylkupferspezies (**III**) gebildet, welche durch ein neues Säuremolekül eine Protonolyse eingeht und zum Intermediat **I** regeneriert wird.



Schema 21. Postulierter Mechanismus für die Kupfer-katalysierte Protodecarboxylierung mit N-Chelatliganden.

In der Mikrowelle ist diese Umsetzung auch gut durchführbar und reduziert die Reaktionsdauer deutlich auf wenige Minuten.¹⁷³ Mit der Verwendung von AgOAc anstelle von Kupfer war es sogar möglich die Temperatur um mehr als 50 °C auf 80-120 °C zu senken.¹⁷⁴ DFT- und experimentelle Studien konnten aufzeigen, dass Silber besser funktionieren kann. Selbst bei niedrigeren Temperaturen um 120 °C kann eine Vielzahl an Benzoesäuren, auch heteroaromatische wie Pyrrole oder Thiophene, protodecarboxyliert werden.^{174,175} Insgesamt sind auf Silber basierende Systeme vorteilhafter für spezielle Substratklassen wie zum Beispiel *ortho*-halogenierte Benzoesäuren, welche entweder gar nicht oder nur unter besonders hohen Temperaturen mit Kupfer umgesetzt werden können.^{176 177}

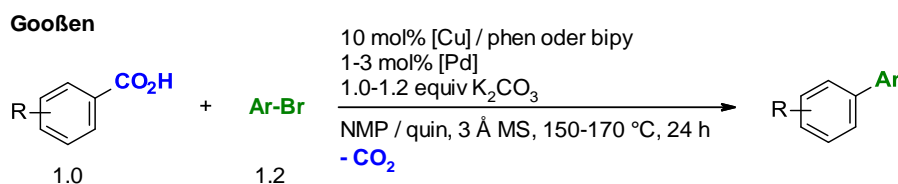
Kozłowski *et al.* protodecarboxylierten sehr elektronenreiche bis-*ortho*-substituierte aromatische Carbonsäuren bei 70 °C mit 20 mol% Pd(O₂CCF₃) in Trifluoressigsäure.¹⁷⁸ Rhodium-katalysierte Protodecarboxylierungen sind ebenfalls auf *ortho,ortho*-disubstituierte Benzoesäuren, Indol-3-carbonsäure, 2- und 4-Nitrophenyllessigsäure beschränkt.¹⁷⁹ Nolan konnte durch Goldkatalyse aktivierte aromatische und heteroaromatische Carbonsäuren protodecarboxylieren.^{180,181}

3.3.6 Decarboxylierende Kreuzkupplungen zur Biarylsynthese

Nilsson gelang es 1966 als erstem Kupfer-Aryle in Protodecarboxylierungsreaktionen mit Aryliodiden zu kuppeln.¹⁸² Da in diesem Protokoll stöchiometrische Mengen an Kupfer verwendet werden und harsche Bedingungen notwendig sind, bestand jedoch ein großer Optimierungsbedarf. Vier Jahrzehnte später konnte Gooßen erstmals ein System zur Kupplung mit Arylbromiden präsentieren, welches 1.5 Äquivalente CuCO₃ für die Decarboxylierung und Pd(acac)₂ als Katalysator für die Kreuzkupplung verwendet.¹⁸³ Es wurden überwiegend

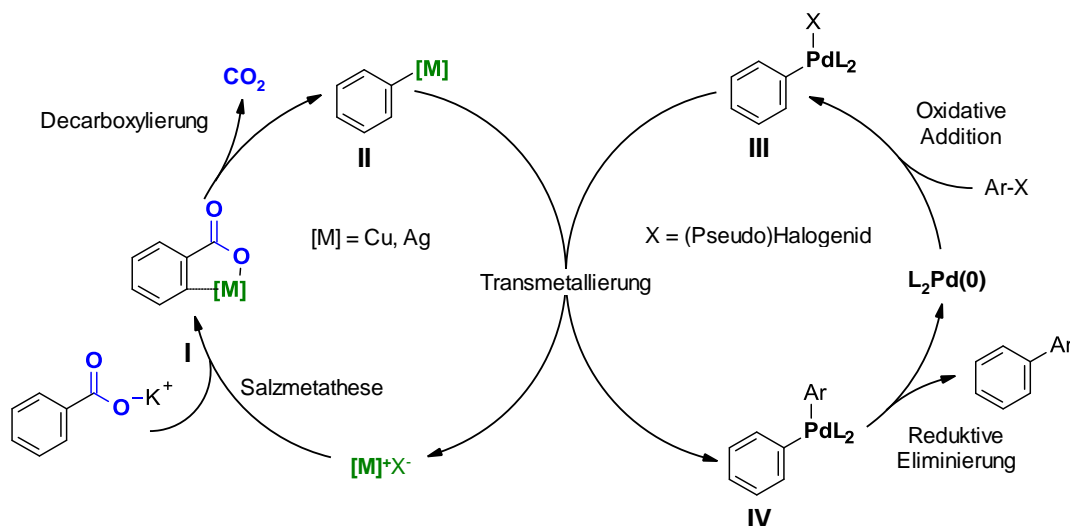
EINLEITUNG

ortho-substituierte Carbonsäuren bei 120 °C umgesetzt. Kurz darauf wurde in der selben Gruppe ein Protokoll präsentiert, welches bei Zusatz von Phenanthrolin oder 2,2'-Bipyridin als Ligand auch Kupfer in katalytischen Mengen verwenden konnte (Schema 22).⁶



Schema 22. Cu/Pd-katalysierte decarboxylierende Kreuzkupplung von aromatischen Carbonsäuren.

In Schema 23 wird der daraus abgeleitete postulierte Mechanismus für bimetallische Systeme dargestellt. Nach einer Salzmetathese koordiniert der Kupfer- oder Silberkatalysator an den Carboxylatsauerstoff (**I**). Nach einem Wechsel zur Arylbindung wird der Katalysator in die C-C(O)-Bindung eingefügt und bildet unter Abspaltung von CO₂ die Organometallspezies **II**. Parallel dazu kommt es zur oxidativen Addition des Arylhalogenids zum Palladiumkatalysator (**III**). Während einer Transmetallierung transferiert die Organometallspezies **II** ihren Arylrest auf den Palladiumkomplex (**IV**), wobei ebenfalls das Metallsalz für den Decarboxylierungszyklus regeneriert wird. Nach der reduktiven Eliminierung wird das Biarylprodukt gebildet und der Palladiumkatalysator zurückgebildet.



Schema 23. Katalysezyklus bei bimetallischen decarboxylierenden Kreuzkupplungen.

In den folgenden Jahren wurden decarboxylierende Kreuzkupplungen stets weiterentwickelt. Unter Verwendung von Carboxylaten war es etwas später auch möglich mit anderen Bedingungen Arylchloride¹⁸⁴ sowie Aryltriflate¹⁸⁵ zu kuppeln. Neben den bimetallischen existieren ebenfalls auch monometallische Varianten^{186,187} der decarboxylierenden

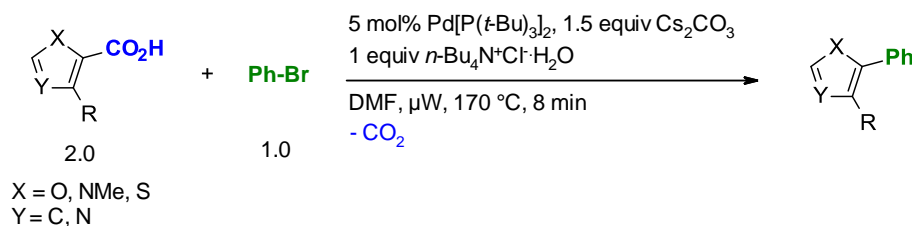
Kreuzkupplung. Unter Verwendung von Kupfer,¹⁸⁸ Palladium¹⁸⁹ oder Nickel¹⁹⁰ lassen sich bisher allerdings nur aktivierte, polyfluorierte aromatische Carbonsäuren zu Biarylen kuppeln.

3.3.6.1 Decarboxylierende Kreuzkupplungen von heteroaromatischen Carbonsäuren

Kreuzkupplungen mit Heteroaromaten, ganz besonders Azaarylverbindungen, stellen eine besondere Herausforderung dar. Aufgrund von π -Elektronenmangel sind deren Organometallverbindungen weniger stabil und weniger nukleophil, was die Transmetallierung langsamer ablaufen lässt.¹⁹¹

Als vergleichsweise einfache Substrate unter den heterozyklischen Carbonsäuren gelten jene mit fünfgliedrigen Ringen (Beispiel Pyrrol). Im Gegensatz zu sechsgliedrigen Pyridinen sind diese elektronenreicher und nukleophiler, da das freie Elektronenpaar des Heteroatoms ebenfalls delokalisiert ist und die Elektronendichte erhöht. Forgone und Bilodeau präsentierten ein Protokoll, welches fünfgliedrige Heterozyklen mit Arylhalogeniden kuppelt (Schema 24).^{186,187}

Bilodeau und Forgone



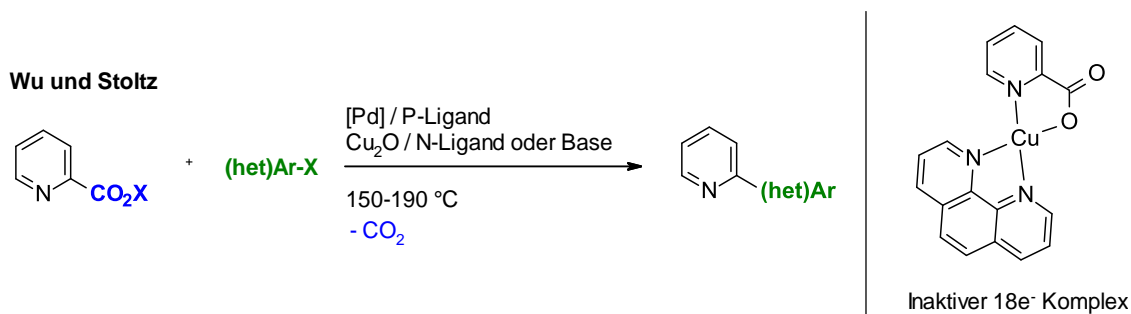
Schema 24. Decarboxylierende Kreuzkupplung von fünfgliedrigen heteroaromatischen Carbonsäuren.

Es wird angenommen, dass der Mechanismus über eine Carbopalladierung mit darauffolgender Decarboxylierung und C-C-Bindungsknüpfung verläuft. Eine andere Möglichkeit wäre eine intramolekulare Variante wobei die Decarboxylierung anschließend an die C-C-Bindungsknüpfung verläuft.¹⁹² Miura stellte Protokolle vor, bei denen 3-Furan- sowie 3-Thiophencarbonsäuren¹⁹³ mit Arylbromiden tetraaryliert und Indol-2- sowie Indol-3-carbonsäuren¹⁹⁴ diaryliert wurden. Zhang und Greaney konnten mit einem System aus PdCl₂ und Triphenylphosphan Thiazol- und Oxazol-5-carbonsäuren mit (Hetero)arylbromiden und -iodiden kuppeln.¹⁹⁵

Bei Pyridinderivaten fungiert das freie Elektronenpaar als Lewis-Base und kann Koordinationsstellen am Katalysator besetzen, was die Aktivität stark beeinträchtigt. Organometallische Pyridinderivate, vor allem solche mit dem Metall in C2-Position, sind zudem instabil und neigen zur Protodecarboxylierung. 2013 konnten die Gruppen von Wu und

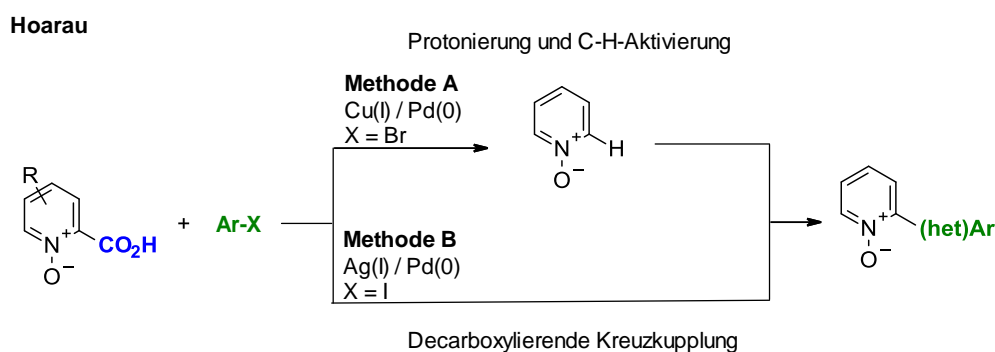
EINLEITUNG

Stoltz etwa zeitgleich Protokolle präsentieren, welche Picolinsäuren mit Arylhalogeniden kuppeln (Schema 25).^{196,197}



Schema 25. Decarboxylierende Kreuzkupplung von Picolinsäurederivaten.

Die Ausbeuten in diesen Protokollen sind bestenfalls mittelmäßig. Zudem verwendeten Stoltz *et al.* sehr hohe Temperaturen in der Mikrowelle und Wu stöchiometrische Mengen an Kupfer. Hoarau präsentierte etwas später ein Protokoll, welches Picolinsäure-*N*-Oxid mit Arylbromiden kuppelt.¹⁹⁸ Dadurch, dass das *N*-Oxid die Elektronendichte im Ring erhöht und zudem in C2-Position dirigieren kann, wurden bessere Ausbeuten als in Protokollen mit simpler Picolinsäure erzielt. Je nach Verwendung von Silber oder Kupfer geht man von zwei verschiedenen Mechanismen aus. Bei Kupfer kann ein vorheriger Protodecarboxylierungsschritt erfolgen, bevor *ortho* zum *N*-Oxid aryliert wird (Schema 26).

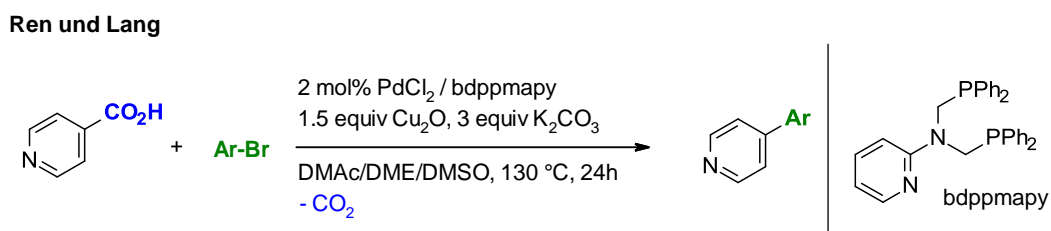


Schema 26. Decarboxylierende Kreuzkupplung von Picolinsäure-*N*-Oxiden.

Von Nachteil ist die Tatsache, dass *N*-Oxide erst hergestellt und nach der Reaktion reduziert werden müssen. Zum einen sind dadurch weitere Reaktionsschritte nötig und zum anderen kommt es zu Ausbeuteverlusten. Durch den stöchiometrischen Einsatz an Kupfer und Silber entstehen zudem große Abfallmengen.

Bei den von Goßen beschriebenen decarboxylierenden Kreuzkupplungen mit Aryltriflaten¹⁹⁹ und -tosylaten²⁰⁰ konnte Pyridin-3-carbonsäure (Nicotinsäure) lediglich in moderaten Ausbeuten umgesetzt werden. In beiden Fällen wurde ein bimetallisches Cu/Pd-System mit Phenanthrolin und einem Phosphorliganden verwendet. Ren und Lang konnten

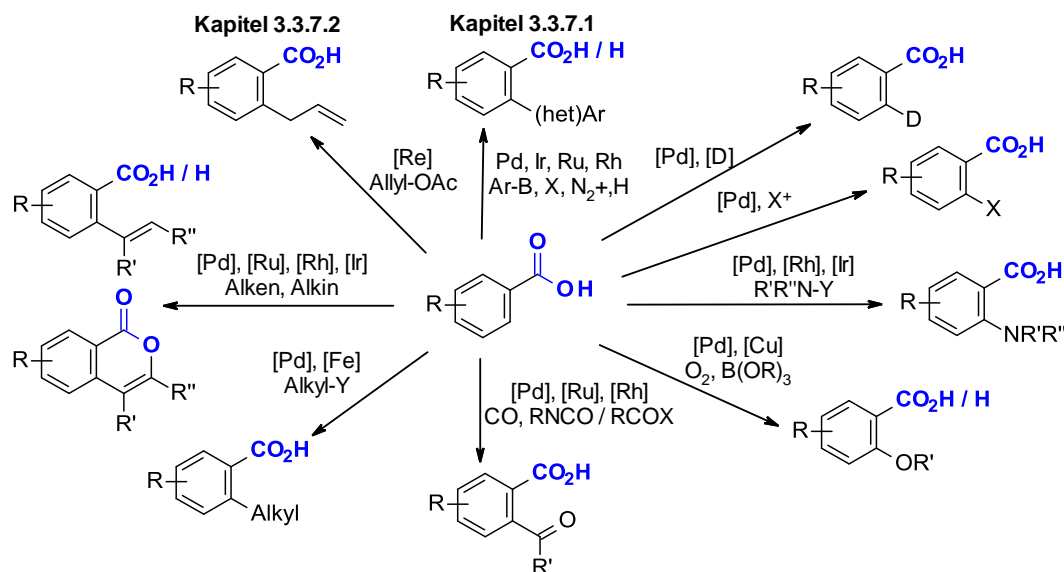
Pyridin-4-carbonsäuren (Isonicotinsäure) mit Arylbromiden in teils guten Ausbeuten kuppeln.²⁰¹ Dabei wurden PdCl₂ in Kombination mit einem zweizähligen *P,N*-Liganden (bdppmapy) und überstöchiometrische Mengen an Kupfer verwendet (Schema 27).



Schema 27. Decarboxylierende Kreuzkupplung von Isonicotinsäure.

3.3.7 Carbonsäuren als *ortho*-dirigierende Gruppe

Die Nutzung von dirigierenden Gruppen ist eine wertvolle Methode zur selektiven Funktionalisierung von organischen Molekülen.^{202,203} Eine Vielzahl an Gruppen, welche aromatische C-H-Bindungen in *ortho*-Position transformieren können sind bekannt.²⁰⁴ Oftmals handelt es sich dabei um stark koordinierende stickstoffhaltige Gruppen wie Amide^{205–210} Pyridine^{211–216} oder Imine.^{217–221} Der Nachteil der Verwendung dirigierender Gruppen ist die Notwendigkeit diese vorher zu installieren und nachher zu entfernen. Es ist somit wünschenswert eine Gruppe zu wählen, die einfach eingefügt und entfernt werden kann. Carbonsäuren erfüllen diese Kriterien. Sie sind einfach und kostengünstig zu erhalten (Kapitel 3.3.2), kommen bereits in vielen organischen Molekülen vor (Kapitel 3.3.1) und lassen sich rückstandlos entfernen (Kapitel 3.3.5) oder weiterfunktionalisieren (Kapitel 3.3.4 und 3.3.6). Oftmals geschieht die Entfernung auch *in situ* nach erfolgreicher Transformation, wobei keine weiteren Schritte nötig sind. Bis heute konnten bereits einige C-C- und C-Heteroatombindungskupplungen realisiert werden (Schema 28).



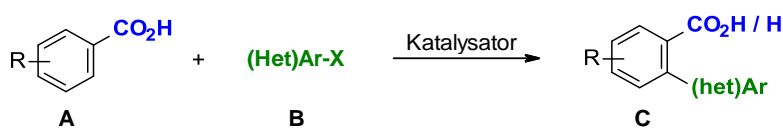
Schema 28. Aromatische Carbonsäuren als dirigierende Gruppe in Übergangsmetall-katalysierten Reaktionen.

Da diese Transformationen Teil dieser Doktorarbeit sind, werden *ortho*-Arylierungen und -Allylierungen in den nachfolgenden Kapiteln behandelt.

3.3.7.1 *Ortho*-Arylierungen von Benzoesäuren

Neben decarboxylierenden Kreuzkupplungen, bei denen die Carbonsäure *ipso*-aryliert und CO₂ abgespalten wird (Kapitel 3.3.6), können Carboxylgruppen die Arylierung auch in *ortho*-Position dirigieren. Diverse Protokolle, welche Palladium,^{222–224} Iridium,²²⁵ Rhodium^{226,227} oder Ruthenium^{228–231} als Katalysator verwenden, wurden bisher veröffentlicht (Tabelle 1).

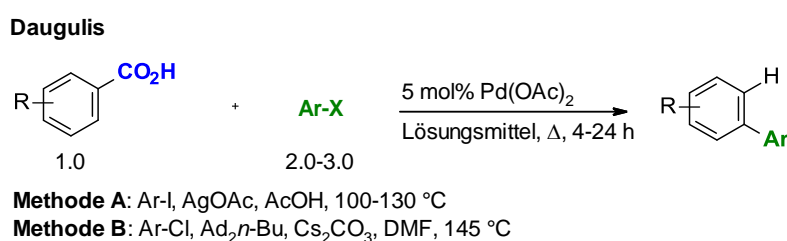
Tabelle 1. Protokolle zur Übergangsmetall-katalysierten *ortho*-Arylierung von (hetero)aromatischen Carbonsäuren.



Übergangsmetall	Autor	Katalysator	B
Palladium	Daugulis	Pd(OAc) ₂ (/ AgOAc)	Ar-Hal
	Yu	Pd(OAc) ₂ / Ag ₂ CO ₃ oder O ₂	Ar-BR ₂
Iridium	Gooßen	[IrCp*Cl ₂] ₂ / [Ag]	Ar-N ₂ ⁺
Rhodium	Su / You	[RhCp*Cl ₂] ₂ / [Ag]	HetAr-H
	Li	„	Ar-CO ₂ H

	Gooßen / Weix	[Ru(<i>p</i> -cym)Cl ₂]	Ar-Hal
Ruthenium	Larrosa	[Ru(<i>t</i> -BuCN) ₆](BF ₄) ₂	„
	Ackermann	[Ru(O ₂ CMes) ₂ (<i>p</i> -cymene)]	„

Das erste Protokoll veröffentlichte Daugulis, wobei er Arylhalogenide mit Palladiumacetat als Katalysator an Benzoensäuren knüpfte (Schema 29).²³² Mit Aryliodiden als Kupplungspartner wird eine stöchiometrische Menge an Silbersalzen benötigt, um das Iod zu entfernen (Bildung von AgI als Triebkraft). Bei der Verwendung von kostengünstigeren aber unreaktiveren Arylchloriden (und -bromiden) wurde anstelle von Silber der Ligand *n*-Butyl-di-1-adamantylphosphan verwendet.

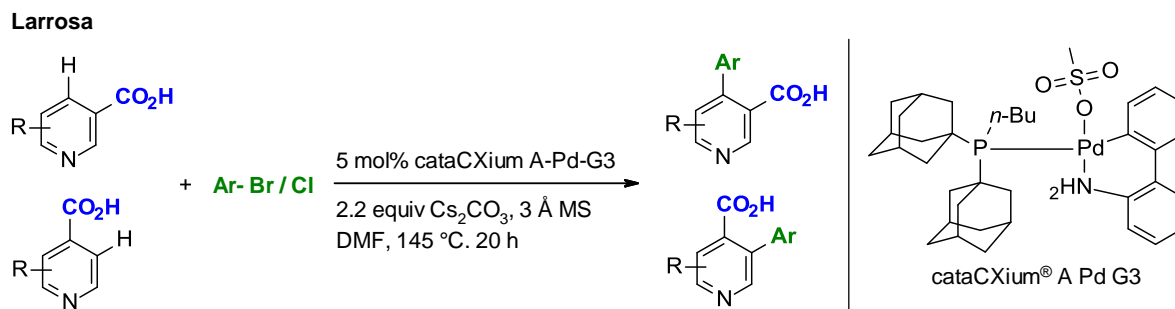


Schema 29. Palladium-katalysierte *ortho*-Arylierung von aromatischen Carbonsäuren mit Arylhalogeniden.

Bei beiden Methoden wird die Säure *in situ* protodecarboxyliert. Bei Benzoensäuren ohne Gruppen *ortho* zur Carboxylgruppe kommt es zur Diarylierung. Bei *meta*-substituierten Benzoensäuren wurde das sterisch begünstigte Monoarylierungsprodukt gebildet (Ausnahme Fluor aufgrund der geringen Größe). 2013 konnte Larrosa bei der Kupplung mit Aryliodiden die Protodecarboxylierung durch den Zusatz einer Base wie K₂CO₃ unterbinden.²³³ Die zusätzliche Base erlaubt den Ligandenaustausch mit dem Pd-Carboxylat-Intermediat und verhindert somit die Decarboxylierung. Einige Jahre später wurde die Anwendungsbreite in der selben Gruppe auf Salicylsäuren erweitert,²³⁴ diese können *in situ* durch die Einführung von CO₂ in die *ortho*-C-H-Bindung von Phenolen erhalten werden. Das Carboxylat dient als transiente dirigierende Gruppe, welche nach der Reaktion entfernt wird. Dadurch erhält man *meta*-substituierte Phenole. Zhou *et al.* konnten bei der Palladium-katalysierten *ortho*-Arylierungen auch Wasser als Lösungsmittel verwenden, wobei Diaryliodoniumsalze als Kupplungspartner verwendet wurden.²³⁵ In den Gruppen von Su und Zhao konnte ein System entwickelt werden, welches bei 30 °C anwendbar ist.²³⁶ Wichtig dafür ist die Benutzung von Aminosäureliganden (Ac-Ile-OH) und dem polyfluorierten HFIP als Lösungsmittel. Palladium-katalysierte Arylierungen von Pyridinderivaten werden überwiegend in C2-Position dirigiert (Kapitel 3.2.4.2). Mit Hilfe der Carboxylgruppe und cataCXium® A-Pd G3 schaffte es Larossa

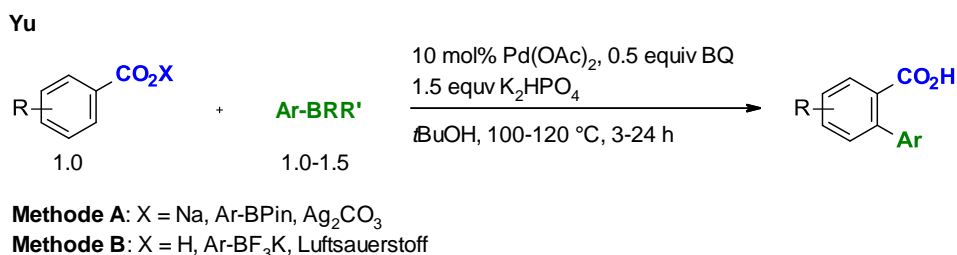
EINLEITUNG

2016 Nicotinsäuren selektiv in C4- und Isonicotinsäuren in C3-Position zu monoarylieren (C4 zu C2 bis zu 9:1, Schema 30).²³⁷



Schema 30. Selektive Palladium-katalysierte *ortho*-Arylierung von Nicotin- und Isonicotinsäuren.

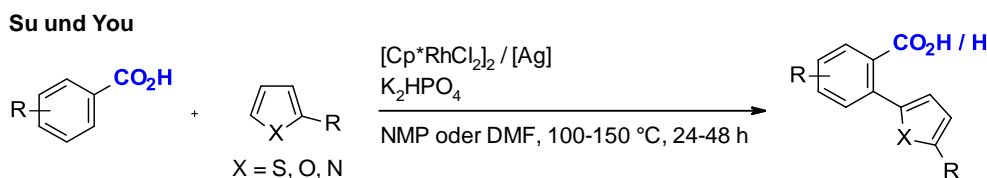
In diesem Fall ist die Carbonsäure eine bessere dirigierende Gruppe als der Stickstoff im Ring. Der Nachteil dieser Methode ist die vergleichsweise niedrige Anwendungsbreite sowie Ausbeute. Neben Kupplungen mit Arylhalogeniden sind für Palladium auch oxidative Kupplungen mit Borsäurederivaten bekannt. Bereits 2007 berichtete Yu von der *ortho*-dirigierenden Methylierung und Arylierung von Benzoesäuren mit Organoborverbindungen (Schema 31).



Schema 31. Oxidative *ortho*-Arylierung von aromatischen Carbonsäuren mit Arylborverbindungen.

In frühen Arbeiten wurden alle Arylierungen mit Phenylborsäurepinacolester durchgeführt und nur von wenigen Beispielen in moderaten bis guten Ausbeuten berichtet.²³⁸ Ohne Natriumkation am Carboxylat konnte die Reaktion nicht durchgeführt werden. Im darauffolgenden Jahr konnte Yu ein optimiertes Protokoll präsentieren. Hier konnte er Benzoe- und Phenyllessigsäuren zusammen mit Aryltrifluorboraten kuppeln.²³⁹ Neben einem Wechsel von Ag₂CO₃ zu Luftsauerstoff konnte zudem die Anwendungsbreite vergrößert werden.

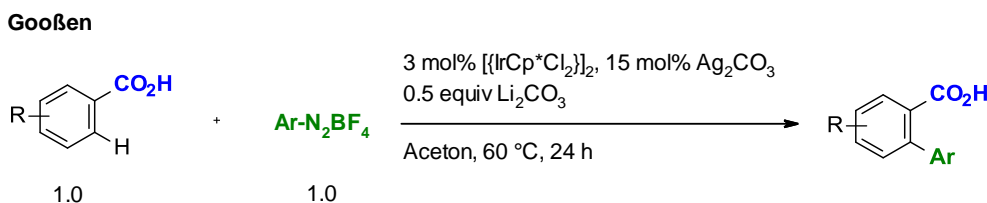
Bei der *ortho*-Arylierung von Benzoesäuren katalysiert Rhodium üblicherweise oxidative C-H,C-H-Kupplungen mit fünfgliedrigen Heterozyklen (Schema 32). Etwa zeitgleich publizierten Su und You die [Cp*₂RhCl₂]₂-katalysierte decarboxylierende *ortho*-Arylierung von Benzoesäuren mit Thiophenen, wobei stöchiometrische Mengen Silber genutzt wurden.^{226,227}



Schema 32. Rhodium-katalysierte *ortho*-Arylierung von aromatischen Carbonsäuren mit fünfgliedrigen Heteroaromaten.

Rhodium ist dabei für die *ortho*-Arylierung zuständig, Silber hauptsächlich für die Decarboxylierung. Unter diesen Bedingungen werden Chlor- oder Bromsubstituenten am Thiophen toleriert, welches selbst in C2-Position kuppelt. In dem Protokoll von You wurden neben Thiophenen auch Furane, Indole, Indolizine oder Koffein mit Benzoesäuren gekuppelt. Der Nachteil beider Methoden ist der Einsatz von teurem $[RhCp^*Cl_2]_2$ (245 € für 500 mg bei Merck im Vergleich zu 55.20 € für Palladium(II)-acetat)²⁴⁰ und teils überstöchiometrischen Mengen an Silbersalzen. Im selben Jahr veröffentlichten You *et al.* ein weiteres Protokoll unter Verwendung von *tert*-Butanol als Lösungsmittel bei einer verminderten Temperatur von 120-130 °C.²⁴¹ Da die Säure unter diesen Umständen nicht decarboxyliert, konnte nach Kupplung mit diversen Thiophenen und Furanen Fluorene, Cumarine und Polyheterozyklen durch intramolekulare elektrophile Substitution oder oxidative Lactonisierung hergestellt werden. Kurz darauf konnten in der Gruppe von Li durch den Einsatz von $[{Rh}(nbd)Cl]_2$ mit Mangan(IV)-oxid als Oxidationsmittel Benzoesäurederivate in Wasser regioselektiv in *ortho*-Position dimerisiert werden.²⁴²

Goßen konnte 2015 eine Iridium-katalysierte Arylierung mit Diazoniumsalzen verwirklichen (Schema 33).²²⁵ Zwar ist $[{IrCp^*Cl_2}]_2$ ein teurer Katalysator (282 € für 500 mg bei Merck),²⁴⁰ aber dafür sind Aryldiazoniumsalze kostengünstiger als Arylhalogenide und können einfach aus gut erhältlichen Anilinen in großer Vielfalt hergestellt werden.^{243–246}



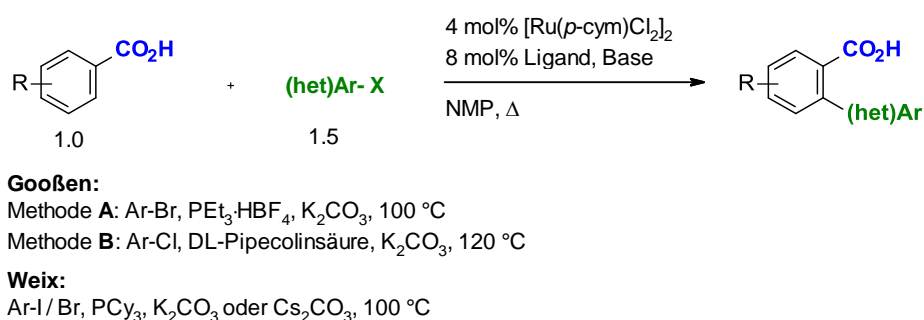
Schema 33. Iridium-katalysierte *ortho*-Arylierung von aromatischen Carbonsäuren mit Aryldiazoniumsalzen.

Die hohe Reaktivität von Diazoniumsalzen ermöglicht zudem eine Reaktion mit einer sehr milden Temperatur von 60 °C, dank der zum einen selbst Halogene als funktionelle Gruppen toleriert werden und zum anderen kostengünstiges und umweltfreundlicheres Aceton als Lösungsmittel verwendet werden kann. Zwar ist die Anwendungsbreite dieses Protokolls groß,

EINLEITUNG

doch Heteroaryldiazoniumsalze können nicht umgesetzt werden. Einige Reaktionen von Pyridinen mit Diazoniumsalzen sind bekannt,^{247,248} allerdings bergen diese ein gewisses Risiko. Aufgrund der heftigen Reaktion mit Pyridinen ist es schwierig heterozyklische Carbonsäuren zu kuppeln. Aryldiazopyridiumsalze werden gebildet und können schnell zu Arylradikalen und Pyridiniumsalzradikalen zerfallen, wobei Stickstoffgas freigesetzt wird.²⁴⁹

2016 präsentierten gleich vier Arbeitsgruppen zeitgleich Ruthenium-katalysierte Protokolle.^{228–231} Der Vorteil gegenüber anderen Metallen, wie Iridium oder Rhodium, ist der vergleichsweise niedrige Preis. Gooßen und Weix verwendeten $[\text{Ru}(p\text{-cym)}\text{Cl}_2]_2$ (84,70 € bei Merck für 1 g)²⁴⁰ als Katalysator (Schema 34).



Schema 34. $[\text{Ru}(p\text{-cym)}\text{Cl}_2]_2$ -katalysierte *ortho*-Arylierung von aromatischen Carbonsäuren mit Arylhalogeniden.

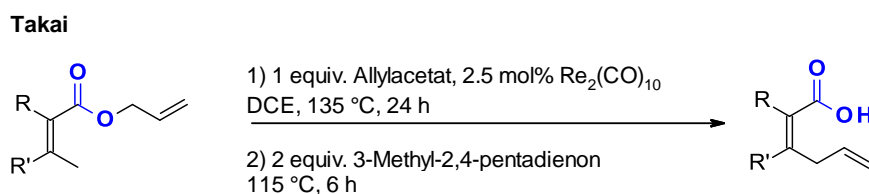
Gooßen *et al.* konnten mit Hilfe des elektronenreichen Phosphanliganden $\text{PEt}_3 \cdot \text{HBF}_4$ den intermediären Rutheniumzyklus gegenüber Arylbromid-Bindungen aktivieren.²²⁸ Wird die Temperatur von 100 auf 120 °C erhöht und eine Aminosäure (DL-Pipecolinsäure) verwendet, können auch kostengünstigere und unreaktivere Arylchloride in guten Ausbeuten umgesetzt werden. Weix *et al.* verwendeten PCy_3 als Ligand und als Kupplungspartner dienten Aryliodide und -bromide.²³⁰ Gerade mit Brompyridinen konnten teils gute Ausbeuten erzielt werden. 2,6-Dimethylnicotinsäure konnte in moderater Ausbeute mit Iodbenzol gekuppelt werden. Im Protokoll von Ackermann wird hauptsächlich $[\text{Ru}(p\text{-cym})(\text{MesCO}_2)_2]_2$ verwendet.²²⁹ Larrosa verwendete in $[\text{Ru}(t\text{BuCN})_6](\text{BF}_4)_2$ in $t\text{BuCN}$ (Lösungsmittel) mit $\text{KOC}(\text{CF}_3)_3$ als zusätzlichem Additiv.²³¹ Zwar werden nur Aryliodide gekuppelt, aber dafür wird kein zusätzlicher Phosphanligand benötigt.

Zusammenfassend kann man sagen, dass das Gebiet der Übergangsmetall-katalysierten *ortho*-Arylierungen zwar tiefgehend erforscht wurde, allerdings fehlt es an etlichen Beispielen für Pyridincarbonsäuren.

3.3.7.2 *Ortho*-Allylierung von Benzoesäuren

Lewis-Säure-vermittelte Friedel-Crafts-ähnliche Allylierungen von elektronenreichen Arenen sind seit einigen Jahren bekannt, jedoch ist deren Anwendungsbreite limitiert und die Regioselektivität beschränkt.^{250–252} (Poly)Fluorierte Arene dagegen können durch Palladium oder Kupfer stereoselektiv allyliert werden.^{253–257} Regioselektive Allylierungen können ebenfalls durch starke, stickstoffhaltige, dirigierende Gruppen garantiert werden,²⁵⁸ jedoch ist die Installation und Entfernung dieser Gruppen mit großem Aufwand verbunden.²⁵⁹

Carbonsäuren sind eine gute Alternative zu anderen dirigierenden Gruppen (Kapitel 3.3.7). Ein Protokoll, welches diese involviert wäre daher von großem Interesse. Bisher ist nur die Rhenium-katalysierte Umlagerung von Takai bekannt, welche von präfunktionalisierten Benzoaten ausgeht (Schema 35).²⁶⁰



Schema 35. Rhenium-katalysierte intermolekulare Allylierung von Benzoe- und Acrylsäuren.

Durch die Benutzung von präformierten Allylbenzoaten und Acrylaten, dem Katalysator $[\text{Re}_2(\text{CO})_{10}]$ und Allylacetat als Additiv wurden die Produkte in moderaten bis guten Ausbeuten erhalten. Die Ausbeuten bei verzweigten Allylen sind allerdings niedrig, dies kann ein Hinweis darauf sein, dass diese Reaktion sensibel auf sterische Hinderungen reagiert. Normale Acrylsäuren konnten auf diesem Wege auch mit Allylalkohol allyliert werden. Zwei mögliche Mechanismen werden diskutiert. Einer beinhaltet die C-H-Aktivierung durch Rhenium gefolgt von einer Insertion in die C-O-Bindung um ein η^1 -Allyl-Intermediat zu generieren welches durch reduktive Eliminierung das Produkt ergibt. Die zweite Möglichkeit beinhaltet eine Insertion des Metalls in die C-O-Bindung um ein η^3 -Allyl-Intermediat zu bilden bevor es zur C-H-Aktivierung kommt. Eine *ortho*-Allylierung von unfunktionalisierten Benzoesäuren sollte im Bereich des Möglichen liegen.

4. Aufgabenstellung

Das Ziel dieser Arbeit bestand darin, neue Katalysatorsysteme und Liganden für nachhaltige C-C- und C-Heteroatom-Bindungsküpfungen zu entwickeln und diese zu etablieren. Diese sollen im Idealfall bisherige Limitierungen überwinden und die Anwendungsbreite vergrößern.

- Der häufig verwendete Katalysatorvorläufer Pd-dba ist für seine oftmals unzuverlässige Reproduzierbarkeit bekannt. Dieser Beobachtung sollte (in Kooperation mit *Umicore*) auf den Grund gegangen und Lösungsvorschläge präsentiert werden. Nachdem in vorherigen Arbeiten eine Testreaktion identifiziert wurde, mit der die katalytische Aktivität schnell und genau vorhergesagt werden konnte, sollte versucht werden eine Korrelation zwischen physikalischen Eigenschaften und der Aktivität herzustellen. Zudem sollte eine Direktsynthese für das katalytisch sehr aktive Toluol-Addukt von Pd₂dba₃ entwickelt werden, welches in vorherigen Arbeiten nur durch langsame Kristallisation aus anderen Proben und in niedrigen Ausbeuten erhalten werden konnte. Das dadurch erhaltene Addukt sollte stabil genug sein, um seine Aktivität nach langfristiger Lagerung unter Luft nicht zu verlieren.
- In der Gruppe von Prof. Dr. Däschlein-Gessner wurden neue Liganden der Klasse YPhos entwickelt, welche sehr elektronenreiche Phosphanliganden mit einer Ylidgruppe sind. Für diese neuen Prototypen sollten Anwendungsmöglichkeiten in Übergangsmetall-katalysierten Reaktionen gefunden werden. Dabei sollten sie sich gegenüber etablierten Liganden bezüglich Reaktionszeit, Temperatur und/oder Anwendungsbreite als überlegen erweisen. Mit Y_{Me}PCy₂ konnten bereits erste vielversprechende Ergebnisse bei der Palladium-katalysierten Buchwald-Hartwig-Aminierung von Arylchloriden erzielt werden.
- Aufgrund ihres Elektronendefizits sowie des Lewis-basischen Stickstoffatoms, an welches Metallatome koordinieren können, sind Pyridincarbonsäuren schwierige Substrate in Übergangsmetall-katalysierten Funktionalisierungen. Dennoch sind sie wichtig für die Herstellung von (hetero)aromatischen Biarylen, welche häufig vorkommende Leitmotive in Pharmazeutika darstellen. Zur Darstellung solcher Biaryle aus Pyridincarbonsäuren bieten sich vor allem decarboxylierende Kreuzkupplungen (a) und *ortho*-Arylierungen (b) an:
 - a) In Zusammenarbeit mit *Pfizer* sollte ein effizientes Protokoll zur Palladium/Kupfer-katalysierten decarboxylierenden Kreuzkupplung von 2-Pyridincarbonsäuren

entwickelt werden. Zwar waren zu diesem Zeitpunkt bereits einige Protokolle bekannt, doch kamen diese kaum über moderate Ausbeuten hinaus.

- b) Bezüglich der *ortho*-Arylierung von aromatischen Carbonsäuren wurden bereits Ruthenium- und Palladiumkatalysierte Protokolle veröffentlicht. Diese weisen allerdings Ausbeutedefizite bei der Arylierung von Pyridincarbonsäuren wie beispielsweise 2-Methoxynicotinsäure auf. Iridium-katalysierte Methoden mit Diazoniumsalzen bieten sich aufgrund der explosiven Reaktivität mit Pyridinen nicht an. Da Rhodium dafür bekannt ist Pyridine mit Arylbromiden in C2-Position arylieren zu können, sollte untersucht werden, ob die gewünschten Pyridincarbonsäuren mit Rhodiumkatalysatoren effizienter umgesetzt werden können und die Carbonsäure die bekannte Selektivität überstimmen kann.
- Im letzten Teil dieser Arbeit sollen Benzoessäurederivate auf ihre Eignung als Ausgangsstoffe für Allylarene hin untersucht werden, welche oftmals als Leitmotiv in Naturstoffen, Pharmazeutika, Funktionsmaterialien oder in der Kosmetikbranche zu finden sind. Da sich Ruthenium in unserer Gruppe bereits bei Hydroarylierungen in *ortho*-Position aromatischer Benzoessäuren bewähren konnte, sollte dieses Reaktionssystem als Grundlage dienen. Nach erfolgreicher Entwicklung eines effektiven Katalysesystems sollten dessen Anwendungsbreite und weiterführende Reaktionen, wie Protodecarboxylierungen und Lactonisierungen, untersucht werden.

5. Ergebnisse und Diskussion

5.1 A comparative study of dibenzylideneacetone palladium complexes in catalysis

In Zusammenarbeit mit Angelino Doppiu und der Firma *Umicore* sollte dem Phänomen der schlechten Reproduzierbarkeit von Reaktionen mit Pd-dba-Katalysatoren auf den Grund gegangen werden. Bereits in vorherigen Arbeiten konnte eine schnelle und einfache Testreaktion identifiziert werden, anhand derer man die katalytische Aktivität einer Pd-dba-Probe einschätzen kann.¹ Bei dieser Testreaktion handelt es sich um die Aminierung von 4-Bromanisol mit Anilin. Bei der Testung von 17 verschiedenen kommerziellen Proben konnten Ausbeuten zwischen 10 und 100 % erzielt werden. Selbst Proben vom selben Hersteller oder aus dem gleichen Gefäß erzielten unterschiedliche Ergebnisse.

Um den Grund dafür zu finden, wurden die Proben daraufhin auf ihre physikalischen und spektroskopischen Eigenschaften untersucht. Bereits bei 200facher Vergrößerung unterschieden sich selbst Proben der selben Pd-dba-Spezies ($\text{Pd}(\text{dba})_2$, $\text{Pd}_2(\text{dba})_3$ oder $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$) optisch deutlich. Elementaranalysen und Schmelzpunktmessungen konnten aufzeigen, dass die erhaltenen Werte stark von denen aus der Literatur abweichen. Zwar sind einige verschiedene Pd-dba-Spezies bekannt, doch ist deren genaue Struktur teilweise noch ungeklärt. Hierfür wurde u.a. die Existenz einer komplexen Mischung aus $\text{Pd}_2(\text{dba})_3$ und zusätzlichem dba postuliert.^{1,24-26} Der Palladiumgehalt kommerziell erhältlicher Proben erstreckte sich in unseren Studien zwischen 15 und 23 %, was ein erneuter Hinweis auf diese These sein kann. In zusätzlichen spektroskopischen Untersuchungen (Feststoff-NMR-, IR- und XRD-Spektren) konnten zwar weitere deutliche Unterschiede festgestellt werden, jedoch konnte daraus keine zuverlässige Korrelation mit der katalytischen Aktivität hergestellt werden. Dafür konnte durch die langsame Kristallisation einer Probe (welche in der Testreaktion schlechte Ergebnisse erzielt hatte) in Toluol ein katalytisch sehr aktives Toluol-Addukt erhalten werden.

Basierend auf den initialen Ergebnissen sollte dieses Projekt im Rahmen der Promotion vollendet werden. Da bereits Ananikov erkannte, dass in kommerziell erhältlichen Proben bis zu 40% an Pd-Nanopartikeln erhalten sein können, sollten unsere Proben ebenfalls darauf untersucht werden.²⁶¹ Dazu sollten zum einen der Anteil an unlöslichen Bestandteilen ermittelt werden, da dieser meist aus unreaktivem „Palladium-Black“ besteht und in homogenen Reaktionen nicht in die Reaktion eingreift, und zum anderen REM- und EDX-Messungen

gemacht werden um die Homogenität des Materials und vorhandene Nanopartikel detektieren zu können. Ebenfalls sollte die Synthese des Toluol-Adduktes verbessert werden, um dieses in höheren Ausbeuten, idealerweise im industriellen Maßstab, erhalten zu können. Zudem sollte der Verfall der katalytischen Aktivität unterschiedlicher Proben unter verschiedenen Lagerbedingungen beobachtet werden.

Der Großteil der Experimente sowie der analytischen Messungen wurden gemeinschaftlich von Herrn Agostino Biafora und mir geplant, durchgeführt und ausgewertet. Die Aufnahme und Auswertung der XRD-Spektren wurden von Dr. Gunder Dörr und Dr. Elizeus Kaigarula ausgeführt. Die ¹³C-MAS-Spektren wurden von Dr. Luca Agnetta und Alexandra Schmidt aufgenommen. Dr. Oliver Groß und Dr. Bert Mallick unterstützten mich bei der Aufnahme der Mikroskopbilder. Die Versuche zur direkten Synthese des Toluol-Adduktes wurden von Herrn Biafora und Herrn Belitz mit meiner Unterstützung durchgeführt. Die Aufnahme und Auswertung der REM und EDX Messungen erfolgten durch Herrn Hans-Josef Bongard vom Max-Planck-Institut für Kohlenforschung in Mülheim. Die Ermittlung der Kristallstruktur des Toluol-Adduktes erfolgte durch Herrn Harald Kelm.

Die Ergebnisse dieses Projektes wurden in meiner Diplomarbeit, der Bachelorarbeit von Herrn Florian Belitz und kürzlich in der Zeitschrift *Organic Process Research and Development* veröffentlicht. Das Manuskript wurde gemeinschaftlich von Herrn Prof. Dr. Gooßen und mir mit Unterstützung von Herrn Biafora angefertigt. Eine angepasste Kopie des Manuskripts wurde mit Erlaubnis der American Chemical Society nachfolgend beigefügt:

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A Comparative Study of Dibenzylideneacetone Palladium Complexes in Catalysis

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Supporting Information

ABSTRACT: Commercial Pd_x(dba)_y from various suppliers was found to vary considerably in appearance, homogeneity, purity, and catalytic activity. The Buchwald–Hartwig amination of 4-bromoanisole (5) with aniline (6) was established as a sensitive test reaction to probe the efficiency of Pd_x(dba)_y batches in catalytic transformations. The yields obtained with 17 different Pd_x(dba)_y batches ranged from 10% to nearly quantitative and could not be predicted reliably on the basis of any physical or spectroscopic descriptor alone. The best results in the catalytic test reaction were consistently achieved with a self-made slowly crystallized Pd₂(dba)₃·toluene adduct. A protocol is disclosed that allows batches of Pd_x(dba)_y with unsatisfactory or inconsistent performance to be converted into this reliable precatalyst.

KEYWORDS: palladium, Pd₂(dba)₃, Pd(dba)₂, Pd catalysis, Pd nanoparticles, amination, reproducibility

complex mixture of species.⁴ Slow crystallization from coordinating solvents results in the formation of defined solvent adducts of Pd₂(dba)₃ (2), for example, Pd₂(dba)₃·CHCl₃ (3), Pd₂(dba)₃·CH₂Cl₂, or Pd₂(dba)₃·C₆H₆, in which the solvent molecules are part of elemental crystal cells (Table 1).⁵

Table 1. Known Pd_x(dba)_y Species

species	appearance	molecular structure of Pd ₂ (dba) ₃ (2)
Pd(dba) ₂ ^a (1)	brown, crystalline ¹	
Pd(dba) ₂ ·C ₆ H ₆	red-violet, crystalline ^{4a}	
Pd ₂ (dba) ₃ ^a (2)	orange-brown, crystalline ^{4b}	
Pd ₂ (dba) ₃ ·CHCl ₃ ^a (3)	purple, crystalline ⁶	
Pd ₂ (dba) ₃ ·CH ₂ Cl ₂	purple needles ⁵	
Pd ₂ (dba) ₃ ·C ₆ H ₆	wine-red, crystalline ^{4d}	
Pd ₂ (dba) ₃ ·PhMe	purple needles ⁵	

^aCommercially available.

INTRODUCTION

Over the past decades, palladium-catalyzed coupling reactions have become established as essential tools for C–C and C–heteroatom bond formation.¹ The pioneering contributions by Heck, Negishi, and Suzuki to this field of research were acknowledged with the Nobel Prize in 2010.² One of the key factors responsible for the tremendous number of synthetic applications achieved with palladium catalysis was the implementation of systematic catalyst screening. The optimal catalyst for a given transformation can be rapidly determined by tuning a common palladium precursor using a range of possible ligands and additives and by optimizing further reaction parameters such as the solvent, base, and temperature. In this context, Pd⁰ adducts of dibenzylideneacetone (dba) are among the most widely used Pd⁰ precursors.

Pd(dba)₂ (1) was first synthesized by Takahashi et al. in 1970.³ The structural formula suggests a defined stoichiometry, but it has meanwhile become clear that instead it is a rather

It was initially assumed that the reaction of Pd⁰–dba adducts with stronger donor ligands, e.g., phosphines or N-heterocyclic carbenes, would give rise to homoleptic PdL_n complexes in which the number of ligands would depend on the palladium-to-ligand stoichiometry.⁷ However, it has repeatedly been observed that dba coordinates rather strongly and remains partially bound to the metal, thus influencing the overall catalyst activity.^{6,8} Fairlamb et al. performed comparative studies with substituted dba derivatives and found a clear influence of the electron-donating nature of the aryl residue on the catalytic activity of Pd–dba-type species.⁹ The more strongly donating the aryl residue, the less stable is the coordination of dba and the easier it is to fully replace it by a phosphine ligand. However, weakening the dba interaction also

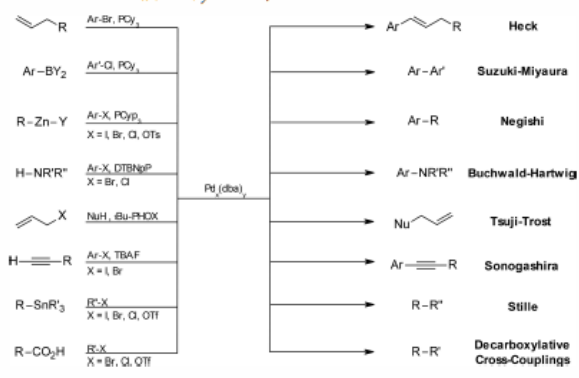
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leads to lower stability of the palladium intermediates and thus shorter catalyst lifetimes. The wealth of applications seem to suggest that Pd complexes with dba itself strike the ideal balance between activity and stability that is required for a reliable in situ conversion to active catalysts bearing customized ligands.

Scheme 1 gives an overview of representative reactions in which dba adducts of palladium are used as catalyst precursors.

Scheme 1. Pd_x(dba)_y-Catalyzed Reactions



They include Heck, Suzuki, Negishi, Buchwald–Hartwig, Tsuji–Trost, Sonogashira, Stille, and our own decarboxylative couplings.¹⁰ In some of these cases, dba acts as the stabilizing agent itself, but in most reactions, phosphines or other ligands are added.

As reaction developers, we are frequently contacted by synthetic chemists from academia or industry who experience substantial deviations in their experimental outcomes from published reactions when using Pd_x(dba)_y precursors, despite all efforts to avoid known pitfalls such as varying solvent quality or different handling of reaction substrates.¹¹ In our experience, this is often a consequence of different traditions in the groups of catalyst developers and synthetic chemists: whereas the former prefer to prepare their own Pd_x(dba)_y complexes using optimized protocols handed down within their research groups, the latter usually rely on commercially available sources. The characteristics of the Pd_x(dba)_y precursor employed substantially affect the yield whenever the reaction under investigation is close to the performance limit of the palladium catalyst and/or the reaction outcome critically depends on the palladium-to-ligand stoichiometry. In contrast, the quality of the Pd_x(dba)_y complex does not immediately influence the reaction outcome if the catalyst activity is so high that comparable results are achieved even if only a fraction of the palladium precursor is converted to the actual catalyst. The outcome is also unaffected if the actual catalytic species is colloidal palladium rather than a defined

Pd_n complex. Ananikov and Zaleskiy found that commercially available Pd_x(dba)_y samples contain up to 40% Pd nanoparticles and proposed that many reactions that are assumed to depend on homogeneous catalysts are in fact catalyzed by such particles.¹² Colacot intensively studied palladium acetate against the two major impurities found in commercial samples, namely, Pd₃(OAc)₅(NO₂) and polymeric [Pd(OAc)₂]_n,¹³ in a variety of cross-coupling reactions.¹³ Whereas the impurities can be as active as pure palladium acetate in certain reactions, pure palladium acetate turned out to be superior in precatalyst formation, in this case a cyclopalladation.

The aim of the present study was to correlate the activity of Pd_x(dba)_y samples with their physical and spectroscopic properties and explore whether descriptors exist to predict their catalytic activity.

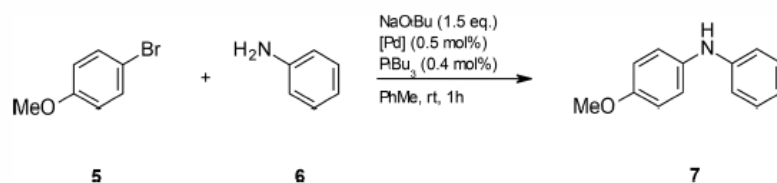
RESULTS AND DISCUSSION

In order to quantify and compare the catalytic activities of a set of commercially available and self-made Pd_x(dba)_y batches, we searched our laboratory database for an easy-to-perform reaction that requires a molecularly defined catalyst and has proven to be particularly sensitive to the choice of the palladium precursor. We evaluated a series of reactions, including Suzuki couplings, the Heck reaction, and amination reactions. All of these reactions showed varying yields depending on the choice of the palladium precursor, but the Buchwald–Hartwig amination of aryl bromides was the most strongly affected. We finally chose the coupling of 4-bromoanisole (5) with aniline (6) (Scheme 2) as a test reaction because it is easy to conduct and gave yields that varied from 10% all the way up to quantitative depending on the choice of the palladium precatalyst.

Using this test reaction, we then investigated the performance of 17 batches of Pd(dba)₂ (1), Pd₂(dba)₃ (2), and Pd₂(dba)₃·chloroform (3) newly purchased from six different suppliers A–F (Table 2). The catalytic reaction was performed three times for every batch, using material from different layers of each container. All commercial materials were used as shipped.

As a reference material, we used a self-made Pd₂(dba)₃·toluene adduct (4). In the original synthetic procedure by Ishii, 4 was obtained by reaction of PdCl₂·dba and sodium acetate followed by crystallization of the resulting Pd–dba adduct from a toluene solution. This way, purple needles with a melting point of 140–141 °C were obtained in 36% yield.⁵ We used an analogous method to convert commercial 1 into a well-defined toluene adduct by slowly crystallizing it from a toluene solution layered with excess pentane. Only the first crop of crystals, which usually corresponded to no more than 50% of the initial amount, was used. In this way, 4 was obtained as dark-purple crystals of cubic or octahedral shape

Scheme 2. Test Reaction of 4-Bromoanisole (5) with Aniline (6)



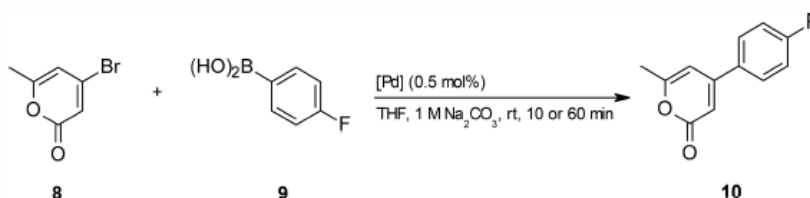
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Table 2. Analytical Data, Catalytic Performance, Microscopy at 200× Magnification, and SEM Images for All Samples under Investigation^{a†}

Species	Pd(dba) ₂							Pd ₂ (dba) ₃						Pd ₂ (dba) ₃ ·CHCl ₃			Pd ₂ (dba) ₃ ·PhMe	
Sample	1A	1B ₁	1B ₂	1C ₁	1C ₂	1D	1E	2A	2B ₁	2B ₂	2C	2D	2E	2F	3A	3D	3E	4
Pd(supp) / %	16.00-21.00	18.40	18.67	20.00	20.33	18.90	18.10	23.24 ^b	23.03	23.03	20.00	15.00-22.00	22.10	15.50	20.56 ^b	20.56 ^b	20.56 ^b	21.12 ^b
Pd(AAS) / %	19.57	n.d.	18.37	19.90	20.22	18.50	16.97	23.24	22.85	22.91	19.89	21.39	20.97	15.50	19.14	n.d.	20.51	
AiC / %	0.41	n.d.	11.26	0.36	5.70	n.d.	2.90	3.02	7.47	6.71	0.62	5.26	2.32	n.d.	2.28	n.d.	2.20	
AsP / %	19.16	n.d.	7.11	19.54	14.52	n.d.	14.07	20.22	15.38	16.20	19.27	16.13	18.65	n.d.	16.86	n.d.	18.31	
Catalytic performance, yield / %																		
Microscopy at 200x magnification																		
SEM																		

^aReaction conditions: **5** (1.0 mmol), **6** (1.0 mmol), NaO^tBu (1.5 mmol), Pd_x(dba)_y (0.5 mol % Pd, calculated from the Pd content reported by the supplier), and P^tBu₃ (0.4 mol %) in toluene (2 mL) at room temperature for 1 h. Yields were determined by GC analysis using *n*-dodecane as an internal standard. Abbreviations: Pd(supp), palladium content reported by the supplier; Pd(AAS), palladium content determined by atomic absorption spectroscopy; AiC, amount of insoluble components; AsP, amount of soluble palladium (equal to Pd(AAS) – AiC) ^bTheoretical amount of palladium.

 Scheme 3. Test Reaction of 4-Bromo-6-methyl-2H-pyrone (**8**) and 4-Fluorophenylboronic acid (**9**)


that were around 0.2 mm in size and had a melting point of 185 °C.

The palladium loadings for the reaction were calculated on the basis of the Pd content specified by the supplier¹⁴ or, if that information was not available, on the basis of the molecular formula provided (Table 1). The palladium content of each sample was double-checked by atomic absorption spectroscopy, which revealed no major inconsistencies between our own measurements and the data provided by the suppliers. The elemental analyses of all samples of **3** (i.e., **3D** and **3E**) showed strong discrepancies between the experimentally found and calculated molecular formulas, suggesting that some samples contain excess dba (Table S1). This is not unexpected since

Pd–dba adducts are often nonstoichiometric in nature and are known to incorporate solvent molecules during crystallization.

Table 2 lists the catalyst specifications for all of the samples investigated and shows the yields obtained in the test reaction along with visible-light microscopy and SEM images. The results were strongly variable, with yields ranging from 10% to nearly 100%. Some catalyst sources consistently gave similar yields, whereas the results obtained with others varied greatly, which indicates inhomogeneity of the material within the batch. The toluene adduct **4** used as a reference material performed consistently well throughout, confirming that the deviations are mostly caused by factors associated with the catalyst precursors rather than by experimental errors.

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We also investigated the palladium precatalysts in the Suzuki–Miyaura coupling of 4-bromo-6-methyl-2H-pyridone (8) and 4-fluorophenylboronic acid (9) (Scheme 3). Fairlamb et al. had established this reaction as a test to investigate the influence of substituents on the dba ligands.^{9a} However, 8 is not commercially available, which complicated the use of this test reaction. Moreover, the yields became too high and too similar to each other even after a short reaction time, which precluded a reliable comparison of precatalysts. Less reactive substrate combinations would be required to test this reaction type. Still, as can be seen from Table S6, the reactivity trends found in this alternative test reaction do not contradict those found for the amination.

Influence of the Pd Content. The results summarized in Table 2 reveal no clear correlation between the Pd content and catalytic performance. This is an important finding because we are aware from requests by synthetic chemists that it is often assumed that batches with a high Pd content have a higher purity and will perform better in catalytic reactions than those with a Pd content that is lower than expected from the molecular formula. Besides the normal Pd content, the relative amount of soluble palladium (AsP, in %) and the amount of insoluble components (AiC, in %, consisting mostly of agglomerated Pd black) were also determined.¹⁵

Especially when working with catalyst stock solutions, it is important to know how much of the material actually dissolves in organic solvents and how much of the bulk material is insoluble metallic palladium. This correlation was verified in a control experiment. The yield obtained in our test reaction dropped from 60% to 28% when the Pd–dba precursor was mixed with Pd black in a 1:1 ratio based on the overall Pd content (Table S7).

However, the results listed in Table 2 do not reveal any such correlation between AsP and catalyst activity. Hence, the AsP is not a reliable predictor for the performance of a batch of Pd–dba material in sensitive catalytic reactions.

Influence of the Molecular Formula Provided. When comparing the activities of commercial samples of 1, 2, and 3, it seems as though the better control of the stoichiometry in the Pd₂(dba)₃·CHCl₃ adduct (3) causes smaller variations with regard to catalyst performance than the other two compounds. Similar yields were obtained both within each batch and when using materials obtained from different suppliers. However, the overall performance of all samples of 3 is mediocre, which sustains the prejudice catalyst developers have against adducts that contain noninnocent components such as chloroform. The activities of the complexes Pd(dba)₂ (1) and Pd₂(dba)₃ (2) are subject to greater variability both within and between batches of 1 and 2 than for 3. Thus, at least for this test reaction, the catalyst performance cannot be predicted on the basis of the dba/Pd ratio. For a comparative study of Pd(dba)₂ versus Pd₂(dba)₃, see also the protocol of Peng.¹⁶

Influence of Particle Shape and Size. Next, all of the samples were investigated by microscopy at 200× magnification. Table 2 shows tremendous differences between the samples (see the Supporting Information for more detailed pictures). In the literature, crystals of 1 are described as brown to red-violet needles.^{3,4a} Such needles were seen for samples 1A, 1C, 2A, 2C, 2E, and 3E. In sample 1A, silver-colored octahedra, indicative of elemental Pd,¹⁷ were found alongside the needles. Samples 1D, 2B, and 2D consist of hexagonal crystals, which have not previously been described for Pd_x(dba)_y. In contrast, samples 1B₁ and 1B₂ are black,

amorphous powders. 1E and 2F consist of cubic crystals. This crystal shape has been reported for microstructures of 2 crystallized from THF/H₂O mixtures.¹⁸ 3A and 3D are violet needles, in agreement with literature reports for 3.⁵ These examples demonstrate how strongly the manufacturing process affects crystal shape and appearance of Pd_x(dba)_y materials.

The only conclusion one might possibly draw from the microscopic investigations in combination with the catalytic test reaction is that amorphous powders should be avoided because both samples of 1 from supplier B gave low yields in the test reaction. Other factors detectable by microscopy, such as crystal shape or color, do not lead to reliable predictions with regard to the catalytic performance of the material.

Scanning Electron Microscopy (SEM) and Energy-Dispersive X-ray Spectroscopy (EDX). We next investigated the solid materials by SEM and EDX to obtain further information on the elemental composition and homogeneity of the samples and to determine the presence, form, and size of palladium nanoparticles (Table 2). All of the samples were sprinkled on Cu grids and embedded in resin (for more information about methods and sample preparation, see the Experimental Section).

The brightness of the material correlates with the Pd content. At the brightest spots in the picture of 1B, a palladium content of 85% was measured by SEM, while the darker areas correspond to a Pd content of around 20%. This is indicative of a mixture of elementary palladium particles with Pd–dba complexes. The palladium particles have sizes of up to 3800 nm, well beyond those of soluble nanoparticles. In contrast, 1C displays a high level of homogeneity with a Pd content of at most 18.6%. A magnification of 250000× was necessary to detect bright spots indicative of elementary palladium. Most of these nanoparticles have a size of 2 nm, whereas very few measuring up to 20 nm seem to be embedded within the crystal matrix and could not be detected on the sample surface, even when the sample was incorporated into a resin and resin slices were prepared (see the Supporting Information and Experimental Section).

Since this highly homogeneous material performs comparatively well in the catalytic test reaction, one might conclude that SEM analysis allows prediction of the catalytic performance on the basis of the homogeneity of the sample and the absence of large, insoluble Pd particles. Indeed, many homogeneous samples performed well, including all of the samples from manufacturer C as well as 2A and 2E, whereas the catalytic activity was lower for many inhomogeneous samples, e.g. 1E and all samples from supplier B. However, this approach has its limitations, considering that 1A and 1D look similar by SEM but have a very different catalytic activities.

The chloroform adducts were also investigated by EDX, a technique that allows visualization of the distribution of different atom types. EDX showed that the distribution of chlorine atoms was remarkably inhomogeneous in sample 3A (Figure 1, EDX 3A Cl K). The highest chlorine concentration was found in areas that also have a high palladium concentration (EDX 3A Pd L). This points toward either chloroform-coated palladium particles or dissociation of chloroform with the formation of palladium chloride particles.

This is interesting, since one would assume from published crystal structures that the chloroform is embedded within the crystal matrix and thus homogeneously distributed.⁵ The same observation applies to sample 3D. However, in this sample, the chloroform was not only adsorbed onto the Pd surface but also

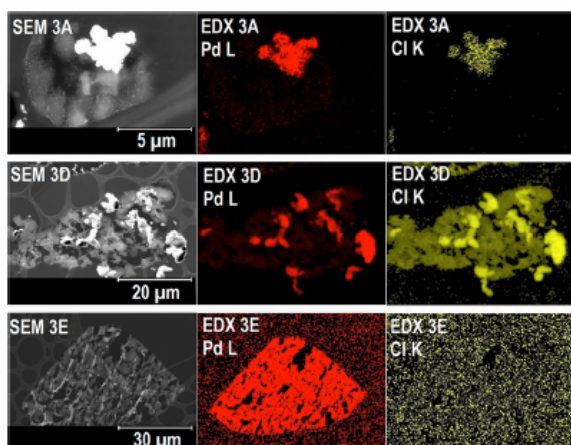


Figure 1. SEM and EDX measurements on samples 3A, 3D, and 3E. Chlorine content is visualized in yellow and palladium content in red.

present inside the crystal matrix (EDX 3D Pd L and EDX 3D Cl K). In our experience, homogeneous solvent adducts of $\text{Pd}_2(\text{dba})_3$ form only if the sample crystallizes very slowly. We thus assume that the commercial materials were rapidly precipitated from a chloroform-containing solution, resulting in nonstoichiometric mixtures of $\text{Pd}_2(\text{dba})_3 \cdot (\text{CHCl}_3)_x$ with chloroform-coated nanoparticles and/or palladium chloride. This may be a reason why the catalytic activity of the $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ samples in our test reaction was relatively low. Interestingly, no chlorine was detected in sample 3E even though ^1H NMR spectroscopy in solution showed that it was present in the sample (EDX 3E Cl). We believe that either the concentration of chloroform was too low for detection or that chloroform-containing particles were removed in the separation step that was part of sample preparation (for more information, see the [Experimental Section](#)). In any case, prediction of the catalytic activity on the basis of EDX is not possible since despite their differences, all of the tested samples of 3 have very similar catalytic activities.

Other Spectroscopic Studies. Several additional investigations were performed with the goal of establishing a correlation between physical or spectroscopic descriptors and the catalytic activity of palladium–dba adducts.

Any solvation process changes the composition of the dba adducts. This is the main problem when investigating the samples in a homogeneous phase, e.g., by ^1H NMR spectroscopy. Solution analysis can thus be used only to detect organic impurities. In this context, we found peaks in all of the tested samples that are indicative of traces of water, pentane, acetone, alcohols, or acetic acid (see [Figures S18–S23](#)). However, these small contaminants did not seem to decisively influence the catalytic activity. The samples were also investigated by ^{13}C magic-angle spinning (MAS) NMR spectroscopy ([Figure S24](#)), IR spectroscopy ([Table S3](#)), and X-ray diffraction (XRD) ([Figure S25](#)). However, none of the observations made in these investigations could be correlated to the performance of the samples in the test reaction (see the [Supporting Information](#)).

We next followed up on the observation that two different batches of 2 obtained from the same supplier had markedly different catalytic activities ([Table 2](#), sample 2B₁ vs 2B₂). A possible explanation is that the material loses activity during

storage, and therefore, newer samples are more active than older ones. A series of control experiments revealed that sample 2C, which had performed rather well in the first set of experiments (94, 86, and 81% yield), gave only 71, 40, and 68% yield after it had been stored under air for 14 months. In sharp contrast, the crystalline $\text{Pd}_2(\text{dba})_3$ -toluene adduct (4) still gave near-quantitative conversion (99, 99, and 99% yield) after this time. We suspected that the relatively high palladium content of 2C was at the origin of these stability issues, because there may have been insufficient dba to shield the Pd from the environment. We thus purchased a fresh sample of 2 from supplier F that had a Pd content of only 15.31% and contained excess dba. The new sample had roughly the same initial catalytic performance as 2C (83, 89, and 86% yield). We divided this batch into several samples that we stored under various conditions, and then we reinvestigated the catalytic activity after 6 months. These investigations revealed that regardless of whether the material was stored under argon or air, in a glass or air-permeable polyethylene vessel, or at room temperature, 40 °C, or 4 °C, the catalytic activity remained almost unchanged ([Figure 2](#)). Although additional systematic stability studies are clearly required, these comparative experiments suggest that excess dba leads to enhanced storability of the Pd catalysts.

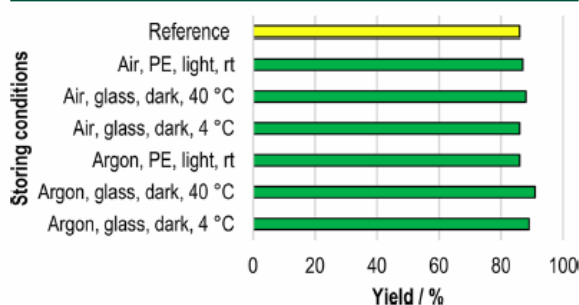


Figure 2. Reaction of 4-bromoanisole (5) with aniline (6) under standard conditions before and after storage of $\text{Pd}_2(\text{dba})_3$ (2) samples under the given conditions for six months.

Improving the Quality of $\text{Pd}(\text{dba})_2$ Batches. The above investigations show how difficult it is for synthetic chemists to be sure that the material they have in stock will perform well in a catalytic transformation. From our experience, it is advisable to convert stock Pd–dba into a crystalline adduct with an inert solvent such as toluene.

The efficiency of this strategy was probed for sample 1D, which had performed particularly poorly in the test reaction ([Table 2](#)) and had then been stored under air at room temperature for more than a year. A 50 mg (0.09 mmol) sample of this material was suspended in 15 mL of toluene (p.a. grade, Acros Organics), and the suspension was stirred for 30 min at room temperature. The resulting deep-red solution was then separated from the insoluble material by filtration through a pad of Celite. The clear filtrate was frozen by cooling the Schlenk flask with liquid nitrogen while applying a slight vacuum. The solidified product solution was then carefully layered with 5 mL of diethyl ether and 30 mL of pentane. After warming to room temperature, slow diffusion of the initially sharply separated solvent layers caused the product to crystallize within a week ([Figure 3](#)). This yielded 16.5 mg (18% yield) of large dark-purple crystals of toluene adduct 4



Figure 3. Crystallization of toluene adduct **4** shortly after removal of the cold bath.

with a melting point of 185 °C. The material thus obtained gave near-quantitative conversion in the test reaction in three independent runs.

The fact that this crystallization is time-consuming and low-yielding explains why it is not a valid large-scale manufacturing process for this material. However, in our hands any attempts to obtain toluene adduct **4** faster and in a higher yield led to nonstoichiometric materials with unreliable catalytic activity (see the Experimental Section). As can be seen from the crystal structure (Figure 4), even after slow crystallization, the

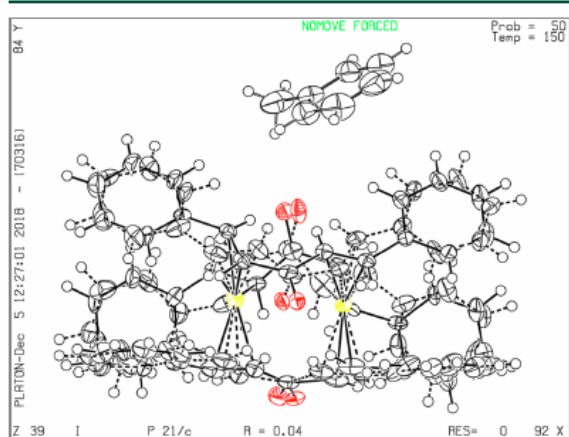


Figure 4. X-ray structure of the $\text{Pd}_2(\text{dba})_3\cdot\text{toluene}$ adduct (**4**) (50% disorder).

material still has a relatively high level of disorder (50%). However, it is a well-defined adduct of two palladium atoms, three dba molecules, and one toluene molecule.

CONCLUSION

This systematic evaluation of physical and spectroscopic properties of various commercial Pd–dba adducts revealed marked differences among the samples with regard to

homogeneity, crystal shape and size, color, and palladium content. As to be expected for a nonstoichiometric adduct, the molecular formula did not always correlate with the palladium content of the samples. Many of the dba adducts contain impurities and particulate Pd. However, no reliable correlation between the spectroscopic or physical data and the catalytic activity seems to exist. We found the Buchwald–Hartwig amination of 4-bromoanisole (**5**) and aniline (**6**) to be a sensitive and easy-to-perform test reaction that allows rapid determination of the catalytic activity of $\text{Pd}_x(\text{dba})_y$ samples. It is recommended that the catalytic activity of a new batch of $\text{Pd}_x(\text{dba})_y$ be investigated first with this known reaction before it is used for new catalytic transformations. The best results in the test reactions were consistently obtained with a self-made $\text{Pd}_2(\text{dba})_3\cdot\text{toluene}$ adduct (**4**), which had been slowly crystallized over several days. It can be stored for years under ambient conditions without losing its catalytic performance, which is superior to most newly purchased commercial samples. Even older and partially decomposed Pd–dba batches with unsatisfactory catalytic performance can easily be converted into this reliable precatalyst.

EXPERIMENTAL SECTION

General Information. All solvents were purchased from Acros Organics in p.a. grade and purified by standard procedures prior to use.¹⁹ 4-Bromoanisole ($\geq 99\%$ purity), tri-*tert*-butylphosphine (98% purity), disodium tetrachloropalladate (99.99% purity), and sodium acetate ($\geq 99\%$ purity) were purchased from Sigma-Aldrich and used without further purification. Aniline ($\geq 99\%$ purity) was purchased from Sigma-Aldrich and purified by standard procedures prior to use.¹⁹ 4-Bromo-6-methyl-2H-pyrene was synthesized according to the literature.²⁰ 4-Fluorophenylboronic acid (97% purity) and dibenzylideneacetone ($\geq 99\%$ purity) were purchased from TCI and used without further purification. Sodium *tert*-butoxide (97% purity) and sodium carbonate (99.5% purity) were purchased from Alfa Aesar and used without further purification. All solvents and liquids were degassed with argon prior to use. Reactions were performed in oven-dried glassware under a nitrogen atmosphere containing a Teflon-coated stirring bar and dry septum. All of the reactions were monitored by gas chromatography (GC) using *n*-dodecane as an internal standard. Response factors of the products with regard to *n*-dodecane 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 \times 320 μm \times 0.25 μm , 100/2.3–30–300/3, 2 min at 60 °C, heating rate 30 °C min^{-1} , 3 min at 300 °C). Elemental analyses were performed on an Elementar Vario Micro Cube. Melting points were measured on a Stanford Research Systems Digimelt MPA161 apparatus. The microscope pictures were taken with a Keyence VHX-500F digital microscope. The sample was placed on a glass slide and illuminated from above (left side) or below (right side). IR spectra were measured on a Perkin Elmer Spectrum 100 ATR-FTIR spectrometer. ¹H NMR spectra were measured on a Bruker DPX 400 FT-NMR spectrometer and recorded at ambient temperature using CD_2Cl_2 as the solvent with proton resonances at 400 MHz. All of the NMR data are reported in parts per million relative to the solvent signal. ¹³C MAS NMR spectra were measured on a Bruker AVANCE III 500 solid state NMR spectrometer. Powder diffractograms were measured on a Siemens D 5005 X-ray powder diffractometer

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Org. Process Res. Dev. XXXX, XXX, XXX–XXX

using Cu K α radiation (wavelength = 0.15406 nm, acceleration voltage = 40 kV, current = 30 mA) over a measurement range of $1^\circ < 2\theta < 100^\circ$. The X-ray analysis of Pd₂(dba)₃·PhMe was done on an Oxford Diffraction Gemini S Ultra diffractometer at 150 K using Mo K α or Cu K α radiation.

General Procedure for the Buchwald–Hartwig Amination. An oven-dried 20 mL vessel was charged with Pd_x(dba)_y (0.5 mol % Pd), NaO^tBu (149 mg, 1.5 mmol), and P^tBu₃ (0.4 mol %). Toluene (2 mL) and **5** (1 mmol) were added along with *n*-dodecane (50 μ L) as the standard. The reaction mixture was allowed to stir for 10 min before **6** (1 mmol) was added. The resulting mixture was stirred at room temperature under a nitrogen atmosphere. After 60 min, the mixture was diluted with ethyl acetate (4 mL), washed with water (2 mL), and extracted with ethyl acetate (3 mL). The organic layer was dried over MgSO₄, filtered, and directly analyzed by GC.

General Procedure for the Suzuki–Miyaura Coupling. An oven-dried 20 mL vessel was charged with Pd_x(dba)_y (0.5 mol % Pd), **8** (0.41 mmol), and **9** (0.41 mmol). THF (1.5 mL) and 1 M Na₂CO₃ (1 mL) were added along with *n*-dodecane (50 μ L) as the standard. The resulting mixture was stirred at room temperature under a nitrogen atmosphere. After 60 min, the mixture was diluted with ethyl acetate (4 mL), washed with water (2 mL), and extracted with ethyl acetate (3 mL). The organic layer was dried over MgSO₄, filtered, and directly analyzed by GC.

Sample Preparation for SEM and EDX Investigations. All of the samples were examined for Pd nanoparticles via SEM (dark- and bright-field pictures). Additionally, the elemental composition of each sample was examined by EDX. The samples were measured by two different methods. On the one hand, they were sprinkled on a lacey film (200 mesh Cu grids) to determine the form and size of the particles. This allowed the determination of the amount of Pd in each particle. The second technique allowed identification of Pd nanoparticles inside the crystal matrix. For that, the samples were incorporated into a resin and sliced with a diamond cutter as follows: The samples were fixed in Beem capsule tips for 16 h at 60 °C. Then the capsules were filled with the Spurr–Hart resin mixture and hardened for 16 h at 60 °C. The hardened samples were trimmed with a Leica EM Trim system or by hand. Then the slices were cut on a Reichert–Jung Ultracut or OM-U3 microtome with a 35° diamond blade (cutting speed = 0.5 mm/s, cutting thickness set at 28 nm). The cuts were transferred to lacey film (400 mesh Cu grid). These slices were tested for the presence, composition, and disposition of Pd nanoparticles. EDX data were recorded on a Thermo Scientific NORAN System 7 X-ray microanalysis system with a Thermo Scientific UltraDry EDS 30 mm² silicon drift detector.

Attempted Accelerated Synthesis of the Toluene Adduct. An oven-dried flask was charged with Na₂PdCl₄ (294 mg, 1.00 mmol) and dibenzylideneacetone (710 mg, 3.00 mmol). Under a nitrogen atmosphere, degassed methanol (8.33 mL) and toluene (41.67 mL) were added. The reaction mixture was heated to 60 °C under an inert gas atmosphere, transferred to a flask with sodium acetate (331 mg, 4.0 mmol), and stirred for 1 h. After cooling to room temperature, the solution was washed with water (3 \times 30 mL) and dried at –20 °C overnight. The resulting dark-purple crystals were washed with cold acetone (187 mg, 0.19 mmol, 19%). In three parallel runs of the Buchwald–Hartwig amination of **5** with **6** (see Scheme 2), yields of 80, 25, and 59% were achieved.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00214.

Crystallographic data for **4** (CIF)

Elemental analyses, melting points, microscope pictures, spectral data (IR, ¹H NMR, ¹³C MAS, XRD), properties of crystals and Pd nanoparticles, catalytic test reactions, SEM and EDX data for the tested commercial samples, and X-ray analysis of the toluene adduct **4** (PDF)

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Author Contributions

#P.W. and A.B. contributed equally. H.-J.B. performed and evaluated the SEM and EDX measurements. H.K. was responsible for the crystal structure. All of the authors contributed to writing the manuscript and approved the final version of the manuscript.

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Notes

The authors declare the following competing financial interest(s): A.D. is an employee of Umicore, a company that provided some of the catalyst batches. In order to minimize competing interests, no manufacturer names are given in this article, and the assignment of samples to suppliers will not be revealed to the public.

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(14) The palladium loadings for the reaction were calculated according to the Pd contents given by the suppliers. In some cases, suppliers A and D gave a range for the Pd content. In those cases, we performed the reaction with the minimum, medium, and maximum possible amounts of Pd in order to display any discrepancies resulting from this number. If no Pd content was given, the corresponding Pd loading for the reaction was calculated according to the theoretical amount of metal from the molecular formula.

(15) A Pd_x(dba)₃ sample was weighed and dissolved in an excess of chloroform. The undissolved solid was separated from the solution by filtration and weighed. Dividing its weight by the weight of the complete sample (from the beginning) gives the AiC (in %). By subtracting the AiC from the measured Pd content (in %, as determined by AAS), we calculate the AsP, from which we expect to display the amount of actually dissolvable Pd in a sample.

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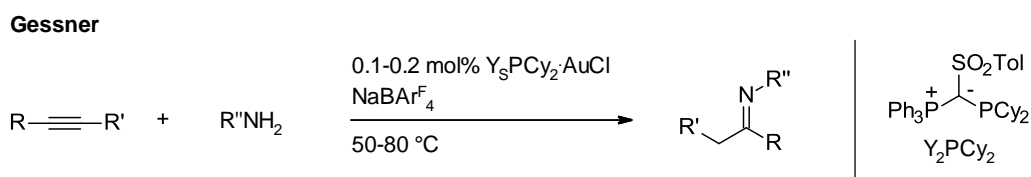
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5.2 A highly active Ylide-Functionalized Phosphine for Palladium-Catalyzed Aminations for Aryl Chlorides

Basierend auf vorherigen Arbeiten, wie der Herstellung von Ylidiiden,²⁶² konnte in der Gruppe von Prof. Dr. Däschlein-Gessner eine neue Phosphor-haltige Ligandenklasse entwickelt werden, welche mit einem Ylid-Substituenten am Phosphoratom ausgestattet ist.²⁶³ Durch die zusätzliche Elektronenzugabe des Ylids zum Phosphorzentrum des Liganden werden diese sehr elektronenreich und können bessere Elektronendonoren als herkömmliche Phosphan- oder NHC-Liganden sein.

Erste Prototypen des YPhos-Liganden, welche auf einem Triphenylphosphangerüst am Phosphor und einer Cyano- oder Tosylgruppe am Kohlenstoff des Ylids basieren, konnten gute Ergebnisse bei Gold-katalysierten Hydroaminierungen erzielen (Schema 36). Ebenfalls konnten Pent-4-insäure intramolekular zum Lacton cyclisiert und Phenylacetylen mit Wasser zu Acetophenon hydratisiert sowie mit α -Methylstyrol [2+2]-cycloaddiert werden.



Schema 36. Gold-katalysierte Hydroaminierung mit YPhos.

In Buchwald-Hartwig-Aminierungen konnte dieser Katalysator allerdings weniger gute Ergebnisse erzielen. Erst eine neue Generation mit einem Tricyclohexyl-Substituenten am Phosphoratom und einer Methylgruppe am Kohlenstoffatom des Ylids erzielte vielversprechende Ergebnisse auch bei niedrigeren Temperaturen, Reaktionszeiten und Katalysatorbeladungen.

Basierend auf den Arbeiten in Prof. Dr. Däschlein-Gessners Gruppe optimierte ich mit der Unterstützung von Herrn Dominik Lichte die Buchwald-Hartwig-Aminierung mit dem neuen Liganden und demonstrierte die Anwendungsbreite mit unterschiedlichen Aminen und Arylchloriden. Zudem führten wir ein Benchmark gegen andere Konkurrenzsysteme aus. Die Entwicklung sowie die Synthese der Liganden wurde von Herrn Dr. Thorsten Scherpf und Ilja Rodstein unter der Leitung von Prof. Dr. Däschlein-Gessner übernommen. Herr Lennart T. Scharf war für die DFT-Rechnungen zuständig.

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Ein hochaktives, Ylid-funktionalisiertes Phosphan für die palladium-katalysierte Aminierung von Arylchloriden

 Philip Weber^a, Thorsten Scherpf^a, Ilja Rodstein, Dominik Lichte, Lennart T. Scharf,
 Lukas J. Goossen^{a*} und Viktoria H. Gessner^{a*}

Abstract: Ylid-funktionalisierte Phosphanliganden (YPhos) wurden entwickelt, um den Voraussetzungen einer Buchwald-Hartwig-Aminierung bei Raumtemperatur zu genügen. Diese Ligandenklasse kombiniert ein besonders hohes Elektronendonatorvermögen, vergleichbar mit dem von NHC-Liganden, mit hohem sterischem Anspruch ähnlich jenem von Biarylphosphanen. Die aktiven Pd-Spezies sind dabei über agostische C-H...Pd- und nicht über Pd-Aren-Wechselwirkungen stabilisiert. Der praktische Vorteil dieser YPhos-Liganden liegt insbesondere in deren einfacher und skalierbarer Synthese ausgehend von leicht zugänglichen sowie günstigen Startmaterialien. Benchmark-Untersuchungen zeigten, dass YPhos-Pd-Komplexe den üblicherweise verwendeten Phosphanliganden in Aminierungen von Arylchloriden bei Raumtemperatur überlegen sind. Der enorme Nutzen dieses Katalysatorsystems konnte durch die Synthese zahlreicher Arylamine in sehr guten Ausbeuten bei geringer Reaktionszeit aufgezeigt werden.

Homogene Katalyse ist ein wichtiger Bereich der modernen organischen Synthese und findet breite Anwendung in der großtechnischen Herstellung von Feinchemikalien bis hin zur stereoselektiven Synthese komplexer Moleküle. Die Entwicklung von Katalysatoren mit neuartigen Aktivitätsbereichen, die Fortschritte in der Selektivität, Nachhaltigkeit und Effizienz chemischer Reaktionen erzielen können, ist eng verbunden mit der Entdeckung neuartiger Ligandensysteme. Zum jetzigen Zeitpunkt sind Phosphane die dominierende Ligandenklasse und werden in wichtigen Prozessen wie Kupplungsreaktionen, Hydrierungen, Hydroformylierungen und weiteren Hydrofunktionalisierungen eingesetzt.^[1] Häufig werden dabei elektronenreiche Phosphanliganden benötigt, um die aktive Metallspezies zu stabilisieren, Bindungsaktivierungsprozesse zu erleichtern oder andere Liganden am

Metallzentrum zu ersetzen. Folglich enthalten kommerzielle und industriell relevante Phosphane wie cataCXium[®] A,^[2] DalPhos^[3] oder Buchwald-artige Biarylphosphanen elektronenschiebende Cyclohexyl(Cy)-, tert-Butyl(t-Bu)- oder Adamantyl(Ad)-Gruppen (Abbildung 1).^[4] Die Entwicklung potenterer Katalysatorsysteme, die bereits unter milden Reaktionsbedingungen aktiv sind, ist durch die eingeschränkte Elektronendonorkapazität dieser Alkylsubstituenten limitiert.

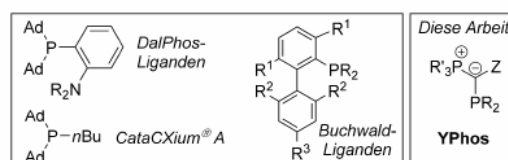


Abbildung 1. Beispiele bedeutender Phosphane mit Anwendung in der homogenen Katalyse.

Kürzlich berichteten wir über eine neue Klasse einzähliger, elektronenreicher Phosphanliganden, die mit einem Ylid-Substituenten am Phosphoratom ausgestattet ist.^[5,6] In Abhängigkeit vom jeweiligen Substitutionsmuster des Ylids können die elektronenschiebenden Eigenschaften dieser so genannten YPhos-Liganden sogar die der üblicherweise verwendeten N-heterocyclischen Carbene (NHCs) übersteigen. Erste Anwendungen in goldkatalysierten Hydroaminierungen ergaben eine hohe Aktivität der YPhos-komplexierten kationischen Goldspezies. Motiviert durch diese ersten Resultate widmeten wir uns dem Anwendungspotential unserer Liganden in weiteren katalytischen Umsetzungen. Wir konzentrierten uns zunächst auf Buchwald-Hartwig-artige C-N-Kupplungen, die wegen der breiten Präsenz von Arylaminen in Naturstoffen, Agrochemikalien sowie Pharmazeutika von besonderer industrieller Bedeutung sind.^[7] Die rapiden Fortschritte dieser Reaktion sind dem rationalen Design von maßgeschneiderten Liganden wie Buchwalds Biarylphosphanliganden,^[8] Hartwigs Ferrocenylphosphanen,^[9] Bellers N-substituierten Heteroarylphosphanen,^[10] sterisch anspruchsvollen Trialkylphosphanen^[11] oder N-heterocyclischen Carbenen^[12] zu verdanken. Trotz der beachtlichen Weiterentwicklungen der letzten beiden Jahrzehnte erfordern die meisten Katalysatorsysteme dennoch eine aufwändige Vor-synthese sowie teilweise hohe Reaktionstemperaturen.

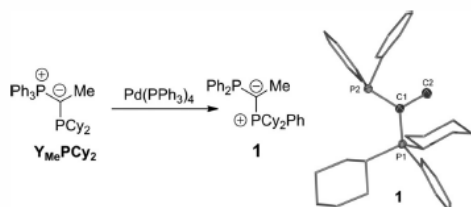
Der YPhos-Ligand Y_{Me}PCy₂, der eine Methylgruppe am Ylid-Grundgerüst aufweist, wurde als geeignete Leitstruktur für die Anwendung dieser Ligandenklasse in der Palladium-

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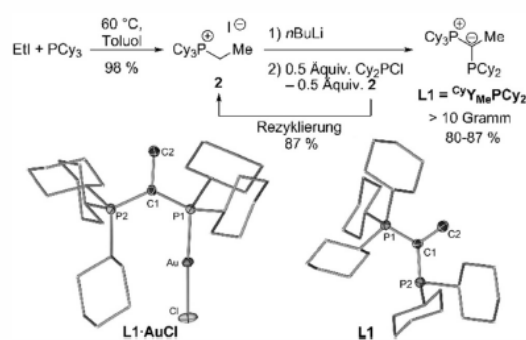
katalyse verwendet (Schema 1). Die Methylgruppe sorgt für ein äußerst elektronenreiches Phosphorzentrum mit einer Donorstärke weit über der einfacher Phosphane wie P^tBu_3 oder PAd_3 und vergleichbar zu jener von NHCs. Erste Test-



Schema 1. Links: Zersetzung von $Y_{Me}PCy_2$ zum Diphenylphosphan **1**; rechts: Molekülstruktur von **1**.^[2,3]

reaktionen in der Aminierung von Arylbromiden sowie -chloriden mit $Y_{Me}PCy_2$, verschiedenen Palladiumquellen und KO^tBu als Base bei Raumtemperatur ergaben jedoch unterschiedliche Ausbeuten, die schwierig zu reproduzieren waren. Um einen Einblick in den Ursprung dieser widersprüchlichen und unbefriedigenden Ergebnisse zu erlangen, wurde eine Lösung des Liganden mit $Pd(PPh_3)_4$ mittels NMR-Spektroskopie analysiert. Das erhaltene Spektrum zeigte vollständigen Umsatz des Liganden und die selektive Bildung eines neuen Produkts, das eindeutig als das Diphenylphosphan **1** – anstatt eines Pd-Komplexes von $Y_{Me}PCy_2$ – identifiziert werden konnte. Diese Befunde ließen darauf schließen, dass unter den Reaktionsbedingungen die P-C_{ph}-Bindung der Phosphoniumgruppe durch Pd^0 aktiviert und auf die basischere PCy_2 -Gruppe übertragen wird. Da die Donorstärke von **1** lediglich moderat ist, verläuft die Aminierung bei Raumtemperatur ineffizient, sobald **1** gebildet wird.

Um das Ligandengerüst und damit die hohe Donorstärke des Liganden beizubehalten, wurde die PPh_3 -Gruppe durch eine PCy_3 -Gruppe ersetzt, da die Pd-vermittelte P-C-Bindungsaktivierung für P-Alkyl-Bindungen langsamer verlaufen sollte. Die Synthese von $^{Cy}Y_{Me}PCy_2$ stellte sich sogar im Multigramm-Maßstab als bemerkenswert einfach heraus (Schema 2).^[13] **L1** ist ausgehend von den einfachen, kommerziell erhältlichen Materialien Ethyliodid, PCy_3 und Cy_2PCl in nur zwei Stufen zugänglich. Dabei wird das in der ersten Stufe generierte Phosphoniumsalz **2** zunächst mit einem Äquivalent *n*-Butyllithium deprotoniert und anschließend mit 0.5 Äquivalenten Cy_2PCl versetzt, um **L1** zu erhalten. Das aus **2** intermediär gebildete Ylid wirkt zugleich als Substrat und als Base und deprotoniert das in situ gebildete α -phosphansubstituierte Phosphoniumsalz zum finalen Liganden. Dieses Verfahren wurde auf eine Ausbeute von mehr als 10 g **L1** hochskaliert. Das Phosphoniumsalz **2** wurde rezykliert (in 87% Ausbeute) und für weitere Ligandsynthesen wiederverwendet. $^{Cy}Y_{Me}PCy_2$ erwies sich als relativ stabil und zeigte an Luft über mindestens 24 Stunden lediglich Spuren von Oxidation oder Zersetzung. Somit kann der Feststoff zum Ansetzen von Reaktionen an der Luft gehandhabt werden. Allerdings treten nach sieben Tagen sichtbare Abbaureaktionen auf.



Schema 2. Oben: Herstellung von **L1**; unten: Molekülstrukturen von **L1** und dem entsprechenden Goldkomplex (Ellipsoide stellen 50% Aufenthaltswahrscheinlichkeit dar; Wasserstoffatome sind nicht gezeigt).^[23]

Der Ligand zeigt zwei charakteristische Dubletts im ^{31}P - $\{^1H\}$ -NMR-Spektrum bei $\delta = 1.0$ und 30.6 ppm mit einer großen Kopplungskonstante von $J = 128.9$ Hz. Dies lässt auf eine *syn*-Anordnung der Methyl- und PCy_2 -Gruppen in Lösung schließen, in Übereinstimmung mit der Festphasenstruktur von $Y_{Me}PCy_2$ (Schema 2, unten).^[5] Der Gold-Chlorid-Komplex von **L1** wurde für die Berechnung des verdeckten Volumens ($\% V_{bur}$)^[14] und zur Quantifizierung der sterischen Eigenschaften des Liganden hergestellt. Mit $\% V_{bur} = 48.5\%$ ist die sterische Abschirmung von **L1** höher als bei einfachen Phosphanen – eingeschlossen PAd_3 ($\% V_{bur} = 40.5\%$)^[6d] – und liegt im Bereich derjenigen von Biarylphosphanen (z. B. JohnPhos: $\% V_{bur} = 50.9\%$).^[14b] was ebenfalls mit der relativ hohen Luftstabilität von $^{Cy}Y_{Me}PCy_2$ übereinstimmt. Der berechnete elektronische Parameter nach Tolman (TEP) von **L1** beträgt 2050.1 cm^{-1} .^[15, 16] Dieser Wert ist erheblich kleiner als für einfache Phosphane (z. B. $TEP(PCy_3) = 2058.1 \text{ cm}^{-1}$)^[16], was darauf schließen lässt, dass es sich bei $^{Cy}Y_{Me}PCy_2$ um einen stärkeren Elektronendonator mit einer zu NHCs vergleichbaren Donorkapazität handelt (vgl. 1,3-Dimesitylimidazol-2-yliden, IMes: $TEP = 2050.7 \text{ cm}^{-1}$)^[17].

Zur Bewertung der Stabilität von **L1** in Gegenwart von Pd^0 wurde ein Pd^0 -**L1**-Addukt aus **L1** und Pd_2dba_3 ($dba =$ Dibenzylidenacetone) hergestellt. NMR-Experimente bestätigten die Intaktheit der P-C-Bindung von **L1** über 24 Stunden. Die Diffusion von Pentan in eine Lösung von Pd_2dba_3 und einem Äquivalent von **L1** in Toluol führte zur Bildung von dunkelroten, zur Einkristallstrukturanalyse geeigneten Kristallen. Die resultierende Molekülstruktur belegt die Bildung des Monophosphan- dba -Komplexes **L1**- $Pd(dba)$ (Abbildung 2)^[18] und bestätigt den sterischen Anspruch des Liganden sowie die Abschirmung des Metallzentrums, was bereits durch das berechnete verdeckte Volumen angedeutet wurde (siehe oben). Die Pd-P- ($2.3318(9) \text{ \AA}$) und Pd-C-Bindungen ($2.118(4)$ und $2.144(4) \text{ \AA}$) zum dba -Liganden sind kurz, jedoch vergleichbar zu jenen in den entsprechenden Biarylphosphankomplexen.^[18]

Interessanterweise wird in im Kristall ein kurzer Pd-H-Kontakt von nur $2.09(2) \text{ \AA}$ (Pd-C: $3.010(2) \text{ \AA}$) beobachtet,

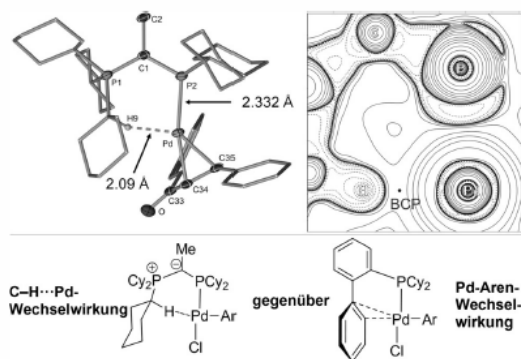
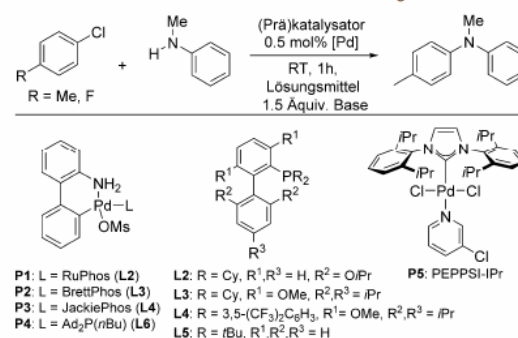


Abbildung 2. Oben: Molekülstruktur von L1-Pd(dba)^[25] und die Topologie der Elektronendichteverteilung nach Laplace von der Bindungsregion zwischen L1 und Palladium (BCP=bindungskritischer Punkt); unten: Metall-Ligand-Wechselwirkung in Pd^{II}-Komplexen mit L1 und Biarylphosphanliganden.

was auf das Vorhandensein einer weiteren stabilisierenden Wechselwirkung zwischen dem Liganden und dem Pd⁰-Zentrum schließen lässt. QT/AIM-Studien (QT/AIM = Quantum theory of atoms in molecules) ergaben außerdem einen bindungskritischen Punkt zwischen Pd und H mit einer Elektronendichte von 0.044e, was für eine agostische Wechselwirkung spricht (Abbildung 2).^[19] Die NBO-Analyse (NBO = natürliche Bindungorbitale), die berechneten Wiberg-Bindungsindizes und die natürlichen Ladungen stimmen ebenfalls mit dieser Interpretation überein (siehe Hintergrundinformationen (SI)). Im ¹H-NMR-Spektrum wurde kein Anzeichen für eine starke Wechselwirkung in Lösung beobachtet, was auf eine lediglich schwache C-H...Pd-Wechselwirkung in L1-Pd(dba) hinweist. Ähnliche, stabilisierende agostische Wechselwirkungen wurden in anderen katalytisch aktiven, niedrig koordinierten Pd-Komplexen mit sterisch anspruchsvollen Liganden beobachtet.^[20] Aufgrund der schwachen C-H...Pd-Wechselwirkung sollte die Dekoordination zur Öffnung einer freien Bindungsstelle einfach sein und weniger Energie benötigen, als es für die Spaltung der Aren-Pd-Wechselwirkung in den Buchwald-Systemen der Fall ist.^[21,22] Hier hat sich die Rotation um die P-C-Bindung für eine schnelle Umsetzung bei Raumtemperatur als zum Teil entscheidend erwiesen.^[21] Basierend auf den oben gezeigten, speziellen Struktureigenschaften von L1 sollten Pd-Komplexe des YPhos-Liganden hervorragend für Buchwald-Hartwig-Aminierungen geeignet sein.

Um die Aktivität von ¹³C₆H₅PCy₂ in C-N-Kreuzkupplungen zu testen und mit derjenigen bekannter Katalysatoren mit anderen Ligandensystemen zu vergleichen, wurden die C-N-Kupplungen von 4-Chlortoluol und 4-Fluorchlorbenzol mit *N*-Methylanilin bei Raumtemperatur als Testreaktionen ausgewählt. Beim Testen verschiedener Reaktionsbedingungen ergaben sich exzellente Aktivitäten bei 0.5 mol % L1 mit 0.25 mol % Pd₂dba₃ oder 0.5 mol % Pd(OAc)₂ sowie 1.5 Äquivalenten KO^tBu in zahlreichen Lösungsmitteln (siehe Tabelle 1 und SI). Beispielsweise wurde für die Aminierung von 4-Chlortoluol in Dioxan innerhalb einer Stunde

Tabelle 1: Aktivität verschiedener literaturbekannter Liganden.



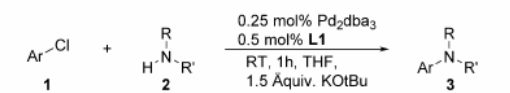
R	(Prä)katalysator	Base	Lösungsmittel	Ausb. [%] ^[a]
Me	L1-Pd ₂ dba ₃	KO ^t Bu	THF	95
Me	L1-Pd ₂ dba ₃	NaO ^t Bu	THF	52
Me	L1-Pd ₂ dba ₃	KO ^t Bu	Dioxan	99
F	L1-Pd ₂ dba ₃	KO ^t Bu	THF	83
F	L1-Pd ₂ dba ₃	NaO ^t Bu	THF	45
F	L1-Pd ₂ dba ₃	KO ^t Bu	Dioxan	88
F	L1-Pd(OAc) ₂	KO ^t Bu	THF	87
F	P1-P5	KO ^t Bu	THF	< 1
F	L2, L3 oder L5-Pd ₂ dba ₃	KO ^t Bu	THF	< 1
F	L5-Pd(OAc) ₂ ^[b]	NaO ^t Bu	Toluol	10 (84) ^[c]
F	L1-Pd(OAc) ₂ ^[b]	NaO ^t Bu	Toluol	78 (88) ^[c]

[a] Reaktionsbedingungen: Arylchlorid (1 mmol), *N*-Methylanilin (1.1 mmol), THF (2 mL), Katalysatorlösung in THF, Base (1.5 Äquiv.), RT, 1 h; Ausbeuten wurden entweder mittels ¹⁹F-NMR-Analyse mit α, α, α -Trifluortoluol als internem Standard oder mittels GC unter Verwendung von *n*-Tetradecan als internem Standard bestimmt. [b] 1 mol % Ligand. [c] Nach 19 h.

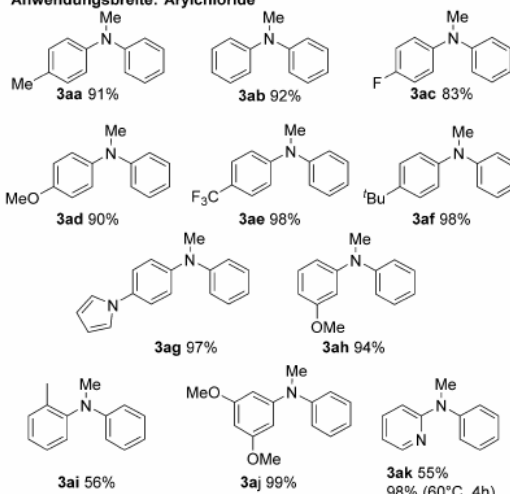
voller Umsatz erzielt. Nahezu gleiche Aktivität wurde in THF beobachtet. Unter diesen Bedingungen konnte keiner der getesteten etablierten C-N-Kupplungskatalysatoren – einschließlich der Biarylphosphankomplexe P1 und P2 (mit RuPhos (L2) und BrettPhos (L3)), des PEPPSI-IPr-Komplexes P5 oder des Ad₂Pd(^tBu)-basierten Präkatalysators cataCXium[®] A PdG3 – vergleichbare Aktivität zeigen. Selbst bei Verwendung des Biaryligen JohnPhos (L5) unter den entsprechenden optimierten Literaturbedingungen^[23] ist der Umsatz mit L1 höher.

Als nächstes untersuchten wir die Anwendungsbreite unter den optimierten Reaktionsbedingungen (Schema 3). L1 erzielte hervorragende Umsetzungen mit einer Vielzahl von Arylchloriden. Selbst elektronenreiche Verbindungen wie 4-Chloranisol reagierten bereits innerhalb von einer Stunde mit *N*-Methylanilin. Sogar anspruchsvollere, *ortho*-substituierte Arene sowie Heterocyclen wie Pyridin gehen die Kupplung bei Raumtemperatur ein. Letztgenannte sind wegen ihres Vorkommens in zahlreichen pharmazeutisch relevanten Verbindungen von besonderem Interesse. Der Katalysator ist bereits bei Raumtemperatur sehr effektiv. Zum Erzielen noch höherer Umsätze kann er aber auch bei leicht erhöhten Temperaturen verwendet werden.

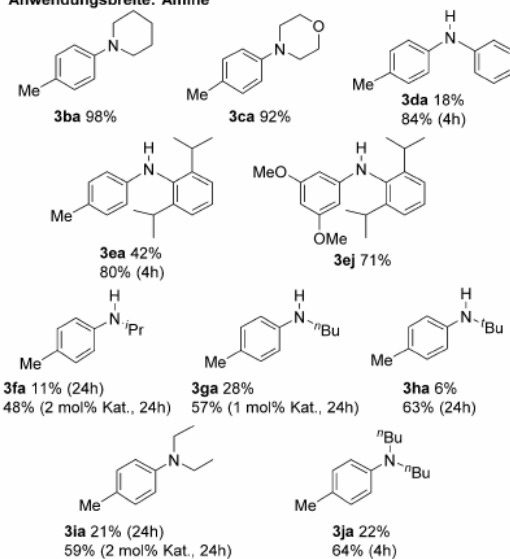
Auch eine Vielzahl von Aminen mit unterschiedlichen sterischen und elektronischen Eigenschaften kann unter



Anwendungsbreite: Arylchloride



Anwendungsbreite: Amine



Schema 3. Anwendungsbreite der C-N-Kreuzkupplung mit Ligand L1. Reaktionsbedingungen: Arylhalogenid (1.0 mmol), Amin (1.1 mmol), L1 (0.5 mol%), Pd₂dba₃ (0.25 mol%), KO^tBu (1.5 mmol), THF (2.0 mL). Bei allen Ausbeuten handelt es sich um Ausbeuten an isoliertem Produkt.

denselben Bedingungen umgesetzt werden. Piperidin und Morpholin zeigen vollständigen Umsatz in unter einer Stunde Reaktionszeit. Sogar schwer umsetzbare Amine wie *tert*-Butylamin oder 2,6-Diisopropylanilin, die gewöhnlich hohe

Katalysatorladungen, erhöhte Temperaturen sowie lange Reaktionszeiten benötigen,^[8a] reagieren unter den Standardbedingungen. Nach unserem besten Wissen ist eine derartig hohe Leistungsfähigkeit in der Kupplung eines solch breiten Spektrums an Arylchloriden und Aminen, einschließlich anspruchsvoller elektronenreicher und sperriger Substrate, bisher mit keinem anderen Liganden bei Raumtemperatur beobachtet worden.^[24]

Ein Ylid-substituiertes Phosphan (YPhos) konnte entwickelt werden, das Pd-Komplexen eine herausragende Aktivität in C-N-Kreuzkupplungsreaktionen verleiht. Selbst schwierige Substrate werden bei Raumtemperatur ohne nötige Feinabstimmung des Liganden für ein bestimmtes Amin oder Herstellung eines bestimmten Pr\u00e4katalysators umgesetzt. Dabei ist der YPhos-Ligand selbst im Multi-gramm-Ma\u00dfstab leicht zug\u00e4nglich. Die ungew\u00f6hnliche Aktivit\u00e4t des Katalysators ist erkl\u00e4rbar durch die starken Donoreigenschaften des Liganden sowie dessen einzigartige Architektur, die niedrig koordinierte Pd-Spezies \u00fcber schwache intramolekulare C-H...Pd-Wechselwirkungen stabilisiert. Diese Wechselwirkung wird bereitwillig aufgebrochen, um eine freie Koordinationsstelle f\u00fcr das Substrat zu \u00f6ffnen. Die vorgestellten Ergebnisse belegen eindrucksvoll die vorteilhaften Eigenschaften des YPhos-Liganden in der homogenen Katalyse, die aktuell weiter erforscht werden.

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Interessenkonflikt

Die Autoren erkl\u00e4ren, dass keine Interessenkonflikte vorliegen.

Stichw\u00f6rter: Agostische Wechselwirkungen · Homogene Katalyse · Kreuzkupplungen · Phosphanliganden · Ylide

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5.3 Ylide-Functionalised Phosphine (YPhos)-Palladium Catalysts: Selective Monoarylation of Alkyl Ketones with Aryl Chlorides

Nachfolgend zum Aminierungsprojekt sollte nach weiteren Anwendungen für die neue Generation der Yphos-Liganden gesucht werden. In der Zwischenzeit wurde in der Gruppe von Frau Prof. Dr. Däschlein-Gessner ein weiterer Ligand entwickelt. Im Vergleich zum vorherigen Liganden ($Y_{Me}PCy_2$) hatte dieser am Phosphoratom (welches nicht zum Ylid gehört) zwei *tert*-Butyl- anstelle zweier Cyclohexylgruppen ($Y_{Me}P^tBu_2$).

Durch diese sterisch anspruchsvolleren Gruppen sollte zuerst versucht werden Ammoniak mit Arylchloriden monoselektiv zu arylieren, jedoch wurde ausschließlich diaryliertes Produkt gebildet. Zwar ist dies eine Verbesserung zu $Y_{Me}PCy_2$ (bei dessen Einsatz auch Triarylierung beobachtet wurde), allerdings erfüllt der neue Ligand nicht den geforderten sterischen Anspruch. Eine C-O-Bindungsknüpfung mit Phenolen kam mit beiden Liganden nicht über moderate Ausbeuten hinaus, da ein Großteil des Arylchlorids vor der Kupplung protodechloriert wurde. Dafür konnte unter den Standardbedingungen der Aminierung Propiophenon fast quantitativ α -aryliert werden.

Ausgehend von diesen ersten Ergebnissen sollte ein Protokoll entwickelt werden, welches auch schwierigere Substrate wie Cyclohexanon in guten Ausbeuten monoaryliert. Ein Großteil der Entwicklung der Reaktion und die Optimierung der Reaktionsbedingungen wurden von Herrn Dr. Xiaoxang Hu, mir und Herrn Dominik Lichte durchgeführt. Die Testung der Anwendungsbreite wurde von Herrn Hu, Herrn Lichte und Frau Ann-Katrin Seitz mit meiner Unterstützung ausgeführt. Die Synthese der Liganden wurde von Herrn Ilja Rodstein unter Leitung von Frau Prof. Dr. Däschlein-Gessner durchgeführt. Für die Aufnahme der Kristallstruktur war Herr Scherpf zuständig. Der Großteil des Manuskriptes wurde von Herrn Hu und Herrn Prof. Gooßen mit Unterstützung von Frau Prof. Gessner verfasst. Die Supporting Information wurde von Herrn Hu, Herrn Lichte, Herrn Rodstein und Frau Seitz verfasst.

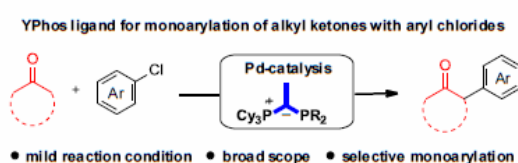
Die Ergebnisse sollen bei der Zeitschrift *Organic Letters* eingereicht werden. Die Kopie einer Vorabversion des Manuskriptes ist nachfolgend beigefügt.

Ylide-Functionalized Phosphine (YPhos)-Palladium Catalysts: Selective Monoarylation of Alkyl Ketones with Aryl Chlorides

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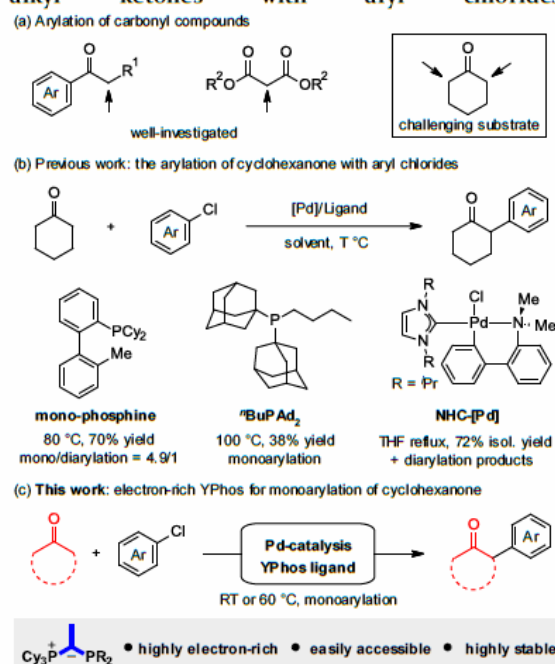
ABSTRACT: Ylide-functionalized phosphine (YPhos) ligands allow the palladium-catalyzed α -arylations of alkyl ketones with aryl chlorides with record setting activity. Using a *tert*-butyl substituted YPhos ligand, some of the most challenging ketones substrates were efficiently and selectively monoarylated at room temperature. A cyclohexyl substituted YPhos ligand was found to be slightly less active but more robust. The synthetic potential was demonstrated by the preparation of a large number of arylated cyclohexanone and other cyclic and acyclic ketones including gram-scale reactions and the succinct synthesis of ϵ -caprolactone derivatives.

The synthesis of α -aryl ketones are of substantial interest in pharmaceutical research and natural product synthesis.¹ Semmelhack *et al.* pioneered transition metal-catalyzed α -arylations of ketones in their synthesis of cephalotaxinone.² Efficient catalysts were later developed featuring electron-rich, sterically hindered phosphines or *N*-heterocyclic carbenes (NHC) in combination with palladium or nickel catalysts.³ Owing to contributions e.g. by Hartwig,⁴ Buchwald,⁵ Miura,⁶ Beller,⁷ and Nolan,⁸ the reaction concept was advanced to a stage that is close to synthetic maturity. The key advantage of Pd/Ni systems is that they permit the use of inexpensive aryl chlorides. Aryl bromides or iodides can also be converted with copper catalysts,⁹ and highly reactive aryl substrates, such as hypervalent iodine reagents,¹⁰ benzynes,¹¹ diazonium salts,¹² nitroarenes,¹³ are amenable to metal-free arylation strategies.

Despite the many advances made in this field,¹⁴ the coupling of small, unbranched alkyl ketones with aryl chlorides still remains a challenge and even the most sophisticated catalyst systems reach their performance limit (Scheme 1a). The main obstacle is the particularly slow reductive elimination of aryl enolates from Pd for sterically unhindered ketones.¹⁵ The monoarylation products are inherently more reactive because the additional aryl group facilitates the reductive elimination step. Moreover, the additional aryl group increases the acidity of any remaining α -C-H bonds, so that predominantly the product

molecules are deprotonated when using equimolar amounts of base. The resulting formation of mixtures of polyarylated products is a particular problem when elevated temperatures are required to convert unreactive aryl chloride substrates.¹⁶

In this context, the coupling of cyclohexanone with aryl chlorides is the ultimate performance test for any α -arylation catalyst. Efficient monoarylation of cyclohexanones at mild conditions has so far only been reported with aryl bromides or imidazolyl sulfonates^{16, 5a, 17}. In case of aryl chlorides, Buchwald reported a 4.9:1 mono-to-diarylation selectivity and 70% yield for cyclohexanone with 2-dicyclohexylphosphino-2'-methylbiphenyl at 80 °C,^{5b} Beller a high selectivity but only 38% yield using *n*-butylbis(1-adamantyl)phosphine (^tBuPAD₂) at 100 °C,⁷ and Nolan a high yield but moderate selectivity using a bulky NHC ligand in refluxing THF.^{18a} However, the catalysts were only tested for cyclohexanone itself, not for substituted derivatives or other cyclic ketones and mostly only in combination with simple chlorobenzene (Scheme 1b). After many years of optimization, the mature ligand structures described above set a standard that is hard to

Scheme 1. Transition metal-catalyzed α -arylation of alkyl ketones with aryl chlorides.


match with any conceptually distinct ligand type. Nevertheless, NHCs and phosphines seem to reach their inherent performance limits, and innovative concepts are vital for further performance leaps. We recently disclosed a new class of ylide-functionalised monophosphine ligands (YPhos).¹⁹ The ylide group induces donor qualities that match or even exceed those of NHCs. Metal–YPhos complexes are easily generated from bench-stable phosphonium salts, which in turn are accessible in great structural diversity from simple precursors. The first catalytic applications of YPhos in Au-catalyzed hydroamination and hydration reactions^{19b} as well as Pd-catalyzed Buchwald–Hartwig aminations²⁰ showcase the potential of this ligand class.

The excellent donor ability of the YPhos class gave us confidence that YPhos catalysts would enable the α -arylation of carbonyl compounds with aryl chlorides, while the modular tunability of its steric demand would facilitate the design of selective mono-arylation catalysts (Scheme 1c).

In order to benchmark our YPhos ligands against the best known catalysts, we chose the challenging arylation of cyclohexanone **1a** with 4-chlorotoluene **2a** as test reaction. The temperature was set to only 60 °C at a catalyst loading of 1 mol% (Table 1). At most, trace amounts of product were observed when employing Pd(COD)Cl₂ together with the benchmark ligands *t*BuPAD₂, BINAP, dppf, and Xantphos (entries 1–4). Solely 2-di-*tert*-butylphosphino-2'-(*N,N*-dimethylamino)biphenyl ('Bu-DavePhos) gave the monoarylation product **3aa** in 37% yield (entry 5). To our delight, our YPhos ligand ^{Cy}Y_{Me}PCy₂ (L1) was more active than these state-of-the-art systems

under the same conditions. With L1, **3aa** was obtained in more than 70% yield along with only traces (< 5%) of diarylation product (entries 6, 8 and 10). Encouraged by the high activity of L1 we turned our attention toward possible room temperature applications. We hypothesized that an even more electron-donating ligand would allow for a further increase in activity and thus also operate at room temperature. Hence, the *tert*-butyl analogue

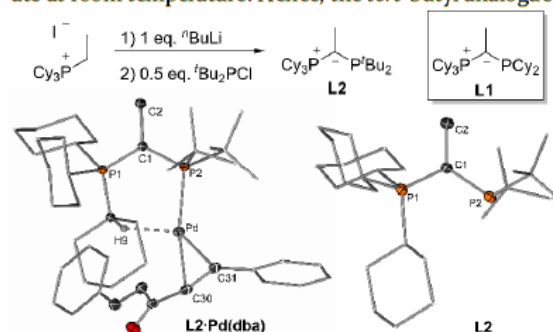
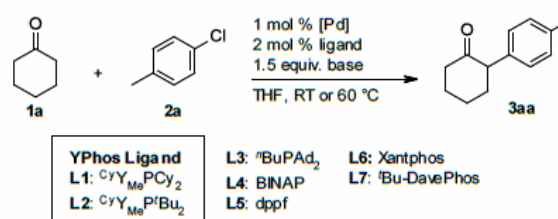


Figure 1. Synthesis and molecular structures of L2 and L2-Pd(dba)₃.

Table 1. Optimization of the arylation reaction.^a



Entry	catalyst	ligand	base	3aa (%)
1	Pd(COD)Cl ₂	L3	KO ^t Bu	n.d.
2	Pd(COD)Cl ₂	L4	KO ^t Bu	n.d.
3	Pd(COD)Cl ₂	L5	KO ^t Bu	n.d.
4	Pd(COD)Cl ₂	L6	KO ^t Bu	3
5	Pd(COD)Cl ₂	L7	KO ^t Bu	37
6	Pd(COD)Cl ₂	L1	KO ^t Bu	73
7	Pd(COD)Cl ₂	L2	KO ^t Bu	61
8	Pd ₂ dba ₃	L1	KO ^t Bu	71
9	Pd(OAc) ₂	L1	KO ^t Bu	56
10	Pd(COD)Cl ₂	L1	NaO ^t	75(68)
11	Pd(COD)Cl ₂	L1	Cs ₂ CO ₃	14
12	Pd(COD)Cl ₂	L1	K ₃ PO ₄	31
13	Pd(COD)Cl ₂	L1	NaOH	30
14	Pd(COD)Cl ₂	L1	Na-	14
15 ^b	Pd(COD)Cl ₂	L1	NaO ^t	4
16 ^b	Pd(COD)Cl ₂	L2	NaO ^t	66
17 ^b	Pd ₂ dba ₃	L2	NaO ^t	68

^a Reaction conditions: 2.0 mmol **1a**, 1.0 mmol **2a**, 1 mol% [Pd], 2 mol% ligand, 1.5 equiv. base, 2.0 mL THF, 60 °C, 16 h. Yields determined by GC analysis using *n*-tetradecane as internal standard, isolated yields in parentheses. ^b Reaction at r.t.

Table 2. Scope of ketones and aryl chlorides.

Scope of ketones	
 3aa, A: 68%; B: 60% (7h)	 3ba, A: 56%; B: 29%
 3ca, A: 65%; B: 10% ^b	 3da, R = Me, A: 68%; B: 55% 3da, R = ^t Bu, A: 64%; B: 52%
 3fa, A: 61%; B: 20%	 3ga, A: 80%; B: 20%
 3ha, A: 87%; B: 70%	 3ia, A: 78% ^b ; B: 48%
 3ja, A: 46% ^{c,d} ; B: 37% ^e	 3ka, A: 71%; B: 15% ^b
 3la, A: 89% ^e ; B: 28%	 3ma, A: 52%; B: 50%
Scope of aryl chlorides	
 3ab, A: 64%; B: 53% (7h)	 3ac, R = OMe, A: 54%; B: 50% (7h)
 3ad, R = ^t Bu, A: 62%; B: 65% (7h)	 3ae, R = F, A: 55%; B: 20%
 3af, A: 70 B: 64% (7h)	 3ag, R = H, A: 73%; B: 50%
 3ah, R = Ph, A: 89%; B: 52%	 3ai, A: 60%; B: 60%
 3aj, A: 52%; B: 23%	 3ak, A: 40%; B: 10% ^b
 3al, A: 46%; B: 50%	 3am, A: 69%; B: 48%
 3an, A: 59%; B: 46%	 3ao, A: 64%; B: 48%
 3ap, A: 42%; B: 28%	
Scope of aryl chlorides with phenyl ethyl ketone	
 3lc, R ¹ = H, R ² = OMe, A: 86% ^g (99% ^f)	 3ld, R ¹ = H, R ² = ^t Bu, A: 90% ^g
 3le, R ¹ = Me, R ² = Me, A: 92% ^g	 3lh, A: 95% ^g
 3lm, A: 91% ^g	 3ln, A: 78% ^g (97% ^f)
 3lp, A: 67% ^g (98% ^f)	 3lq, A: 59% ^{e, g}

^a Reaction conditions: Method A: 2.0 mmol 1a, 1.0 mmol 2a, 1 mol% Pd(COD)Cl₂, 2 mol% L1, 1.5 equiv. NaO^tBu, 2.0 mL THF, 60 °C, 16 h, isolated yields. Method B: 2.0 mmol 1a, 1.0 mmol 2a, 0.5 mol% Pd₂(dba)₃, 2 mol% L2, 1.5 equiv. NaO^tBu, 2.0 mL THF, r.t., 16 h, isolated yields. ^b mono/diarylation = 17:1. ^c 10 mmol 1j, 1 mol% Pd₂dba₃, 1.5 equiv. LiO^tBu. ^d 80 °C. ^e 0.5 mol% Pd(COD)Cl₂, 1 mol% L1 at r.t. ^f 1 mol% Pd(COD)Cl₂, 2 mol% L1 was used, GC yield. ^g Reaction at 60 °C. ^h GC yield.

of L1, ^cY_{Me}P^tBu₂ (L2) was synthesized in one step starting from (tricyclohexyl)ethylphosphonium iodide (Figure 1) and isolated as colourless solid in an overall yield of 60 %. L2 is characterized by two doublets in the ³¹P{H} NMR spectrum with coupling constants of 146.9 Hz and is – with a buried volume (%V_{bur}) of 51.3 % – sterically more demanding than L1 (%V_{bur} = 45.2) and most common phosphine ligands.^{19b}

As hypothesized, L2 gave high yields exclusively of the desired monoarylation product even at room temperature, when using Pd₂dba₃ as Pd source and NaO^tBu as base (entry 17). This sets a new record for the coupling of the challenging cyclohexanone substrate with an aryl chloride. To the best of our knowledge, no efficient room-temperature coupling has yet been accomplished for this substrate combination with any other catalyst. At elevated temperatures, L2 gave slightly lower yields than L1 due

to competing catalyst decomposition. To gain insight into the structure of the Pd catalyst with L2 we attempted its isolation. Despite the high reactivity we were able to isolate single crystals of the Pd(dba) complex. In the structure (Figure 1), a short C–H...Pd distance (Pd–C 2.974(4) Å) to one of the cyclohexyl groups of the phosphonium moiety is observed. This suggests the presence of a stabilising agostic interaction in the complex analogous to L1.²¹ To probe the scope of the new catalyst class we used both the robust ^cY_{Me}PCy₂-based protocol A (1 mol% Pd(COD)Cl₂, 2 mol% ^cY_{Me}PCy₂, 1.5 equiv. NaO^tBu, 2.0 mL THF at 60 °C) and the highly efficient but sensitive ^cY_{Me}P^tBu₂-based protocol B (0.5 mol% Pd₂dba₃, 2 mol% ^cY_{Me}P^tBu₂, 1.5 equiv. NaO^tBu, 2.0 mL THF at RT). As shown in Table 2, a wide range of alkyl and aryl ketones were selectively monoarylated in the reaction with *p*-chlorotoluene in moderate to good yields. Remarkably,

substituted cyclohexanones were smoothly converted (3ba-3ea). Cyclic ketones with larger ring sizes all the way up to cyclopentadecanone also gave good results (3fa-3ia). After adapting the reaction conditions (LiO^tBu, 80 °C), even acetone, another challenging substrate, was smoothly converted to exclusively give the monoarylation product 3ja in 46% isolated yield. Aryl and heteroaryl ketones are also suitable substrates (3ka-3ma). Notably, aryl ethyl ketone 1l was efficiently converted at room temperature already with 0.5 mol% catalyst. This compares favourably with literature protocols, which call for elevated temperatures (50-130 °C) or higher catalyst loadings.^{1b}

The scope of the α -arylation of cyclohexanone with respect to aryl chlorides is also outlined in Table 2. Aryl chlorides bearing electron-donating (Me, ^tBu, OMe) and electron-withdrawing (F) substituents in the *ortho*-, *meta*-, and *para*-position were converted successfully (3ab-3aj), and various sensitive substituents were tolerated (3al, 3am). The successful conversion of highly electron-rich aryl chlorides confirms that the oxidative addition step is strongly facilitated by the YPhos ligands. Sterically crowded *ortho*-substituted chloroarenes and even 9-chloroanthracene were successfully converted, albeit in only moderate yield (3ag, 3ah, 3ak). Heteroaryl chlorides also gave good results (3an, 3ao, 3ap).

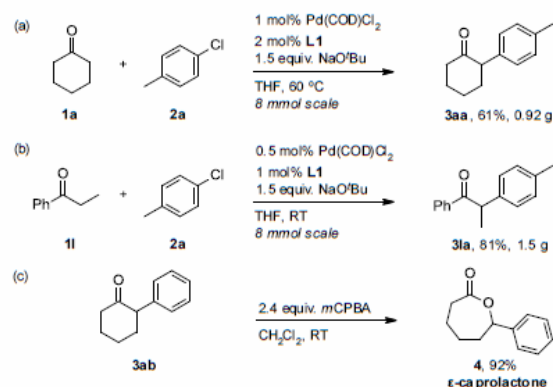
The arylation of phenyl ethyl ketone 1l is also broadly applicable with regard to the aryl chloride coupling partner. High yields are obtained, even when reducing the catalyst loading to 0.5 mol%.

Overall, protocol A based on the more robust ligand L1 seems to be more generally applicable and higher yielding. However, the activity of L2 at room temperature is certainly impressive. Further ligand refinement is required to identify a ligand that combines the record-setting activity of L2 with the robustness of L1. The preparative utility of the new protocol was demonstrated by gram-scale arylations forming 3aa and 3la (Scheme 2a and b). Scheme 2c demonstrates that a reaction sequence consisting of an α -arylation and Baeyer-Villiger oxidation gives easy access to ϵ -caprolactone derivatives such as 4. This opens up a convenient entry to modified poly- ϵ -caprolactone (PCL), a polymer with various pharmaceutical and biomedical applications.²²

Ylide-functionalized phosphine ligands were shown to be highly efficient in the Pd-catalyzed α -arylation of ketones.

A wide range of challenging cyclohexanones and other cyclic ketones were converted under mild conditions. The cyclohexyl-substituted YPhos ligand L1 is a robust ligand that gives best yields at 60 °C. The *tert*-butyl analogue L2 is active already at room temperature. It appears plausible that systematic variation of the ligand backbone will enable the design of ligands that combine the high reactivity of L2 with the robustness of L1.

Scheme 2. Synthetic application of this method.



ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full analysis data for new compounds, and copies of NMR spectra (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

brief description (file type, i.e., PDF)

brief description (file type, i.e., PDF)

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally. (match statement to author names with a symbol)

Notes

The authors hold patent WO2019030304 covering YPhos ligands L1 and L2.

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5.4 Cu/Pd-Katalysierte Decarboxylierende Kreuzkupplung von Pyridinsäurederivaten

In Zusammenarbeit mit der Firma *Pfizer* sollte unter Leitung von Herrn Dr. David C. Blakemore und Herrn Dr. Brian O’Neill eine auf Palladium und Kupfer basierende Methode zur decarboxylierenden Kreuzkupplung von 2-Pyridincarbonsäuren entwickelt werden. Im Vordergrund stand die Synthese von 2-Arylpyridinen, vorzüglich 2,2’-Bipyridin oder 2-(2-Pyridinyl)-pyrimidin. Zwar werden diese in der Industrie oftmals noch durch Suzuki-Miyaura-Kupplungen ausgehend von 2-Pyridylboraten hergestellt, jedoch sind diese (wie bereits in Kapitel 3.2.4.4 erwähnt) instabil, weniger gut zugänglich und protodeborieren meist schon bevor es zu einer Kreuzkupplung kommen kann. Dieses Phänomen lässt sich anhand von Einträgen aus dem elektronischen Laborjournal von Pfizer demonstrieren (Tabelle 2), wobei 2-Pyridinborate, im Gegensatz zu 3- oder 4-Pyridinboraten, nur einen kleinen Anteil an Reaktionen mit Ausbeuten über 20% darstellen.¹⁰¹ Pfizer kam bei eigenen Versuchen ausgehend von Pyridincarbonsäuren nicht über niedrige bis moderate Ausbeuten hinaus.

Tabelle 2. Palladiumkatalysierte Suzuki-Miyaura-Kupplungen von Pyridinboraten von Pfizer.

Substratklasse	Prozentsatz an Reaktionen mit Ausbeuten >20%
2-Pyridinborate	7%
3-Pyridinborate	52%
4-Pyridinborate	34%

Im vorangegangenen Kapitel 3.3.6.1 konnte gezeigt werden, dass in den Gruppen von Wu und Stoltz bereits erste Protokolle zur decarboxylierenden Kreuzkupplung von Picolinsäuren veröffentlicht wurden. Die von *Pfizer* gewünschten Produkte konnten, wenn überhaupt, nur in niedrigen Ausbeuten erhalten werden. Zudem haben wir festgestellt, dass bei der Verwendung von Triphenylphophanen als Ligand auch Arylgruppen des Liganden mit der Carbonsäure kuppeln (bis zu 30 %). Dies und die Tendenz zur Protodecarboxylierung bevor es zur Kupplung kommt, waren die größten Herausforderungen. Zwar konnte Hoarau auch eine Route über Pyridin-*N*-oxide präsentieren, allerdings wiesen diese zum einen teilweise Selektivitätsprobleme auf und zum anderen muss die *N*-Oxid-Gruppe vorher installiert und nachher entfernt werden, was zu weiteren Ausbeuteverlusten führt.

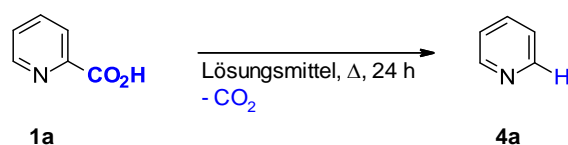
Die ersten Ergebnisse der nachfolgenden Unterkapitel wurden gemeinschaftlich mit Frau Dagmar Hackenberger erarbeitet. Anfänglich erhielten wir Unterstützung von Herrn Dr. Jie Tang und Herrn Dr. Pratik Yadav.

5.4.1 Studien zur decarboxylierenden Kreuzkupplung von 2-Picolin- und 2-Pyrimidincarbonsäure

5.4.1.1 Protodecarboxylierung von Picolinsäure

Dass Picolinsäuren metallfrei decarboxyliert werden können ist bekannt.²⁶⁴ Dies wird im Kontext der hier geplanten Umsetzungen nachteilig sein, da mit der Protodecarboxylierung eine für uns unerwünschte Nebenreaktion besteht. Die Herausforderung wird es sein, ein Katalysatorsystem zu finden, welches der Protodecarboxylierung auch bei höheren Temperaturen zuvorkommen kann. Um das Substrat und dessen Reaktivität besser ergründen zu können, wurden Protodecarboxylierungsstudien durchgeführt. Schon bei Temperaturen ab 140 °C konnte in NMP eine Protodecarboxylierung beobachtet werden (Tabelle 3).

Tabelle 3. Metallfreie Protodecarboxylierung von Picolinsäure **1a**.^[a]



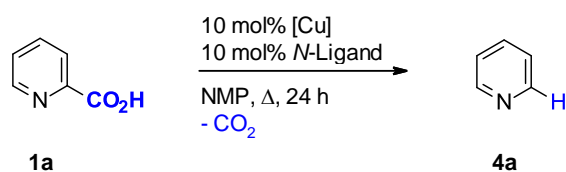
Eintrag	T (° C)	Lösungsmittel	Ausbeute 4a (%)
1	120	NMP	>5
2	140	„	21
3	„	DMSO	80
4	„	DMSO / NMP (1:1)	58
5	„	Mes	>5
6	„	DMSO 1:1 Mes	43
7	160	NMP	50
8	180	„	43
9	190	„	69

[a] **1a** (0.5 mmol), Lösungsmittel (2 mL), Δ, 24 h. Die Ausbeute wurde via GC-Analyse mit *n*-Dodecan als internem Standard bestimmt.

Mit steigender Temperatur konnte, in der Versuchsreihe mit NMP, ein größerer Anteil an Protodecarboxylierung detektiert werden (69% bei 190 °C, Eintrag 9). Mit DMSO anstelle von NMP als Lösungsmittel konnten bei 140 °C bereits 80% Ausbeute erzielt werden (Eintrag 3).

Da wir planten unsere ersten Studien an bereits existierenden Protokollen wie dem von Stoltz *et al.* zu orientieren, wollten wir den katalytischen Effekt des dort verwendeten Kupfers auf die Decarboxylierung untersuchen (Tabelle 4).

Tabelle 4. Kupfer-katalysierte Protodecarboxylierung von Picolinsäure **1a**.^[a]



Eintrag	T (°C)	N-Ligand	[Cu]	Ausbeute 4a (%)
1	120	Phen	Cu ₂ O	n.d.
2	140	„	„	36
3 ^[b]	„	„	„	73
4 ^[c]	160	„	„	78
5 ^[c]	180	„	„	79
6	190	„	„	82
7	„	BPhen	„	75
8	„	Me ₄ -Phen	„	80
9	„	2,2'-bipy	„	75
10	„	Phen	CuCl	56
11	„	„	CuBr	63
12	„	„	CuI	62
13 ^[d]	„	„	Cu ₂ O	79

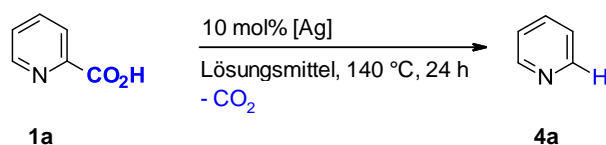
[a] **1a** (0.5 mmol), 10 mol% [Cu], 10 mol% N-Ligand, NMP (2 mL), Δ, 24h. Die Ausbeute wurde via GC-Analyse mit *n*-Dodecan als internem Standard bestimmt. [b] DMSO (2 mL), 16 h. [c] Zusätzlich 1.0 equiv NH₄Cl. [d] 20 mol% N-Ligand, 20 mol% Cu.

ERGEBNISSE UND DISKUSSION

Auch bei einem Einsatz von Kupfer werden mindestens 140 °C für die Protodecarboxylierung benötigt (Eintrag 2), wobei eine Verwendung von DMSO als Lösungsmittel die Ausbeute deutlich erhöhen konnte (Eintrag 3). Ab einer Temperatur von 160 °C können bereits sehr gute Ausbeuten erzielt werden (Eintrag 4). Bei 190 °C konnte das gewünschte Produkt in 82 % Ausbeute erhalten werden (Eintrag 6). Eine Erhöhung der Katalysatorbeladung oder die Verwendung anderer Katalysatoren brachte eine leichte Verschlechterung der Ausbeute (Eintrag 7-13). Verglichen mit den Ausbeuten der metallfreien Protodecarboxylierung konnte mit dem Einsatz von Kupfer ein leicht verbessertes Ergebnis erzielt werden.

Larrosa *et al.* veröffentlichten bereits ein Protokoll, welches heteroaromatische Carbonsäuren mit katalytischen Mengen an Silber in DMSO protodecarboxylieren konnte.¹⁷⁷ Basierend darauf untersuchten wir, ob mit Silber anstelle von Kupfer bessere Ergebnisse bei niedrigen Temperaturen erzielt werden konnten (Tabelle 5).

Tabelle 5. Silber-Katalysierte Protodecarboxylierung von Picolinsäure **1a**.^[a]



Eintrag	[Ag]	Lösungsmittel	Ausbeute 4a (%)
1 ^[b]	Ag ₂ CO ₃	DMSO	9
2 ^[c]	„	„	50
3	„	„	>99
4	„	DMF	54
5	„	DMAc	42
6	„	NMP	40
7	„	Mes	10
8	„	Diglyme	>5
9 ^[d]	„	DMSO / NMP (1:1)	65
10 ^[d]	„	DMSO / Mes (1:1)	60
9	AgOAc	NMP	45

10

AgTFA

"

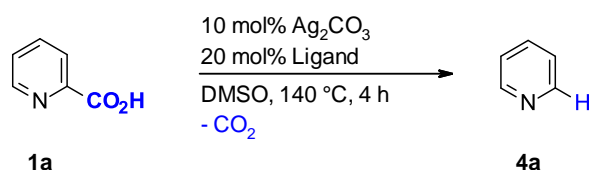
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[a] **1a** (0.5 mmol), 10 mol% [Ag], Lösungsmittel (2 mL), 140 °C, 24h. Die Ausbeute wurde via GC-Analyse mit *n*-Dodecan als internem Standard bestimmt. [b] 120 °C [c] 130 °C. [d] 16 h. 20 mol% Ag₂CO₃.

Im Gegensatz zu Kupfer und der metallfreien Variante konnte mit Silber und DMSO bei 120 °C bereits eine Protodecarboxylierung detektiert werden (Eintrag 1). Bei einer Erhöhung der Reaktionstemperatur auf 140 °C war die Umsetzung bereits quantitativ (Eintrag 3). Andere Lösungsmittel und Lösungsmittelgemische konnten kein so gutes Ergebnis erzielen, vor allem unpolare Lösungsmittel waren sehr ineffektiv (Eintrag 4-10). Andere Silberquellen konnten in NMP ähnliche Ergebnisse erzielen wie Ag₂CO₃ (Eintrag 9-10).

Um mögliche Ligandeneffekte zu detektieren, wurde die Reaktionszeit auf vier Stunden verkürzt (Tabelle 6).

Tabelle 6. Silber-Katalysierte Protodecarboxylierung von Picolinsäure **1a** mit zusätzlichen Liganden.^[a]



Eintrag	Ligand	Ausbeute 4a (%)
1	-	24
2	PPh ₃	13
3	Phen	12
4	Me ₂ Phen	12
5	Me ₄ Phen	9
6	Ph ₂ Phen	11
7	(NO ₂)Phen	22
8	BiPy	22
9	Me ₂ BiPy	31
10	MeO ₂ BiPy	24

ERGEBNISSE UND DISKUSSION

11	BiQuin	24
12	Pyridine	14
13	Lutidine	19
14	DMAP	11
15	White Ligand	41
16 ^[b]	"	Spuren
17 ^[c]	-	29

[a] **1a** (0.5 mmol), 10 mol% Ag₂CO₃, 20 mol% Ligand, DMSO (1 mL), 140 °C, 4h. Die Ausbeute wurde via GC-Analyse mit *n*-Dodecan als internem Standard bestimmt. [b] NMP (1 mL) [c] Ohne Ag₂CO₃.

Ohne Ligand wurden 24% Ausbeute detektiert (Eintrag 1), mit den meisten eingesetzten Liganden wurden schlechtere Ergebnisse erzielt. Liganden, die auf Bipyridin basieren, erzielten bessere Ergebnisse (Eintrag 9 und 10). Mit Christina Whites Ligand konnte eine deutliche Verbesserung auf 41% beobachtet werden (Eintrag 15), in NMP klappte dies allerdings nicht (Eintrag 16). Ohne Katalysator konnten ebenfalls 29% Ausbeute beobachtet werden (Eintrag 17), was die Effizienz von DMSO als Lösungsmittel für die Decarboxylierung weiter unterstreicht.

Die Ergebnisse in diesem Unterkapitel verdeutlichen wie einfach es ist, unter den gewählten Bedingungen Picolinsäure zu protodecarboxylieren. Da dies bei der decarboxylierenden Kreuzkupplung eine unerwünschte Nebenreaktion ist, die eine Produktbildung verhindern kann, muss demzufolge ein Katalysatorsystem gefunden werden welches diese Nebenreaktion unterdrücken kann.

5.4.1.2 Decarboxylierende Kreuzkupplung von Picolinsäure

Als erste Modelreaktion wurde die decarboxylierende Kreuzkupplung von Kalium-2-pyridincarboxylat **1a'** mit Brombenzol **2a** ausgewählt. Mit ähnlichen Bedingungen wie aus der Veröffentlichung von Stoltz *et al.*¹⁹⁷ (allerdings rein thermisch ohne Mikrowelle) konnten 31% Ausbeute erhalten werden (Tabelle 7).

Tabelle 7. Erste Experimente zur decarboxylierenden Kreuzkupplung von Kalium-2-pyridincarboxylat **1a'**.^[a]

KC(=O)c1ccncc1 + c1ccc(Br)cc1
 $\xrightarrow[\text{NMP, 190 °C, 24 h, -CO}_2]{\text{Pd}_2/\text{PPh}_3, [\text{M}]/\text{N-Ligand}}$
c1ccc(cc1)c2ccncc2 + c1ccc(cc1)c2ccncc2 + c1ccc(cc1)-c2ccccc2

1a' **2a** **3aa** **4a** **5a**

Eintrag	[M]	N-Ligand	Ausbeute (%)		
			3a	4a	5a
1	5 mol% Cu ₂ O	30 mol% Py	31	41	Spuren
2	“	10 mol% Phen	31	26	6
3	10 mol% Cu ₂ O	20 mol% Phen	35	27	Spuren
4	15 mol% Cu ₂ O	30 mol% Phen	33	29	6
5	10 mol% CuCl	10 mol% Phen	30	41	4
6	10 mol% CuBr	“	20	50	5
7	10 mol% CuI	“	17	43	6
8 ^[b]	5 mol% Cu ₂ O	“	6	11	Spuren
9	5 mol% Ag ₂ CO ₃	-	9	4	“
10	10 mol% Ag ₂ CO ₃	-	11	7	“
11	-	-	n.d	36	6

[a] **1a'** (0.5 mmol), **2a** (1.0 mmol), 5 mol% PdI₂, 15 mol% PPh₃, [M], N-Ligand, NMP (2 mL), 190 °C, 24h. Die Ausbeute wurde via GC-Analyse mit *n*-Tetradecan als internem Standard bestimmt. [b] 170 °C.

Beim Wechsel des N-Liganden von Pyridin auf Phenanthrolin blieb die Ausbeute von Produkt **3a** gleich, es konnten dabei noch 26% an unerwünschtem Protodecarboxylierungsprodukt **4a** detektiert werden (Eintrag 2). Eine Erhöhung der Kupfermenge erbrachte ähnliche Ergebnisse (Eintrag 5 und 6). Bei der Verwendung von Kupferhalogeniden kam es zu keiner Verbesserung,

ERGEBNISSE UND DISKUSSION

dafür wurde mehr Nebenprodukt **4** gebildet (Eintrag 7-9). Eine Verminderung der Reaktionstemperatur von 190 auf 170 °C resultierte in einem starken Abfall der Ausbeute (Eintrag 8). Silbercarbonat war weniger aktiv als Kupferoxid (Eintrag 9 und 10). Ohne Metalle kam es zu keiner Produktbildung. Die Reaktionsoptimierung wurde mit den Bedingungen aus Eintrag 2 fortgeführt.

Daraufhin wurde die Palladiumquelle variiert (Tabelle 8).

Tabelle 8. Variation der Palladiumquelle für die decarboxylierende Kreuzkupplung von Kalium-2-pyridincarboxylat **1a'**.^[a]

Reaction scheme: **1a'** + **2a** $\xrightarrow[\text{-CO}_2]{\text{5 mol\% [Pd] / 15 mol\% PPh}_3, \text{5 mol\% CuO}_2 / \text{10 mol\% Phen, NMP, 190 }^\circ\text{C, 24 h}}$ **3a** + **4a** + **5a**

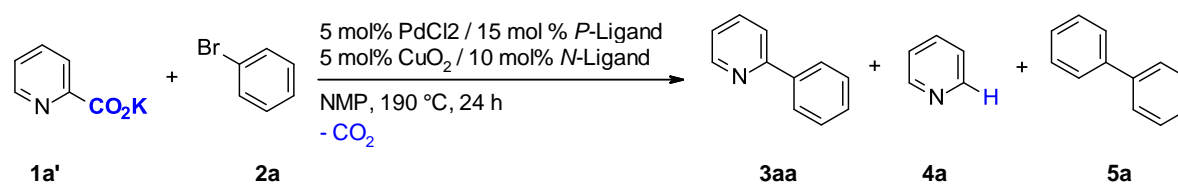
Eintrag	[Pd]	Ausbeute (%)		
		3a	4a	5a
1	PdI ₂	31	23	Spuren
2	PdCl₂	44	33	5
3	PdBr ₂	36	13	Spuren
4	PdOAc ₂	22	26	8
5	Pd(acac) ₂	17	30	7
6	Pd(COD)Cl ₂	22	28	5
7	Pd(F ₆ -acac) ₂	15	22	6
8	Pd ₂ dba ₃	14	27	5
9 ^[b]	PdCl ₂	17	10	Spuren

[a] **1a'** (0.5 mmol), **2a** (1.0 mmol), 5 mol% [Pd], 15 mol% PPh₃, 5 mol% Cu₂O, 10 mol% Phen, NMP (2 mL), 190 °C, 24h. Die Ausbeute wurde via GC-Analyse mit *n*-Tetradecan als internem Standard bestimmt. [b] 3 mol% [Pd]. [c] 2 mol% [Pd].

Das beste Ergebnis wurde mit Palladium(II)-Chlorid erzielt (Eintrag 2). Eine Reduzierung der Palladiumbeladung von 5 auf 3 mol% führte zu deutlichen Einbußen bei der Ausbeute. Die Reaktionsoptimierung wurde mit den Bedingungen aus Eintrag 2 fortgeführt.

Als nächstes wurden diverse *P*- und *N*-Liganden getestet (Tabelle 9).

Tabelle 9. Variation der Liganden für die decarboxylierende Kreuzkupplung von Kalium-2-pyridincarboxylat **1a'**.^[a]



Eintrag	<i>N</i> -Ligand	<i>P</i> -Ligand	Ausbeute (%)		
			3aa	4a	5a
1	Phen		44	33	5
2	Me ₄ Phen		30	20	4
3	BPhen		33	30	6
4	NO ₂ Phen		5	28	4
5	Bipy		34	18	4
6 ^[b]	Py		26	63	7
7 ^[b]	Chinuclidin		28	33	7
8 ^[b]	2,6-Lutidin		26	36	6
9 ^[b]	DMAP		28	29	7
11	-		27	19	5
12	Phen	JohnPhos	19	33	Spuren
13	„	Sphos	16	20	4
14	„	Xphos	21	30	4
15	„	P(<i>o</i> -Tol) ₃	12	22	4
16	„	P(<i>p</i> -Tol) ₃	23	31	4
17	„	BINAP	37	37	Spuren

ERGEBNISSE UND DISKUSSION

[a] **1a'** (0.5 mmol), **2a** (1.0 mmol), 5 mol% PdCl₂, 15 mol% *P*-Ligand, 5 mol% Cu₂O, 10 mol% *N*-Ligand, NMP (2 mL), 190 °C, 24h. Die Ausbeute wurde via GC-Analyse mit *n*-Tetradecan als internem Standard bestimmt. [b] 30 mol% *N*-Ligand.

Unter allen getesteten Liganden konnte Phenanthrolin die beste Ausbeute erzielen (Eintrag 1). Auch ohne *N*-Ligand kann die Reaktion durchgeführt werden (Eintrag 11). Unter allen getesteten *P*-Liganden konnte lediglich BINAP ähnliche Ergebnisse wie Triphenylphosphan erzielen (Eintrag 1 und 7).

Unter der Voraussetzung, dass diese den hohen Reaktionstemperaturen standhielten, wurden unterschiedliche Lösungsmittel und Lösungsmittelmischungen ausgetestet (Tabelle 10).

Tabelle 10. Variation des Lösungsmittels für die decarboxylierende Kreuzkupplung von Kalium-2-pyridincarboxylat **1a'**.^[a]

$5 \text{ mol\% PdCl}_2 / 15 \text{ mol\% PPh}_3$
 $5 \text{ mol\% Cu}_2\text{O} / 10 \text{ mol\% Phen}$
 Lösemittel, 190 °C, 24 h
 - CO₂

Eintrag	Lösungsmittel	Ausbeute (%)		
		3aa	4a	5a
1	NMP	44	33	5
2	NMP / Mes = 1:1	61	14	5
3	NMP / Mes = 3:1	53	20	4
4	NMP / Mes = 1:3	41	17	5
5	NMP / Chinolin = 1:1	43	28	5
6	NMP / Chinolin = 3:1	49	35	4
7	NMP / Chinolin = 1:3	33	32	4

[a] **1a'** (0.5 mmol), **2a** (1.0 mmol), 5 mol% PdCl₂, 15 mol% PPh₃, 5 mol% Cu₂O, 10 mol% Phen, Lösungsmittel (2 mL), 190 °C, 24h. Die Ausbeute wurde via GC-Analyse mit *n*-Tetradecan als internem Standard bestimmt.

Die Ausbeute konnte durch eine Mischung von NMP mit Mesitylen deutlich verbessert werden. Das beste Ergebnis konnte bei einem 1:1-Verhältnis erzielt werden (61%, Eintrag 2). Mischungen von NMP und Chinolin erzielten ein wenig schlechtere Resultate (Eintrag 5-7).

Mit einem Lösungsmittelgemisch aus NMP und Mesitylen (1:1) wurden weitere Palladiumquellen und elektronenarme Liganden getestet (Tabelle 11).

Tabelle 11. Testung neuer Palladiumquellen und P-Liganden unter verbesserten Bedingungen.^[a]

$5 \text{ mol\% [Pd]} / 15 \text{ mol\% P-Ligand}$
 $5 \text{ mol\% CuO}_2 / 10 \text{ mol\% Phen}$
 $\text{NMP 1:1 Mes, } 190 \text{ }^\circ\text{C, 24 h}$
 $-\text{CO}_2$

Eintrag	[Pd]	P-Ligand	Ausbeute (%)		
			3aa	4a	5a
1	PdCl₂	PPh₃	61	14	5
2	(MeCN) ₂ PdCl ₂	„	40	8	6
3	(PPh ₃) ₂ PdCl ₂	„	49	0	4
4	(PCy ₃) ₂ PdCl ₂	„	36	13	3
6	(PhCN) ₂ PdCl ₂	„	39	12	6
7	(allyl) ₂ PdCl ₂	„	41	17	4
8	(IPrPdCl ₂) ₂	„	43	18	4
9	SIPrPd(cinnamyl)Cl	„	42	6	5
10	XPhos Pd G2	„	32	26	10
11	K ₂ PdCl ₄	„	48	14	6
12	(MeCN) ₄ Pd(BF ₄) ₂	„	31	34	8
13	(MeCN) ₄ Pd(OTf) ₂	„	35	25	6
14	(MeCN) ₂ Pd(OTs) ₂	„	50	17	6
15	PdCl ₂	PPh ₂ Py	47	18	3
16		P(<i>p</i> -CF ₃ C ₆ H ₄) ₃	42	16	7
17		P(<i>p</i> -ClC ₆ H ₄) ₃	31	14	3

ERGEBNISSE UND DISKUSSION

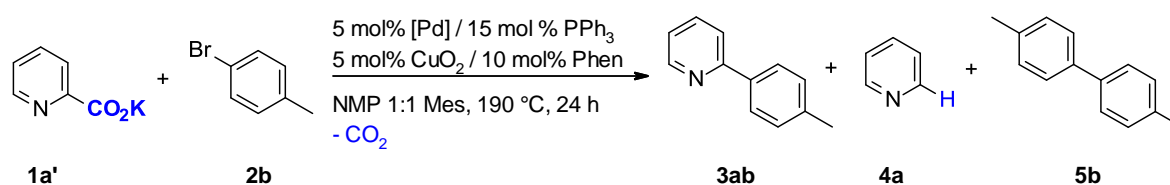
18	P(2-furyl) ₃	30	25	4
19	P(<i>p</i> -FC ₆ H ₄) ₃	40	8	4

[a] **1a'** (0.5 mmol), **2a** (1.0 mmol), 5 mol% [Pd], 15 mol% *P*-Ligand, 5 mol% Cu₂O, 10 mol% Phen, NMP 1:1 Mes (2 mL), 190 °C, 24h. Die Ausbeute wurde via GC-Analyse mit *n*-Tetradecan als internem Standard bestimmt.

Wieder war PdCl₂ die beste Wahl (Eintrag 1). Generell konnten elektronenarme Liganden besser abschneiden als elektronenreiche. Allerdings blieb PPh₃ der beste Ligand.

Um zu überprüfen, ob der Ligand selbst als Arylierungsreagenz dient, wechselten wir bei einer erneuten Variation der Palladiumquelle das Elektrophil auf 4-Bromtoluol (Tabelle 12).

Tabelle 12. Variation der Palladiumquelle bei der Kupplung mit 4-Bromtoluol **2b**.^[a]



Eintrag	[Pd]	Ausbeute (%)		
		3ab	4a	5b
1	PdCl₂	35	19	5
2	PdBr ₂	10	41	3
3	PdI₂	34	24	6
4	(MeCN) ₂ PdCl ₂	26	23	4
5	(PPh ₃) ₂ PdCl ₂	28	28	4
6	Li ₂ PdCl ₄	12	26	5
7	Pd(acac) ₂	29	29	6
8	(MeCN) ₄ Pd(OTf) ₂	27	26	5
9	SIPrPd(cinnamyl)Cl	31	29	4
10	Pd(dba) ₂	30	26	4

[a] **1a'** (0.5 mmol), **2b** (1.0 mmol), 5 mol% [Pd], 15 mol% PPh₃, 5 mol% Cu₂O, 10 mol% Phen, NMP 1:1 Mes (2 mL), 190 °C, 24h. Die Ausbeute wurde via GC-Analyse mit *n*-Tetradecan als internem Standard bestimmt.

Neben dem gewünschten Produkt konnten 5-15% 2-Phenylpyridin (**3**) detektiert werden, was der Beweis dafür ist, dass PPh₃ als Kupplungspartner an der Arylierung beteiligt ist. Ansonsten konnten PdCl₂ und PdI₂ die besten Resultate erzielen.

Daraufhin wurden mit PdCl₂ und PdI₂ einige modifizierte Liganden getestet (Tabelle 13).

Tabelle 13. Variation modifizierter *P*-Liganden für die Kupplung mit 4-Bromtoluol **2b**.^[a]

Cc1ccc(Br)cc1 + Cc1ccc(cc1)C(=O)[O-][K+]
 $\xrightarrow[\text{NMP 1:1 Mes, 190 }^\circ\text{C, 24 h}]{\text{5 mol\% [Pd] / 15 mol\% PPh}_3, \text{ 5 mol\% Cu}_2\text{O / 10 mol\% Phen}}$
Cc1ccc(cc1)c2ccncc2 + Cc1ccc(cc1)c2ccncc2 + Cc1ccc(cc1)-c2ccc(C)cc2

 -CO₂

Eintrag	Pd-Quelle	<i>P</i> -Ligand	Ausbeute (%)		
			3ab	4a	5b
1	PdCl ₂	PPh ₃	35	19	5
2	„	P(<i>m</i> -tol) ₃	35	23	5
3	„	P(<i>o</i> -tol) ₃	15	17	5
4	„	P(<i>p</i> -tol) ₃	43	24	6
5	„	P(<i>p</i> -MeOC ₆ H ₄) ₃	22	29	1
6	„	P(<i>p</i> -FC ₆ H ₄) ₃	19	27	4
7	PdI ₂	PPh ₃	34	24	6
8	„	P(<i>m</i> -tol) ₃	30	19	6
9	„	CyJohnPhos	29	25	4
10	„	P ^{<i>i</i>} PrPh ₂	32	29	5
11	„	PCyPh ₂	30	31	5
12	„	dppf	23	32	3
13	„	BINAP	21	31	5

ERGEBNISSE UND DISKUSSION

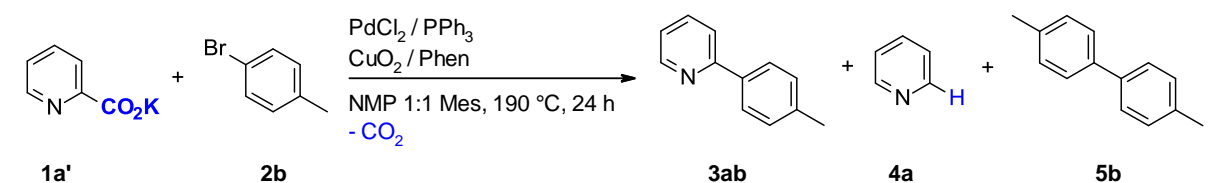
14^[b] „ PPh₃ 28 12 Spuren

[a] **1a'** (0.5 mmol), **2b** (1.0 mmol), 5 mol% [Pd], 15 mol% *P*-Ligand, 5 mol% Cu₂O, 10 mol% Phen, NMP 1:1 Mes (2 mL), 190 °C, 24h. Die Ausbeute wurde via GC-Analyse mit *n*-Tetradecan als internem Standard bestimmt. [b] Es wurden 200 mg 3Å MS hinzugefügt.

Modifizierte PPh₃-Liganden brachten alle ähnliche Ergebnisse. Das *para*-Tolyl-Derivat erzielte aufgrund seiner Beteiligung als Arylierungsreagenz wie erwartete das beste Resultat (Eintrag 4). Mit PdI₂ wurden ähnliche Ausbeuten wie mit PdCl₂ erhalten. CyJohnPhos erzielte mit 29% Ausbeute das beste Ergebnis ohne selbst zu arylieren.

Im Anschluss daran wurde ein letzter Versuch unternommen, mit PdCl₂ und Kupferoxid die Ladung des Katalysators zu variieren (Tabelle 14).

Tabelle 14. Variation der Katalysatorbeladung für Kupplung mit 4-Bromtoluol **2b**.^[a]



Eintrag	PdCl ₂ (mol%)	PPh ₃ (mol%)	Cu ₂ O (mol%)	Phen (mol%)	Ausbeute (%)		
					3ab	4a	5b
1	5	12	5	10	35	19	5
2	7.5	18	"	"	39	7	5
3	10	24	"	"	28	10	5
4	5	12	7.5	15	32	9	7
5	"	"	10	20	53	3	13

[a] **1a'** (0.5 mmol), **2b** (1.0 mmol), PdCl₂, PPh₃, Cu₂O, Phen, NMP 1:1 Mes (2 mL), 190 °C, 24h. Die Ausbeute wurde via GC-Analyse mit *n*-Tetradecan als internem Standard bestimmt.

Eine Erhöhung der Katalysatorbeladung brachte keine deutliche Verbesserung der Ausbeute (Eintrag 2). Wenn 10 mol% PdCl₂ und 24 mol% PPh₃ eingesetzt wurden, senkte sich die Ausbeute ein wenig (Eintrag 3). Bei einer Erhöhung der Menge an Cu₂O konnte die Ausbeute leicht erhöht werden (Eintrag 4 und 5), allerdings nahm auch der Anteil an unerwünschtem Nebenprodukt zu.

Unter anderem testeten wir auch andere Gegenionen am 2-Pyridincarboxylat. Im Vergleich zu Kalium konnten Lithium und Cäsium nur halb so gut abschneiden. Unter den getesteten Elektrophilen waren Arylbromide die beste Alternative. Nur Iodide waren ebenbürtig, diese

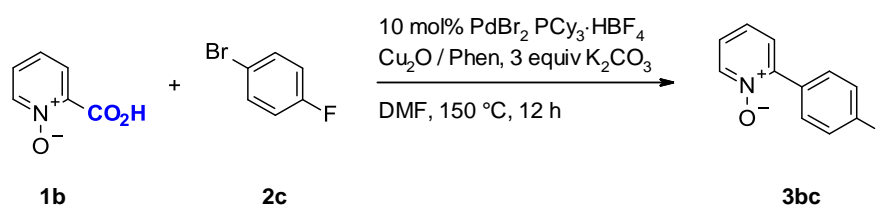
sind allerdings um einiges teurer. Chloride und Triflate sind deutlich schlechter und maximal wurden Spuren des gewünschten Produktes erhalten. In der Hoffnung, dass diese das Lewis-basische Stickstoffatom besetzen, wurden einige Lewis-Säuren (Bi(OTf)₃, In(OTf)₃, Mg(OTf)₂, Zn(OTf)₂ und Ca(OTf)₂) hinzugefügt, diese hatten allerdings einen negativen Effekt auf die Ausbeute.

Nach ernüchternden Ergebnissen wurden die Untersuchungen von Picolinsäure eingestellt. Um der Theorie nachzugehen, dass Modifizierungen der Picolinsäure die Reaktivität verbessern können wurde daraufhin mit Picolinsäure-*N*-oxid (Kapitel 5.4.1.3) und elektronenziehenden Substituenten in C3-Position (Kapitel 5.4.2) weitergearbeitet.

5.4.1.3 Decarboxylierende Kreuzkupplung von Picolinsäure-*N*-oxid

Nachdem erste Reaktionen mit dem Kaliumsalz der Picolinsäure nicht über moderate Ausbeuten herauskamen, erhofften wir uns mit Picolinsäure-*N*-oxid als Ausgangssubstrat bessere Ausbeuten erzielen zu können. Dabei wurde das Kupfer-Protokoll von Hoarau als Startpunkt gewählt (Tabelle 15).¹⁹⁸

Tabelle 15. Decarboxylierende Kreuzkupplung von Picolinsäure-*N*-Oxid **1b**.^[a]



Eintrag	Cu ₂ O (mol%)	Phen (mol%)	Ausbeute 3bc (%)
1	50	100	63
2	„	50	75
3 ^[b]	„	„	58
4	„	25	52
5	25	50	55
6	„	25	66
7	„	-	18
8	10	-	14

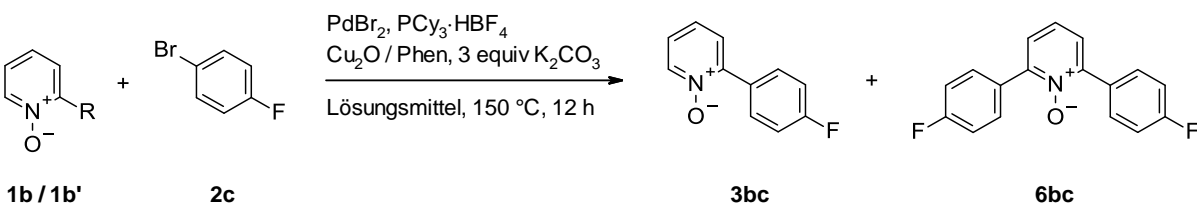
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[a] **1b** (0.5 mmol), **2c** (1.0 mmol), 10 mol% PdBr₂, 10 mol% PCy₃·HBF₄, Cu₂O, Phen, DMF (2.5 mL), 150 °C, 12h. Die Ausbeute wurde via ¹⁹F-NMR mit 1,4-Difluorbenzol als internem Standard bestimmt.
[b] 2 equiv K₂CO₃.

Das beste Resultat konnte mit den Bedingungen aus der Literatur erzielt werden (Eintrag 2). Mit dem Einsatz von weniger Base, Kupfer oder Phenanthrolin fiel die Ausbeute ab.

Um die Anwendung in C-H-Aktivierungen zu untersuchen wurde auch reines Pyridin-*N*-oxid im weiteren Optimierungsprozess getestet (Tabelle 16).

Tabelle 16. Variation der Katalysatormenge und des Lösungsmittels.^[a]



Eintrag	R	PdBr ₂ (mol%)	PCy ₃ H·BF ₄ (mol%)	Cu ₂ O (mol%)	Phen (mol%)	Lösungsmittel	Ausbeute (%)	
							3bc	6bc
1	CO ₂ H	10	10	50	50	DMF	58	3
2	„	-	-	„	„	„	-	-
3	„	10	10	-	-	„	12	-
4	„	„	„	50	50	Dioxan	28	-
5	„	-	-	„	„	„	-	-
6	„	10	10	-	-	„	23	-
7	H	10	10	50	50	DMF	24	-
8	„	-	-	„	„	„	-	-
9	„	10	10	-	-	„	8	-
10	„	„	„	50	50	Dioxan	40	7
11	„	-	-	„	„	„	-	-
12	„	10	10	-	-	„	8	-

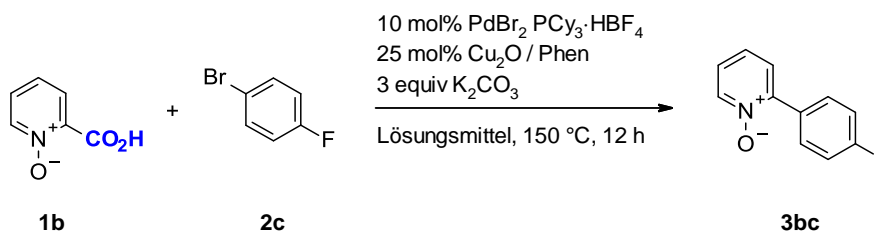
[a] **1b / 1b'** (0.5 mmol), **2c** (1.0 mmol), PdBr₂, PCy₃·HBF₄, Cu₂O, Phen, Lösungsmittel (2.5 mL), 150 °C, 12h. Die Ausbeute wurde via ¹⁹F-NMR mit 1,4-Difluorbenzol als internem Standard bestimmt.

Unter Standardbedingungen konnten 58% Ausbeute und Spuren an diaryliertem Nebenprodukt detektiert werden (Eintrag 1). Ohne Palladium wurden 0% und ohne Kupfer 12% Ausbeute erhalten (Eintrag 2 und 3). Wurde wie bei Silber Dioxan als Lösungsmittel verwendet, sanken

die Ausbeuten (Eintrag 4-6). Bei Pyridin-*N*-oxid sind sehr ähnliche Trends zu beobachten, allerdings mit niedrigeren Ausbeuten in DMF (Eintrag 1-3) und etwas erhöhten Ausbeuten unter Standardbedingungen in Dioxan (Eintrag 4).

Darauf basierend führten wir eine Variation des Lösungsmittels bei einer niedrigeren Kupferladung durch (Tabelle 17).

Tabelle 17. Variation des Lösungsmittels für die decarboxylierende Kreuzkupplung von Picolinsäure-*N*-oxid **1b**.^[a]

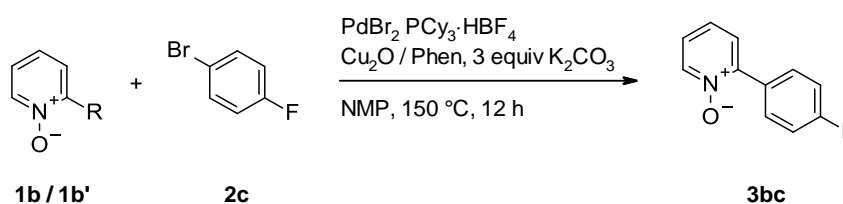


Eintrag	Lösungsmittel	Ausbeute 3bc (%)
1	DMF	40
2	Dioxan	40
3	Chinolin	55
4	NMP	67
5	NMP / Chinolin (1:1)	66
6	NMP / Mes (1:1)	40

[a] **1b** (0.5 mmol), **2c** (1.0 mmol), 10 mol% PdBr₂, 10 mol% PCy₃·HBF₄, 25 mol% Cu₂O, 25 mol% Phen, Lösungsmittel (2.5 mL), 150 °C, 12h. Die Ausbeute wurde via ¹⁹F-NMR mit 1,4-Difluorbenzol als internem Standard bestimmt.

In NMP und einer Mischung aus NMP / Chinolin (1:1) konnten 67 und 66% erreicht werden (Eintrag 4-5). Darauf basierend führten wir Vergleichsstudien zwischen Pyridin-*N*-oxid und Picolinsäure-*N*-oxid in NMP aus (Tabelle 18).

Tabelle 18. Variation der Katalysatorbeladung für die Kreuzkupplung von Picolinsäure-*N*-oxid.^[a]



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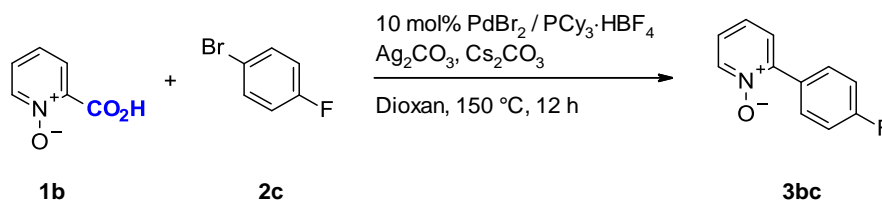
Eintrag	R	PdBr ₂ (mol%)	PCy ₃ H·BF ₄ (mol%)	Cu ₂ O (mol%)	Phen (mol%)	Ausbeute 3bc (%)
1	CO ₂ H	10	10	25	25	63
2	„	-	-	„	„	-
3	„	10	10	-	-	5
4	H	„	„	25	25	10
5	„	-	-	„	„	-
6	„	10	10	-	-	8

[a] **1b** / **1b'** (0.5 mmol), **2c** (1.0 mmol), PdBr₂, PCy₃·HBF₄, Cu₂O, Phen, 3 Äquivalente K₂CO₃, Lösungsmittel (2.5 mL), 150 °C, 12h. Die Ausbeute wurde via ¹⁹F-NMR mit 1,4-Difluorbenzol als internem Standard bestimmt.

Picolinsäure-*N*-oxid erzielt mit einem auf Kupfer basierenden Katalysatorsystem höhere Ausbeuten an Produkt **3bc** als Pyridin-*N*-oxid.

Neben den Kupfer-basierten Protokollen wurde zusätzlich das auf Silber basierende Protokoll von Hoarau getestet (Tabelle 19).

Tabelle 19. Silber-Katalysierte decarboxylierende Kreuzkupplung von **1b**.^[a]



Eintrag	Ag ₂ CO ₃ (eq.)	Cs ₂ CO ₃ (eq.)	Ausbeute 3bc (%)
1	0.5	3.0	68
2	1.0	3.0	93
3	1.0	1.5	83

[a] **1b** (0.5 mmol), **2c** (1.0 mmol), 10 mol% PdBr₂, 10 mol% PCy₃·HBF₄, Ag₂CO₃, Cs₂CO₃, Dioxan (2.5 mL), 150 °C, 12h. Die Ausbeute wurde via ¹⁹F-NMR mit 1,4-Difluorbenzol als internem Standard bestimmt.

Wieder konnte mit dem Literaturprotokoll das beste Ergebnis erzielt werden (93%, Eintrag 2). Mit weniger Base fiel die Ausbeute leicht (Eintrag 3).

Die gleichen Reaktionen wurden mit einem auf Silber basierenden System durchgeführt (Tabelle 20).

Tabelle 20. Variation der Katalysatormenge und des Lösungsmittels.^[a]

Eintrag	R	PdBr ₂ (mol%)	PCy ₃ ·H·BF ₄ (mol%)	Ag ₂ CO ₃ (mol%)	Lösungsmittel	Ausbeute (%)	
						3bc	6bc
1	CO ₂ H	10	10	100	Dioxan	66 (55)	11
2	„	-	-	„	„	-	-
3	„	10	10	-	„	32	4
4	„	„	„	100	DMF	25	-
5	„	-	-	„	„	-	-
6	„	10	10	-	„	11	-
7	H	10	10	100	Dioxan	88	7
8	„	-	-	„	„	-	-
9	„	10	10	-	„	37	2
10	„	„	„	100	DMF	54	5
11	„	-	-	„	„	-	-
12	„	10	10	-	„	14	-

[a] **1b** / **1b'** (0.5 mmol), **2c** (1.0 mmol), PdBr₂, PCy₃·HBF₄, Ag₂CO₃, Cs₂CO₃, Lösungsmittel (2.5 mL), 150 °C, 12h. Die Ausbeute wurde via ¹⁹F-NMR mit 1,4-Difluorbenzol als internem Standard bestimmt.

Unter Standardbedingungen wurden 66% (55% isoliert) Produkt und 11% diaryliertes Nebenprodukt erhalten (Eintrag 1). Ohne Palladium wurde kein Produkt und ohne Silber wurden 32% Produkt gebildet. Ähnliche Trends wurden beobachtet, wenn DMF verwendet wurde, die Ausbeuten waren allerdings niedriger (Eintrag 4-6). Auch hier wurde reines Pyridin-*N*-oxid getestet. In beiden Lösungsmitteln waren die Ausbeuten höher als bei der Säure, Dioxan war besser (88%, Eintrag 7). Zusammenfassend kann man sagen, dass ein System, welches auf Silber basiert besser für Pyridin-*N*-oxid funktioniert.

Für das Produkt testeten wir zwei Systeme zur Reduktion des *N*-Oxids. Für ein Protokoll basierend auf Zinkstaub und NH₄Cl von Fagnou *et al.* konnten wir 83% Ausbeute erhalten.²⁶⁵ Bei der metallfreien Deoxygenierung von González, welche Alkohole und Basen verwendet, konnten wir 53% Ausbeute erhalten.²⁶⁶ Aufgrund des zusätzlichen Aufwandes und den

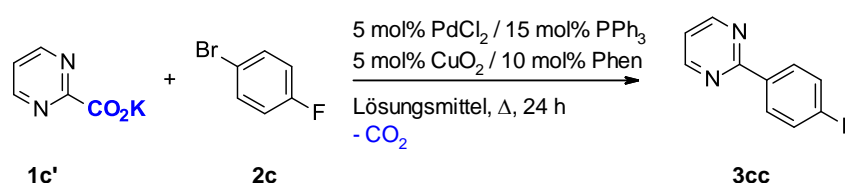
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Ausbeuteverlusten bei der Reduktion wurden keine weiteren Studien mit *N*-Oxiden durchgeführt.

5.4.1.4 Decarboxylierende Kreuzkupplung von Pyrimidin-2-carbonsäure

Ein weiteres Ziel war es, Pyrimidin-2-carbonsäure mit Arylbromiden zu kuppeln. Basierend auf den Standardbedingungen unserer decarboxylierenden Kreuzkupplung von Picolinsäure wurde die Temperatur und das Lösungsmittel variiert (Tabelle 21). Da auch bei dieser Reaktion Triphenylphosphan als Arylierungsreagenz fungiert, wurde 4-Fluorbrombenzol (**2c**) als Kupplungspartner gewählt und die Ausbeute über ¹⁹F-NMR bestimmt.

Tabelle 21. Decarboxylierende Kreuzkupplung von Kalium-2-Bipyrimidincarboxylat **1c'**.^[a]



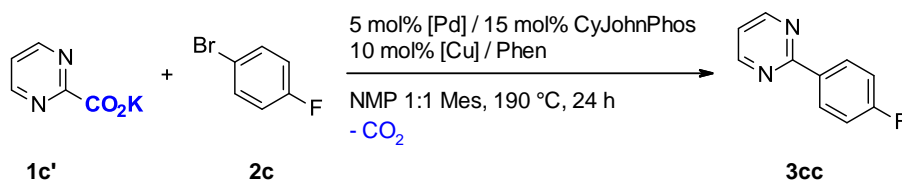
Eintrag	T (°C)	Lösungsmittel	Ausbeute 3cc (%)
1	190	NMP / Mes (1:1)	38 / 50 ^[b]
2	"	NMP	20
3	"	Chinolin	36
4	"	NMP / Chinolin (1:1)	36
5	"	Chinolin / Mes (1:1)	26
6	"	NMP / DMF (1:1)	11
7	170	NMP / Mes (1:1)	15
8	150	NMP / Mes (1:1)	>5

[a] **1c'** (0.5 mmol), **2c** (1.0 mmol), 5 mol% PdCl₂, 15 mol% PPh₃, 5 mol% CuO₂, 10 mol% Phen, Lösungsmittel (2 mL), 190 °C, 24h. Die Ausbeute wurde via ¹⁹F-NMR mit 1,4-Difluorbenzol als internem Standard bestimmt. [b] μWelle.

Während das Produkt bei 190 °C noch in moderaten Ausbeuten erhalten werden konnte (Eintrag 1), fielen die Ausbeuten bei niedrigeren Temperaturen rapide (Eintrag 7-8). Alle anderen getesteten Lösungsmittel bzw. -gemische zeigten vergleichbare oder schlechtere Resultate (Eintrag 2-6).

Um die von Triphenylphosphan ausgehende Bildung unerwünschter Nebenprodukte zu unterbinden, wurde im weiteren Verlauf der Untersuchungen CyJohnPhos als *P*-Ligand verwendet. Zunächst führten wir eine Variation der Palladium- und Kupferquelle durch (Tabelle 22).

Tabelle 22. Variation der Palladium- und Kupferquelle.^[a]



Eintrag	[Pd]	[Cu]	Ausbeute 3cc %
1	PdCl ₂	Cu ₂ O	38 / 50 ^[b]
2	PdBr ₂	„	40
3	PdI ₂	„	26
4	Pd(OAc) ₂	„	24
5	Pd(acac) ₂	„	36
6	Pd(F ₆ -acac) ₂	„	28
7	Pd(COD)₂Cl₂	„	52 / 45^[b]
8	Pd(TFA) ₂	„	38
9	Pd(White Catalyst) ₂	„	41
10	Pd(dba) ₂	„	40
12	Pd(COD) ₂ Cl ₂	CuCl	45
13	„	CuBr	46
14	„	CuI	58

[a] **1c'** (0.5 mmol), **2c** (1.0 mmol), 5 [Pd], 15 mol% CyJohnPhos, 10 mol% [Cu], 10 mol% Phen, NMP 1:1 Mes (2 mL), 190 °C, 24h. Die Ausbeute wurde via ¹⁹F-NMR mit 1,4-Difluorbenzol als internem Standard bestimmt. [b] Mikrowelle 50 °C (5 min) → 190 °C 1h.

Pd(COD)₂Cl₂ konnte die Ausbeute bis auf 52% steigern (Eintrag 7). Bei den getesteten Kupferquellen zeigten sich nur geringe Unterschiede, wobei CuI das beste Ergebnis erzielte (Eintrag 14).

5.4.2 Synthesis of 3-Substituted 2-Arylpyridines via Cu/Pd-Catalyzed Decarboxylative Cross-Coupling of Picolinic Acids with (Hetero)Aryl Halides

Nachdem vorangehende Untersuchungen wenig erfolgreich waren, wurden Substituenten an verschiedenen Positionen der Picolinsäure auf deren sterische und/oder elektronische Effekte auf die Reaktion getestet. Dabei stellte sich heraus, dass Fluor in C3-Position zu einer deutlich gesteigerten Ausbeute führte (Tabelle 23).

Tabelle 23. Decarboxylierende Kreuzkupplung von substituierter Picolinsäure.^[a]

Eintrag	R	Ausbeute (%)		
		3xb	4x	5b
1	H	35	10	5
2	6-Me	27	20	>5
3	6-OMe	-	-	-
4	6-Cl	-	14	>5
5	6-F	-	-	-
6	4-Cl	>5	-	7
7	3-Cl	-	Spuren	>5
8	3-F	58	n.d.	>5

[a] **1x'** (0.5 mmol), **2b** (1.0 mmol), 5 mol% PdCl₂, 15 mol% PPh₃, 10 mol% Cu₂O, 10 mol% Phen, NMP 1:1 Mes (2 mL), 190 °C, 24h. Die Ausbeute wurde via GC-Analyse mit *n*-Dodecan als internem Standard bestimmt.

Basierend auf diesen Ergebnissen sollte nun ein Protokoll mit verschiedenen Substituenten in C3-Position entwickelt werden. Das Projekt wurde in Zusammenarbeit mit Frau Dagmar Hackenberger durchgeführt. Die Studien zur Optimierung der decarboxylierenden Kreuzkupplung des Kalium-3-fluorpyridin-2-carboxylats und der Anwendungsbreite erfolgten gemeinschaftlich. Die Protodecarboxylierungsexperimente der 3-Fluorpyridin-2-carbonsäure und weiterführende nukleophile aromatische Substitutionen wurden von Frau Hackenberger durchgeführt. Frau Hackenberger verfasste das Manuskript mit Herrn Prof. Gooßen. Ich

unterstütze Frau Hackenberger bei der Auswertung der analytischen Daten und der Erstellung der „Supporting Information“.

Die Ergebnisse dieses Unterkapitels wurden in der Zeitschrift *Journal of Organic Chemistry* veröffentlicht. Eine angepasste Kopie des Manuskripts wurde mit Erlaubnis der American Chemical Society nachfolgend beigefügt:

„Reprinted (adapted) with permission from D. Hackenberger, P. Weber, D. C. Blakemore, L. J. Goossen, *J. Org. Chem.* **2017**, 82, 3917-3925: *Synthesis of 3-Substituted 2-Arylpyridines via Cu/Pd-Catalyzed Decarboxylative Cross-Coupling of Picolinic Acids with (Hetero)Aryl Halides*. Copyright 2017 American Chemical Society.”

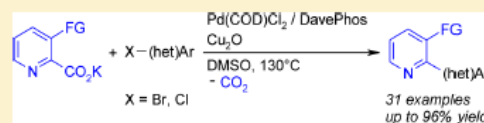
Synthesis of 3-Substituted 2-Arylpyridines via Cu/Pd-Catalyzed Decarboxylative Cross-Coupling of Picolinic Acids with (Hetero)Aryl Halides

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S Supporting Information

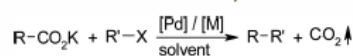
ABSTRACT: A decarboxylative cross-coupling of 3-substituted picolinic acids with (hetero)aryl halides is presented. In the presence of catalytic Cu₂O and Pd(1,5-cyclooctadiene)Cl₂ with 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl as the ligand, both electron-rich and electron-deficient aryl bromides and chlorides as well as heteroaryl bromides were successfully coupled with various picolinate salts under mild conditions in yields up to 96%. This protocol provides an efficient entry to 2-(hetero)arylpyridines, an attractive substance class in drug discovery.



Within the last decades, decarboxylative cross-coupling reactions have emerged as a powerful methodology for the regioselective formation of C–C and C–heteroatom bonds.^{1–3} The key advantage of this reaction type is that it draws on stable and readily available carboxylic acids as the coupling partners. As a result, a steadily growing number of atom-economic and waste-minimized protocols including decarboxylative Heck-type reactions,^{4–7} redox-neutral cross-couplings,^{8–11} allylations,^{12,13} oxidative couplings,^{14,15} C–H arylations,^{16–19} Chan–Evans–Lam-type reactions,²⁰ and photoredox-induced couplings have recently been disclosed.^{21,22}

In redox-neutral decarboxylative cross-couplings, carboxylic acids are used as the source of carbon nucleophiles in place of sensitive and costly organometallic reagents. In this reaction variant, a Cu^I or Ag^I catalyst mediates the extrusion of CO₂ to form the carbon nucleophile, which is then transmetalated to a Pd complex, where the coupling with the carbon electrophile takes place (Scheme 1). Bimetallic Cu/Pd systems proved to

Scheme 1. Redox-Neutral Decarboxylative Cross-Couplings^a



^aM = Cu, Ag; R = (hetero)aryl, vinyl, acyl; R' = (hetero)aryl, alkenyl; X = I, Br, Cl, OTf, OTs, OMs.

have a particularly broad scope with regard to both coupling partners.^{8,23,24} Various aromatic carboxylates have successfully been coupled with a broad range of (hetero)aryl halides and pseudohalides, and key limitations such as the restriction to benzoates bearing electron-withdrawing *ortho*-substituents have recently been overcome with customized catalyst systems.²⁵

Among the heterocyclic carboxylates, five-membered ring heteroarenes such as oxazole-, thiazole-, pyrrole-, thiophene-, and furancarboxylic acids react with particular ease and can be

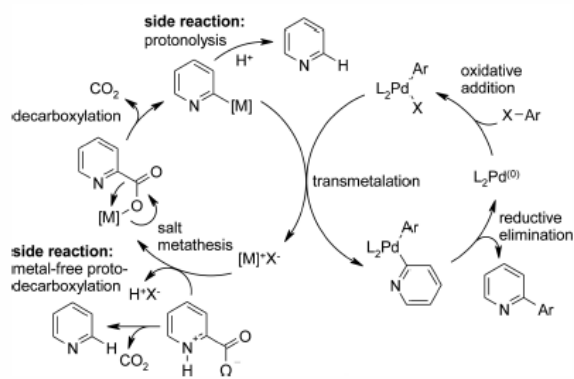
coupled even with monometallic catalyst systems.^{26,27} In contrast, pyridinecarboxylic acids belong to the most challenging substrates in decarboxylative couplings. 3-Pyridinecarboxylic acids can be converted under standard conditions but tend to give low yields,²⁸ whereas 4-pyridinecarboxylic acids require customized catalyst systems.²⁹ Arguably, the coupling of 2-pyridinecarboxylic acids poses the greatest challenge due to the instability of the 2-metallapyridines³⁰ and their tendency toward protodecarboxylation even in the absence of a metal catalyst (see the Supporting Information, Table S1).^{31–36} In order to allow a regioselective cross-coupling step, the unwanted protodecarboxylation, which starts at 120 °C, needs to be suppressed, and the high activation barrier of the metal-mediated decarboxylation pathway has to be lowered (Scheme 2).

Several dedicated catalyst systems have been designed specifically for decarboxylative couplings of 2-pyridinecarboxylates. Wu and Stoltz disclosed bimetallic Cu/Pd catalyst systems that allow decarboxylative cross-couplings of picolinic acid with (hetero)aryl bromides, albeit in only moderate yields at temperatures as high as 190 °C or with high catalyst loadings (Scheme 3, (1)).^{35,36} Hoarau et al. used an indirect strategy for their coupling that involves the protection/activation of the picolinic acids by upfront conversion into the *N*-oxides (Scheme 3, (2)).³⁸ Stoichiometric amounts of a silver or copper salt along with the palladium catalyst were still required to obtain reasonable yields. This protocol follows a mechanism that is related to the direct arylation of pyridine *N*-oxides.^{39–42}

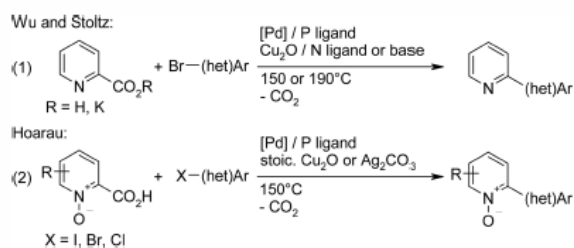
To date, the importance of the 2-arylpyridine structural unit remains in stark contrast to the lack of effective and flexible tools for its preparation. 2-Aryl-3-fluoropyridines, in particular,

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Scheme 2. Competing Reaction Pathways in the Coupling of 2-Pyridinecarboxylic Acids^{36,37}


Scheme 3. Decarboxylative Cross-Coupling of Picolinic Acid Derivatives



would be interesting pharmacophores and, in addition, could be used as synthetic hubs for further derivatization via nucleophilic

aromatic fluorine substitution.^{43–50} The C–H arylation of *N*-oxides would likely give mixtures of regioisomers and require subsequent reduction.^{40,51} Suzuki–Miyaura couplings are challenging for this substrate class because of the instability of some heterocyclic boronates, particularly the 2-pyridyl derivatives.^{30,52} Data from the Pfizer internal electronic laboratory notebook shows that of 358 reactions attempted using pyridine-2-boronates, only 28 experiments, corresponding to <8% of examples, achieved a yield of at least 20%.⁵³ A decarboxylative cross-coupling of 3-fluoropicolinic acid appeared to be the most promising and versatile approach to directing the formation of the new bond between the nitrogen atom and the fluorine substituent.

In search of an efficient and generally applicable protocol for the synthesis of 3-fluoro-2-arylpyridines, the utility of various literature protocols was investigated in the coupling of potassium 3-fluoropicolinate (1a) with 1-bromo-4-fluorobenzene (2a). ¹⁹F NMR was employed to determine yields and selectivity for cross-coupling versus protodecarboxylation. When restricting the catalyst loading to a maximum of 10 mol % of copper/5 mol % of palladium and the temperature to 130 °C, the desired product was obtained in low yields. The best result was obtained using a catalyst system consisting of Cu₂O/1,10-phenanthroline and PdCl₂/PPh₃, which had previously been optimized for similar transformations (Table 1, entry 1).^{35,36} A decisive increase in yield was observed when switching the solvent from NMP to DMSO (entry 2). Only a 1:1 mixture of NMP/mesitylene gave comparable results, whereas other solvents such as DMF, DMAc, or mesitylene were inferior for this substrate combination (see the Supporting Information, Table S2). Systematic variation of the palladium source showed Pd(COD)Cl₂ to be the most effective, with a yield increased to 74% yield (entries 3–5). In investigations of

 Table 1. Optimization of the Reaction Conditions^a

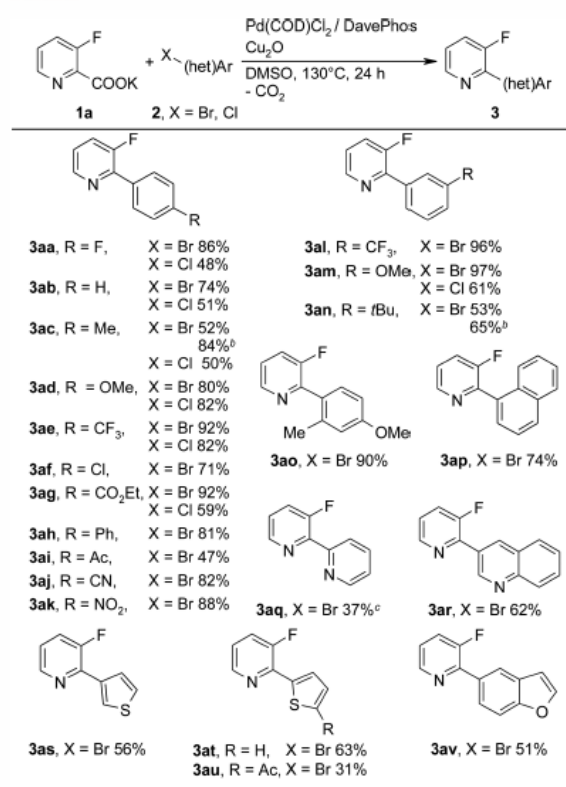
entry	[M]	N ligand	[Pd]	P ligand	3aa (%)	4a (%)
1 ^b	Cu ₂ O	phen	PdCl ₂	PPh ₃	19	trace
2	Cu ₂ O	phen	PdCl ₂	PPh ₃	60	7
3	Cu ₂ O	phen	Pd(COD)Cl ₂	PPh ₃	74	8
4	Cu ₂ O	phen	PdI ₂	PPh ₃	54	11
5	Cu ₂ O	phen	Pd(acac) ₂	PPh ₃	67	9
6 ^c	CuCl	phen	Pd(COD)Cl ₂	PPh ₃	66	nd
7	Ag ₂ CO ₃	phen	Pd(COD)Cl ₂	PPh ₃	66	10
8	Cu ₂ O	Me ₄ -phen	Pd(COD)Cl ₂	PPh ₃	83	nd
9	Cu ₂ O	NO ₂ -phen	Pd(COD)Cl ₂	PPh ₃	49	17
10	Cu ₂ O	Me ₄ -phen	Pd(COD)Cl ₂	P(<i>p</i> -Tol) ₃	84	trace
11	Cu ₂ O	Me ₄ -phen	Pd(COD)Cl ₂	BINAP	75	nd
12	Cu ₂ O	Me ₄ -phen	Pd(COD)Cl ₂	PCy ₃	28	trace
13	Cu ₂ O	Me ₄ -phen	Pd(COD)Cl ₂	CyJohnPhos	82	10
14	Cu ₂ O	Me ₄ -phen	Pd(COD)Cl ₂	DavePhos	92	7
15	Cu ₂ O	–	Pd(COD)Cl ₂	DavePhos	93	trace
16	–	–	Pd(COD)Cl ₂	DavePhos	7	32
17	Cu ₂ O	–	–	–	nd	nd

^aReaction conditions: 1a (0.5 mmol), 2a (1.0 mmol), [M] (5 mol %), N ligand (10 mol %), [Pd] (5 mol %), P ligand (15 mol %), DMSO (2 mL), 130 °C, 24 h; ¹⁹F NMR yield with 1,4-difluorobenzene as internal standard; NO₂-phen = 5-nitro-1,10-phenanthroline, Tol = tolyl, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, CyJohnPhos = (2-biphenyl)dicyclohexylphosphine, DavePhos = 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl; nd = not detected. ^bIn NMP (2 mL). ^c10 mol % of [M] was used.

silver- and copper-based decarboxylation catalysts, Cu₂O was identified as the most efficient in combination with 3,4,7,8-tetramethyl-1,10-phenanthroline (Me₄-phen) (entries 6–9). The choice of the phosphine ligand was similarly critical (entries 10–14). Not only did the phosphine affect the yields, but in addition, undesired P–C bond cleavage resulted in aryl group transfer to the pyridine with formation of hard-to-separate 2-arylpicoline byproducts. Because the quality of pharmacological structure–activity relationships is strongly affected by such structurally related impurities, a key criterion for the choice of the phosphine ligand was its stability under the reactions conditions. In this respect, DavePhos turned out to be most effective. Notably, with this ligand, the optimal yield and selectivity was obtained in the absence of Me₄-phen (entry 15). Control experiments confirmed that both Pd and Cu are essential components of the catalyst system (entries 16 and 17).

In the presence of 5 mol % of Pd(COD)Cl₂, 15 mol % of DavePhos, and 5 mol % of Cu₂O, the desired product was formed in 93% yield within 24 h at 130 °C in DMSO. This optimized protocol is applicable to the coupling of 1a with a broad range of aryl bromides substituted in the *ortho*-, *meta*-, or *para*-position (Table 2). Common functionalities including

Table 2. Scope with Regard to the Electrophilic Coupling Partner^a

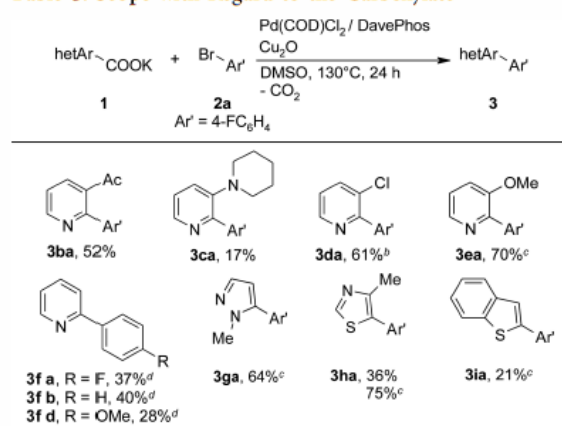


^aReaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), Cu₂O (5 mol %), Pd(COD)Cl₂ (5 mol %), DavePhos (15 mol %), DMSO (2 mL), 130 °C, 24 h. Yields of isolated products. ^b**1a** (0.5 mmol), **2** (1.0 mmol), Cu₂O (5 mol %), phen (10 mol %), PdCl₂ (5 mol %), CyJohnPhos (15 mol %), NMP/mesitylene (1:1, 2 mL), 150 °C, 24 h. Yield of isolated products. ^c**1a** (0.75 mmol), **2** (0.5 mmol).

ether, ester, carbonyl, trifluoromethyl, cyano, and nitro groups are tolerated. Heteroaryl bromides were also found to be suitable coupling partners. We were pleased to find that aryl chlorides, which are available in greater structural diversity and are less expensive, but less reactive, were smoothly converted without further adjustments to the catalyst or conditions. As the main side reactions, homocoupling of the excess aryl halide and protodecarboxylation of the picolinic acid were observed.

Having thus established a versatile protocol for our synthetic needs, we briefly investigated whether this catalyst system is advantageous also for other heteroaromatic carboxylates (Table 3). 3-Acetylpicolinate was also converted in moderate yield,

Table 3. Scope with Regard to the Carboxylate^a

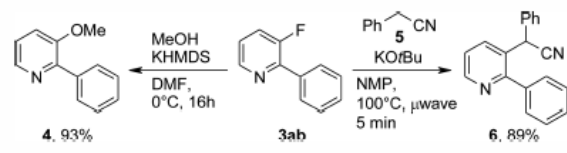


^aReaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), Cu₂O (5 mol %), Pd(COD)Cl₂ (5 mol %), DavePhos (15 mol %), DMSO (2 mL), 130 °C, 24 h. Yields of isolated products. ^bAg₂CO₃ (5 mol %) was used instead of Cu₂O. ^c**1** (0.5 mmol), **2** (1.0 mmol), Cu₂O (5 mol %), phen (10 mol %), PdCl₂ (5 mol %), CyJohnPhos (15 mol %), NMP/mesitylene (1:1, 2 mL), 150 °C, 24 h. Yields of isolated products. ^d**1f** (0.5 mmol), **2** (1.0 mmol), Cu₂O (5 mol %), Pd(COD)Cl₂ (5 mol %), DavePhos (15 mol %), NMP/mesitylene (1:1, 2 mL), 190 °C, 24 h. Yields of isolated products.

whereas the yield was low for 3-piperidylpicolinate. 3-Chloropicolinate (**1d**) was converted most effectively using a silver-based decarboxylation catalyst, which is in line with observations made for *ortho*-chloro-substituted benzoates.²⁴ Slightly modified reaction conditions (5 mol % of PdCl₂, 15 mol % of CyJohnPhos, 5 mol % of Cu₂O, and 10 mol % of phen in 2 mL of NMP/mesitylene (1:1) at 150 °C) were necessary to efficiently convert 3-methoxypicolinate (**1e**). Remarkably, picolinic acids devoid of substituents in the 3-position could only be converted at 190 °C. This indicates that a substituent *ortho* to the carboxylate facilitates decarboxylation not only for benzoates but also for picolates. Picolinic acids substituted in another position of the heteroaromatic ring (4-Cl, 5-F, 6-F/Cl/OMe) did not react under our reaction conditions, again underlining the unique reactivity of pyridines substituted in the 3-position. Further studies revealed that five-membered heteroaromatic carboxylates, including *N*-methylpyrazole, thiazole, or benzothiophene derivatives, can also be converted in reasonable yields using the new catalyst system. As side products, homocoupling products of the aryl halides were detected along with unreacted starting materials.

In order to demonstrate the utility of the 2-aryl-3-fluoropyridines as synthetic hubs for further derivatization via nucleophilic aromatic fluorine substitution, **3ab** was applied in a C–O and a C–C bond formation (Scheme 4). Reaction of **3ab**

Scheme 4. Derivatization of **3ab**



with methanol, which can also be replaced by more complex alcohols, in the presence of potassium bis(trimethylsilyl)amide (KHMDS)⁴⁵ gave the desired product **4**, and treatment of **3ab** in the presence of nitrile **5** and potassium *tert*-butoxide under microwave conditions furnished compound **6**,⁴⁴ both in good yield.

In conclusion, an efficient protocol for the Cu/Pd-catalyzed decarboxylative cross-coupling of picolinic acid derivatives with (hetero)aryl bromides and chlorides has been developed, which gives convenient access to otherwise hard to synthesize 3-substituted arylpyridines. It draws on stable picolinate salts as the source of the nucleophile, proceeds at reasonable temperatures, and requires only catalytic amounts of transition metals.

EXPERIMENTAL SECTION

General Remarks. Chemicals and solvents were either purchased (puriss. p.A.) from commercial suppliers or purified by standard procedures prior to use.⁵⁴ All reactions were performed in oven-dried glassware under an argon atmosphere containing a Teflon-coated stirrer bar and dry septum. Microwave-assisted reactions were performed in sealed microwave vessels using the Biotage Initiator 2.5 EXP microwave system (external IR sensor) with the Initiator Remote Viewer reaction monitoring software. Solvents and liquid reactants were degassed with argon. Reactions were monitored by ¹⁹F NMR using 1,4-difluorobenzene as an internal standard or by GC using dodecane as an internal standard. Response factors of the products with regard to dodecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using a 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⁻¹, 3 min at 300 °C). Column chromatography was performed on a flash chromatography machine. NMR spectra were recorded at ambient temperature using CDCl₃ or DMSO-*d*₆ as solvent, with proton, carbon, and fluorine resonances at 400/300/200/250, 151/101/75/63/50, and 377/235/41 MHz, respectively. Mass spectral data were acquired on a GC-MS and on a GC-HRMS with a TOF mass analyzer. The ionization was achieved by EI. Infrared spectra were recorded on a FT-IR spectrometer with an ATR sampling accessory. Melting points were measured on a melting point apparatus.

General Procedure for the Synthesis of Potassium Carboxylate Salts. A 250 mL round-bottomed flask was charged with the carboxylic acid (20.0 mmol) and ethanol (20 mL). A solution of potassium *tert*-butoxide (2.24 g, 20.0 mmol) in ethanol (20 mL) was added dropwise over 1 h. After complete addition, the reaction mixture was stirred for another 1 h at rt. A gradual formation of a precipitate was observed. The resulting solid was collected by filtration, washed sequentially with ethanol (2 × 10 mL) and diethyl ether (10 mL), and dried in vacuum to provide the corresponding potassium carboxylate. If after the addition of the potassium *tert*-butoxide solution a formation of a precipitate was not observed, the solution was concentrated in vacuum. The resulting solid was collected by filtration, washed with diethyl ether (10 mL), and dried in vacuum to provide the corresponding potassium carboxylate.

General Procedure for the Biaryl Synthesis. Method A. An oven-dried 20 mL vessel was charged with copper(I) oxide (3.61 mg, 25.0 μmol, 5 mol %), dichloro(1,5-dicyclooctadien)palladium(II) (7.13 mg, 25.0 μmol, 5 mol %), DavePhos (29.5 mg, 75 μmol, 15 mol %), and the potassium carboxylate **1** (0.50 mmol). DMSO (2 mL) and the aryl halide **2** (1 mmol) were added, and the resulting mixture was stirred at 130 °C under a dry atmosphere of argon. After 24 h, the mixture was allowed to cool to rt, washed with distilled water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂, cyclohexane/ethyl acetate gradient) yielding the corresponding biaryl **3**.

Method B. An oven-dried 20 mL vessel was charged with copper(I) oxide (3.61 mg, 25.0 μmol, 5 mol %), palladium(II) chloride (4.44 mg, 25.0 μmol, 5 mol %), 1,10-phenanthroline (9.01 mg, 50 μmol, 10 mol %), CyJohnPhos (26.3 mg, 75 μmol, 15 mol %), and the potassium carboxylate **1** (0.50 mmol). NMP/mesitylene (2 mL, 1/1) and the aryl bromide **2** (1 mmol) were added, and the resulting mixture was stirred at 150 °C under a dry atmosphere of argon. After 24 h, the mixture was allowed to cool to rt, washed with distilled water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂, cyclohexane/ethyl acetate gradient) yielding the corresponding biaryl **3**.

3-Fluoro-2-(4-fluorophenyl)pyridine (3aa) [CAS: 511522-74-0]. Compound **3aa** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene **2a** (177 mg, 111 μL, 1.0 mmol). **3aa** was isolated (SiO₂, cyclohexane/ethyl acetate = 6/1) as a colorless solid (82 mg, 86%). Compound **3aa** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-chloro-4-fluorobenzene **2a'** (133 mg, 108 μL, 1.0 mmol). **3aa** was isolated (SiO₂, cyclohexane/ethyl acetate = 6/1) as a colorless solid (45 mg, 48%): mp 63–64 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.49–8.54 (m, 1H), 7.96–8.03 (m, 2H), 7.50 (ddd, 1H, *J* = 11.0, 8.3, 1.5 Hz), 7.25–7.31 (m, 1H), 7.14–7.22 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 163.4 (d, *J*_{C–F} = 249.3 Hz), 157.4 (d, *J*_{C–F} = 259.8 Hz), 145.4 (d, *J*_{C–F} = 5.5 Hz), 145.2 (d, *J*_{C–F} = 10.5 Hz), 131.4 (dd, *J*_{C–F} = 5.5, 3.3 Hz), 130.7 (dd, *J*_{C–F} = 8.6, 6.4 Hz), 124.2 (d, *J*_{C–F} = 19.9 Hz), 128.4 (d, *J*_{C–F} = 4.4 Hz), 115.4 (d, *J*_{C–F} = 21.6 Hz); ¹⁹F NMR (CDCl₃, 377 MHz) δ –112.1, –123.0; IR ν 3048, 3021, 1603, 1516, 1447, 1227, 833, 756 cm⁻¹; MS *m/z* (%) 191.0 (100) [M]⁺, 190 (58), 172 (16), 170 (10), 74 (12), 50 (16); HRMS (EI) *m/z* [M]⁺ calcd for C₁₁H₇F₂N 191.0547; found 191.0548.

3-Fluoro-2-phenylpyridine (3ab) [CAS: 1214342-78-5]. Compound **3ab** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and bromobenzene **2b** (159 mg, 106 μL, 1.0 mmol). **3ab** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless solid (64 mg, 74%). Compound **3ab** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and chlorobenzene **2b'** (113 mg, 102 μL, 1.0 mmol). **3ab** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless solid (44 mg, 71%): mp 48–49 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.50–8.58 (m, 1H), 7.93–8.04 (m, 2H), 7.42–7.55 (m, 4H), 7.25–7.31 (m, 1H); ¹³C NMR (CDCl₃, 101 MHz) δ 157.5 (d, *J*_{C–F} = 258.9 Hz), 146.2 (d, *J*_{C–F} = 10.9 Hz), 145.4 (d, *J*_{C–F} = 5.5 Hz), 135.3 (d, *J*_{C–F} = 5.4 Hz), 129.2, 128.8 (d, *J*_{C–F} = 5.4 Hz), 128.4, 124.1 (d, *J*_{C–F} = 20.0 Hz), 123.4 (d, *J*_{C–F} = 3.6 Hz); ¹⁹F NMR (CDCl₃, 377 MHz) δ –123.0; IR ν 3064, 1596, 1431, 1250, 1188, 798 cm⁻¹; MS *m/z* (%) 173 (100) [M]⁺, 172 (78), 145 (11), 125 (11), 51 (13), 50 (23); HRMS (EI) *m/z* [M]⁺ calcd for C₁₁H₇FN 173.0641; found 173.0639.

3-Fluoro-2-(4-methylphenyl)pyridine (3ac). Compound **3ac** was prepared following methods A and B, respectively, from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-bromo-4-methylbenzene **2c** (175 mg, 126 μL, 1.0 mmol). **3ac** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless solid (48 mg, 52% (method A); 79 mg, 84% (method B)). Compound **3ac** was

prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-chloro-4-methylbenzene **2c'** (129 mg, 1.0 mmol). **3ac** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless solid (47 mg, 50%); mp 51–52 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.45–8.58 (m, 1H), 7.90 (dd, 2H, J = 8.3, 1.5 Hz), 7.47 (ddd, 1H, J = 11.0, 8.3, 1.0 Hz), 7.31 (d, 2H, J = 8.3 Hz), 7.20–7.27 (m, 1H), 2.43 (s, 3H); ¹³C NMR (CDCl₃, 101 MHz) δ 157.4 (d, J_{C-F} = 259.8 Hz), 146.2 (d, J_{C-F} = 10.9 Hz), 145.2 (d, J_{C-F} = 5.4 Hz), 139.2, 132.5 (d, J_{C-F} = 5.4 Hz), 129.1, 128.6 (d, J_{C-F} = 6.4 Hz), 123.9 (d, J_{C-F} = 20.9 Hz), 123.0 (d, J_{C-F} = 3.6 Hz), 21.3; ¹⁹F NMR (CDCl₃, 377 MHz) δ –123.0; IR ν 3050, 3027, 2921, 1596, 1444, 1405, 1251, 1187, 1106 cm⁻¹; MS, m/z (%) 187 (100) [M]⁺, 186 (60), 185 (17), 91 (12), 63 (10), 50 (11); HRMS (EI) m/z [M]⁺ calcd for C₁₂H₁₀FN 187.0797; found 187.0796.

3-Fluoro-2-(4-methoxyphenyl)pyridine (3ad) [CAS: 847226-10-2]. Compound **3ad** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-bromo-4-methoxybenzene **2d** (187 mg, 1.0 mmol). **3ad** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a yellow oil (82 mg, 80%). Compound **3ad** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-chloro-4-methoxybenzene **2d'** (145 mg, 1.0 mmol). **3ad** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a yellow oil (83 mg, 82%): ¹H NMR (CDCl₃, 400 MHz) δ 8.45–8.53 (m, 1H), 7.97 (dd, 2H, J = 8.8, 1.5 Hz), 7.46 (ddd, 1H, J = 11.3, 8.3, 1.3 Hz), 7.18–7.25 (m, 1H), 6.97–7.07 (m, 2H), 3.88 (s, 3H); ¹³C NMR (CDCl₃, 101 MHz) δ 160.4, 157.3 (d, J_{C-F} = 259.8 Hz), 145.8 (d, J_{C-F} = 10.0 Hz), 145.2 (d, J_{C-F} = 5.5 Hz), 130.1 (d, J_{C-F} = 5.5 Hz), 127.9 (d, J_{C-F} = 5.4 Hz), 123.9 (d, J_{C-F} = 20.9 Hz), 122.7 (d, J_{C-F} = 4.5 Hz), 113.8, 55.3; ¹⁹F NMR (CDCl₃, 377 MHz) δ –123.2; IR ν 3064, 3006, 2838, 1611, 1513, 1436, 1307, 1245, 1175, 1023 cm⁻¹; MS, m/z (%) 203 (100) [M]⁺, 188 (54), 160 (35), 159 (22); HRMS (EI) m/z [M]⁺ calcd for C₁₂H₁₀FNO 203.0746; found 203.0745.

3-Fluoro-2-[4-(trifluoromethyl)phenyl]pyridine (3ae) [CAS: 1261805-54-2]. Compound **3ae** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-bromo-4-(trifluoromethyl)benzene **2e** (227 mg, 1.0 mmol). **3ae** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless oil (111 mg, 92%). Compound **3ae** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-chloro-4-(trifluoromethyl)benzene **2e'** (184 mg, 1.0 mmol). **3ae** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless oil (99 mg, 82%): ¹H NMR (CDCl₃, 250 MHz) δ 8.51–8.61 (m, 1H), 8.13 (d, 2H, J = 8.1 Hz), 7.75 (d, 2H, J = 8.4 Hz), 7.46–7.60 (m, 1H), 7.30–7.38 (m, 1H); ¹³C NMR (CDCl₃, 151 MHz) δ 157.8 (d, J_{C-F} = 260.8 Hz), 145.6, 144.5 (d, J_{C-F} = 9.7 Hz), 138.6, 131.0 (q, J_{C-F} = 33.3 Hz), 129.1 (d, J_{C-F} = 6.9 Hz), 125.4 (q, J_{C-F} = 4.2 Hz), 124.6, 124.3, 124.37 (q, J_{C-F} = 273.3 Hz); ¹⁹F NMR (CDCl₃, 377 MHz) δ –62.7, –122.5; IR ν 3067, 1619, 1597, 1446, 1406, 1323, 1252, 1163, 1114, 1068, 1016 cm⁻¹; MS, m/z (%) 241 (100) [M]⁺, 222 (19), 221 (17), 172 (27), 68 (15), 50 (12); HRMS (EI) m/z [M]⁺ calcd for C₁₂H₇F₃N 241.0515; found 241.0519.

2-(4-Chlorophenyl)-3-fluoropyridine (3af) [CAS: 1233702-02-7]. Compound **3af** was prepared following method A from 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-chloro-4-bromobenzene **2f** (191 mg, 1.0 mmol). **3af** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless solid (73 mg, 71 mmol): mp 74–75 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.52 (d, 1H, J = 4.5 Hz), 7.95 (dd, 2H, J = 8.5, 1.3 Hz), 7.41–7.55 (m, 3H), 7.24–7.33 (m, 1H); ¹³C NMR (CDCl₃, 101 MHz) δ 157.5 (d, J_{C-F} = 260.7 Hz), 145.3, 144.9 (d, J_{C-F} = 10.0 Hz), 135.4, 133.6, 130.1 (d, J_{C-F} = 5.5 Hz), 128.7, 124.3 (d, J_{C-F} = 20.9 Hz), 123.8; ¹⁹F NMR (CDCl₃, 377 MHz) δ –123.0; IR ν 3048, 3016, 1599, 1497, 1445, 1398, 1254, 1190, 1092 cm⁻¹; MS, m/z (%) 209 (33) [M]⁺, 208 (16), 207 (100) [M]⁺, 172 (55), 145 (10), 75 (7), 50 (9); HRMS (EI) m/z [M]⁺ calcd for C₁₁H₇³⁵ClFN 207.0251; found 207.0249.

4-(3-Fluoro-2-pyridinyl)benzoic Acid Ethyl Ester (3ag) [CAS: 1246461-83-5]. Compound **3ag** was prepared following method A from 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 4-bromobenzoic acid ethyl ester **2g** (231 mg, 1.0 mmol). **3ag**

was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a yellow oil (113 mg, 92%). Compound **3ag** was prepared following method A from 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 4-chlorobenzoic acid ethyl ester **2g'** (188 mg, 1.0 mmol). **3ag** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a yellow oil (72 mg, 59%): ¹H NMR (CDCl₃, 400 MHz) δ 8.51–8.59 (m, 1H), 8.11–8.21 (m, 2H), 8.01–8.10 (m, 2H), 7.52 (ddd, 1H, J = 10.9, 8.4, 1.0 Hz), 7.30–7.35 (m, 1H), 4.42 (q, 2H, J = 7.1 Hz), 1.43 (t, 3H, J = 7.2 Hz); ¹³C NMR (CDCl₃, 101 MHz) δ 166.3, 157.8 (d, J_{C-F} = 261.6 Hz), 145.6 (d, J_{C-F} = 5.4 Hz), 145.0 (d, J_{C-F} = 10.9 Hz), 139.4 (d, J_{C-F} = 5.5 Hz), 130.8, 129.6, 128.7 (d, J_{C-F} = 6.4 Hz), 124.3 (d, J_{C-F} = 25.4 Hz), 124.2, 61.1, 14.3; ¹⁹F NMR (CDCl₃, 377 MHz) δ –122.1; IR ν 3064, 2984, 1711, 1443, 1402, 1367, 1267, 1186, 1095, 1016 cm⁻¹; MS, m/z (%) 245 (59) [M]⁺, 217 (47), 201 (16), 200 (100), 172 (27), 125 (10); HRMS (EI) m/z [M]⁺ calcd for C₁₄H₁₂FNO₂ 245.0852; found 245.0847.

2-[1,1'-Biphenyl]-4-yl-3-fluoropyridine (3ah). Compound **3ah** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 4-bromo-1,1'-biphenyl **2h** (259 mg, 1.0 mmol). **3ah** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless solid (100 mg, 81%); mp 97–98 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.52–8.59 (m, 1H), 8.09 (dd, 2H, J = 8.4, 1.6 Hz), 7.72–7.77 (m, 2H), 7.64–7.71 (m, 2H), 7.45–7.56 (m, 3H), 7.36–7.42 (m, 1H), 7.28–7.32 (m, 1H); ¹³C NMR (CDCl₃, 101 MHz) δ 156.3 (d, J_{C-F} = 259.8 Hz), 145.7 (d, J_{C-F} = 10.1 Hz), 145.2 (d, J_{C-F} = 5.5 Hz), 142.0, 140.5, 134.0 (d, J_{C-F} = 5.5 Hz), 129.2 (d, J_{C-F} = 6.4 Hz), 128.8, 127.6, 127.17, 127.15, 124.3 (d, J_{C-F} = 20.9 Hz), 123.4 (d, J_{C-F} = 3.6 Hz); ¹⁹F NMR (CDCl₃, 377 MHz) δ –122.7; IR ν 3062, 3024, 1594, 1485, 1440, 1397, 1246 cm⁻¹; MS, m/z (%) 249 (100) [M]⁺, 248 (23), 51 (8), 50 (10), 44 (8); HRMS (EI) m/z [M]⁺ calcd for C₁₇H₁₂FN 249.0954; found 249.0938.

1-[4-(3-Fluoro-2-pyridinyl)phenyl]ethanone (3ai). Compound **3ai** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-(4-bromophenyl)ethanone **2i** (203 mg, 1.0 mmol). **3ai** was isolated (SiO₂, cyclohexane/ethyl acetate = 6/1) as a colorless solid (50 mg, 47%); mp 88–89 °C; ¹H NMR (CDCl₃, 200 MHz) δ 8.57 (dt, 1H, J_d = 4.5, J_i = 1.5 Hz), 8.03–8.15 (m, 4H), 7.47–7.60 (m, 1H), 7.28–7.38 (m, 1H), 2.66 (s, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ 197.8, 157.8 (d, J_{C-F} = 261.6 Hz), 145.6 (d, J_{C-F} = 5.1 Hz), 144.8 (d, J_{C-F} = 10.2 Hz), 139.6 (d, J_{C-F} = 5.9 Hz), 137.2, 128.9 (d, J_{C-F} = 6.2 Hz), 128.4, 124.34 (d, J_{C-F} = 20.9 Hz), 124.30 (d, J_{C-F} = 4.0 Hz), 26.7; ¹⁹F NMR (CDCl₃, 377 MHz) δ –122.1; IR ν 3078, 3009, 1674, 1603, 1443, 1400, 1246 cm⁻¹; MS, m/z (%) 215 (17) [M]⁺, 201 (14), 200 (100), 172 (30); HRMS (EI) m/z [M]⁺ calcd for C₁₃H₁₀FNO 215.0746; found 215.0741.

4-(3-Fluoro-2-pyridinyl)benzotriazole (3aj) [CAS: 1352794-83-2]. Compound **3aj** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 4-bromobenzotriazole **2j** (184 mg, 1.0 mmol). **3aj** was isolated (SiO₂, cyclohexane/ethyl acetate = 6/1) as a colorless solid (81 mg, 82%); mp 124–125 °C; ¹H NMR (CDCl₃, 75 MHz) δ 8.57 (dt, 1H, J_d = 4.4, J_i = 1.6 Hz), 8.10–8.17 (m, 2H), 7.74–7.81 (m, 2H), 7.55 (ddd, 1H, J = 11.1, 8.3, 1.3 Hz), 7.32–7.40 (m, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 157.8 (d, J_{C-F} = 262.0 Hz), 145.7 (d, J_{C-F} = 5.5 Hz), 143.9 (d, J_{C-F} = 9.9 Hz), 139.5 (d, J_{C-F} = 5.5 Hz), 132.2 (d, J_{C-F} = 0.7 Hz), 129.3 (d, J_{C-F} = 6.6 Hz), 124.8 (d, J_{C-F} = 4.0 Hz), 124.6 (d, J_{C-F} = 20.9 Hz), 118.7, 112.7 (d, J_{C-F} = 1.1 Hz); ¹⁹F NMR (CDCl₃, 377 MHz) δ –121.9; IR ν 3061, 2226, 1605, 1595, 1441, 1402, 1248, 1099 cm⁻¹; MS, m/z (%) 198 (100) [M]⁺, 197 (56), 50 (8); HRMS (EI) m/z [M]⁺ calcd for C₁₂H₇FN₂ 198.0593; found 198.0585.

3-Fluoro-2-(4-nitrophenyl)pyridine (3ak). Compound **3ak** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-bromo-4-nitrobenzene **2k** (204 mg, 1.0 mmol). **3ak** was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless solid (96 mg, 88%); mp 140–141 °C; ¹H NMR (CDCl₃, 200 MHz) δ 8.59 (dt, 1H, J_d = 4.5 Hz, J_i = 1.5 Hz), 8.30–8.40 (m, 2H), 8.16–8.26 (m, 2H), 7.51–7.63 (m, 1H), 7.34–7.45 (m, 1H); ¹³C NMR (CDCl₃, 50 MHz) δ 157.9 (d, J_{C-F} = 262.0), 148.0, 145.8 (d, J_{C-F} = 5.5 Hz), 143.4 (d, J_{C-F} = 9.9 Hz), 141.3 (d, J_{C-F} = 5.9 Hz), 129.6 (d, J_{C-F} = 6.6 Hz), 125.0 (d, J_{C-F} = 4.4 Hz),

124.6 (d, $J_{C-F} = 20.5$ Hz), 123.5; ^{19}F NMR ($CDCl_3$, 377 MHz) δ -121.6; IR ν 3076, 1593, 1514, 1440, 1342, 1188, 1103 cm^{-1} ; MS m/z (%) 218 (100) [M] $^+$, 188 (38), 172 (35), 160 (19), 145 (20), 125 (17), 44 (15); HRMS (EI) m/z [M] $^+$ calcd for $C_{11}H_7FN_2O_2$ 218.0492; found 218.0486.

3-Fluoro-2-[3-(trifluoromethyl)phenyl]pyridine (3al) [CAS: 1261634-22-3]. Compound **3al** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-bromo-3-(trifluoromethyl)benzene **2l** (227 mg, 1.0 mmol). **3al** was isolated (SiO_2 , cyclohexane/ethyl acetate = 9/1) as a colorless oil (116 mg, 96%); 1H NMR ($CDCl_3$, 400 MHz) δ 8.49–8.61 (m, 1H), 8.30 (s, 1H), 8.19 (d, 1H, $J = 7.8$ Hz), 7.71 (d, 1H, $J = 8.0$ Hz), 7.62 (t, 1H, $J = 7.8$ Hz), 7.54 (ddd, $J = 11.0, 8.3, 1.3$ Hz), 7.29–7.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): 157.6 (d, $J_{C-F} = 261.6$ Hz), 145.6 (d, $J_{C-F} = 5.4$ Hz), 144.5 (d, $J_{C-F} = 10.9$ Hz), 136.0 (d, $J_{C-F} = 5.5$ Hz), 131.8–132.1 (m), 130.9 (q, $J_{C-F} = 31.8$ Hz), 128.9, 125.7–125.9 (m), 125.5–125.7 (m), 124.4 (d, $J_{C-F} = 20.9$ Hz), 124.2 (d, $J_{C-F} = 4.5$ Hz), 123.9 (q, $J_{C-F} = 273.4$ Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ -62.6, -122.8; IR ν 3071, 1597, 1444, 1421, 1334, 1303, 1252, 1163, 1119, 1074 cm^{-1} ; MS, m/z (%) 241 (100) [M] $^+$, 222 (20), 221 (19), 172 (25), 69 (16), 50 (12); HRMS (EI) m/z [M] $^+$ calcd for $C_{12}H_7F_3N$ 241.0515; found 241.0503.

3-Fluoro-2-(3-methoxyphenyl)pyridine (3am) [CAS: 1269225-56-0]. Compound **3am** was prepared following method A from 3-fluoropyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-bromo-3-methoxybenzene **2m** (191 mg, 1.0 mmol). **3am** was isolated (SiO_2 , cyclohexane/ethyl acetate = 6/1) as an orange oil (99 mg, 97%). Compound **3am** was prepared following method A from 3-fluoropyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-chloro-3-methoxybenzene **2m'** (145 mg, 1.0 mmol). **3am** was isolated (SiO_2 , cyclohexane/ethyl acetate = 6/1) as an orange oil (62 mg, 61%); 1H NMR ($CDCl_3$, 400 MHz) δ 8.52–8.54 (m, 1H), 7.54–7.60 (m, 2H), 7.50 (ddd, 1H, $J = 11.0, 8.3, 1.5$ Hz), 7.41 (t, 1H, $J = 7.9$ Hz), 7.26–7.30 (m, 1H), 6.98–7.03 (m, 1H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 159.7, 157.5 (d, $J_{C-F} = 260.4$ Hz), 146.0 (d, $J_{C-F} = 10.3$ Hz), 145.3 (d, $J_{C-F} = 5.1$ Hz), 136.6 (d, $J_{C-F} = 5.1$ Hz), 129.4, 124.1 (d, $J_{C-F} = 21.3$ Hz), 123.5 (d, $J_{C-F} = 3.7$ Hz), 121.3 (d, $J_{C-F} = 7.3$ Hz), 115.4, 113.8 (d, $J_{C-F} = 5.1$ Hz), 55.3; ^{19}F NMR ($CDCl_3$, 377 MHz) δ -122.4; IR ν 3068, 2935, 2836, 1585, 1463, 1439, 1417, 1288, 1253, 1229 cm^{-1} ; MS, m/z (%) 203 (97) [M] $^+$, 202 (100), 174 (39), 173 (27), 172 (46), 159 (14); HRMS (EI) m/z [M] $^+$ calcd for $C_{12}H_{10}FNO$ 203.0746; found 203.0744.

2-[3-(tert-Butyl)phenyl]-3-fluoropyridine (3an). Compound **3an** was prepared following method A from 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-bromo-3-(1,1-dimethylethyl)benzene **2n** (213 mg, 1.0 mmol). **3an** was isolated (SiO_2 , cyclohexane/ethyl acetate = 9/1) as a colorless liquid (61 mg, 53%); 1H NMR ($CDCl_3$, 400 MHz) δ 8.54 (dt, 1H, $J_d = 4.5$ Hz, $J_t = 1.5$ Hz), 8.00 (d, 1H, $J = 1.5$ Hz), 7.76 (dq, 1H, $J_d = 7.5$ Hz, $J_q = 1.6$ Hz), 7.40–7.53 (m, 3H), 7.23–7.30 (m, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 157.5 (d, $J_{C-F} = 262.5$ Hz), 151.3, 146.8 (d, $J_{C-F} = 10.9$ Hz), 145.1 (d, $J_{C-F} = 5.4$ Hz), 134.7 (d, $J_{C-F} = 4.5$ Hz), 128.1, 126.4, 126.0 (d, $J_{C-F} = 5.4$ Hz), 125.8 (d, $J_{C-F} = 4.5$ Hz), 124.1 (d, $J_{C-F} = 20.9$ Hz), 123.3 (d, $J_{C-F} = 3.6$ Hz), 34.8, 31.3; ^{19}F NMR ($CDCl_3$, 377 MHz) δ -122.9; IR ν 3064, 2963, 2868, 1596, 1438, 1409, 1364, 1249 cm^{-1} ; MS, m/z (%) 229 (28) [M] $^+$, 215 (15), 214 (100), 199 (11), 185 (10), 43 (15); HRMS (EI) m/z [M] $^+$ calcd for $C_{13}H_{16}FN$ 229.1267; found 229.1285.

3-Fluoro-2-(5-methoxy-2-methylphenyl)pyridine (3ao). Compound **3ao** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 1-bromo-4-methoxy-2-methylbenzene **2o** (207 mg, 1.0 mmol). **3ao** was isolated (SiO_2 , cyclohexane/ethyl acetate = 9/1) as a yellow oil (98 mg, 90%); 1H NMR ($CDCl_3$, 400 MHz) δ 8.41–8.47 (m, 1H), 7.36–7.45 (m, 1H), 7.19–7.29 (m, 2H), 6.74–6.81 (m, 2H), 3.78 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 159.9, 157.0 (d, $J_{C-F} = 256.1$ Hz), 148.1 (d, $J_{C-F} = 14.5$ Hz), 145.1 (d, $J_{C-F} = 5.4$ Hz), 138.3, 131.1 (d, $J_{C-F} = 1.8$ Hz), 127.6 (d, $J_{C-F} = 3.6$ Hz), 123.3 (d, $J_{C-F} = 2.7$ Hz), 123.2 (d, $J_{C-F} = 14.5$ Hz), 115.7, 111.2, 55.2, 19.9; ^{19}F NMR ($CDCl_3$, 377 MHz) δ -121.2; IR ν 3061, 3002, 2930, 2835, 1608,

1575, 1507, 1436, 1283, 1240, 1185 cm^{-1} ; MS, m/z (%) 217 (67) [M] $^+$, 216 (28), 198 (77), 197 (100), 183 (25), 182 (24), 154 (23); HRMS (EI) m/z [M] $^+$ calcd for $C_{13}H_{12}FNO$ 217.0903; found 217.0901.

3-Fluoro-2-(1-naphthalenyl)pyridine (3ap). Compound **3ap** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 2-bromonaphthalene **2p** (213 mg, 1.0 mmol). **3ap** was isolated (SiO_2 , cyclohexane/ethyl acetate = 9/1) as a colorless solid (82 mg, 74%); mp 93–94 °C; 1H NMR ($CDCl_3$, 400 MHz) δ 8.59–8.68 (m, 1H), 7.89–8.03 (m, 2H), 7.76 (d, 1H, $J = 8.0$ Hz), 7.56–7.69 (m, 3H), 7.46–7.56 (m, 2H), 7.37–7.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 157.5 (d, $J_{C-F} = 257.9$ Hz), 147.4 (d, $J_{C-F} = 14.5$ Hz), 145.4 (d, $J_{C-F} = 5.4$ Hz), 133.7, 132.8 (d, $J_{C-F} = 3.6$ Hz), 131.2, 129.5, 128.4, 127.9 (d, $J_{C-F} = 1.0$ Hz), 126.5, 125.9, 125.2 (d, $J_{C-F} = 1.8$ Hz), 125.1, 123.9 (d, $J_{C-F} = 3.6$ Hz), 123.6 (d, $J_{C-F} = 20.0$ Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ -120.3; IR ν 3047, 3010, 1592, 1561, 1447, 1395, 1341, 1253, 1201 cm^{-1} ; MS, m/z (%) 223 (34) [M] $^+$, 222 (100), 221 (7), 111 (8), 50 (9); HRMS (EI) m/z [M] $^+$ calcd for $C_{15}H_{10}FN$ 223.0797; found 223.0785.

3-Fluoro-2,2'-bipyridine (3aq) [CAS: 1863378-49-7]. Compound **3aq** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (136 mg, 0.75 mmol) and 2-bromopyridine **2q** (80 mg, 0.75 mmol). **3aq** was isolated (SiO_2 , cyclohexane/ethyl acetate = 1/1) as a colorless oil (32 mg, 37%); 1H NMR ($CDCl_3$, 200 MHz) δ 8.81 (d, 1H, $J = 4.8$ Hz), 8.59 (dt, 1H, $J_d = 4.5$ Hz, $J_t = 1.5$ Hz), 7.94–8.04 (m, 1H), 7.77–7.89 (m, 1H), 7.48–7.62 (m, 1H), 7.31–7.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 158.0 (d, $J_{C-F} = 264.3$ Hz), 153.5 (d, $J_{C-F} = 6.4$ Hz), 149.6, 145.5 (d, $J_{C-F} = 5.5$ Hz), 144.8 (d, $J_{C-F} = 9.1$ Hz), 136.7, 124.9 (d, $J_{C-F} = 3.6$ Hz), 124.7 (d, $J_{C-F} = 20.9$ Hz), 124.2 (d, $J_{C-F} = 5.4$ Hz), 123.6; ^{19}F NMR ($CDCl_3$, 377 MHz) δ -122.5; IR ν 3059, 3011, 1585, 1454, 1422, 1256, 1196, 802 cm^{-1} ; MS, m/z (%) 174 (100) [M] $^+$, 173 (33), 147 (20), 146 (20), 76 (15), 51 (26), 50 (25); HRMS (EI) m/z [M] $^+$ calcd for $C_{10}H_6FN_2$ 174.0593; found 174.0597.

3-(3-Fluoro-2-pyridinyl)quinoline (3ar). Compound **3ar** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 3-bromoquinoline **2r** (104 mg, 0.50 mmol). **3ar** was isolated (SiO_2 , cyclohexane/ethyl acetate = 4/1) as a colorless solid (70 mg, 62%); mp 138–139 °C; 1H NMR ($CDCl_3$, 200 MHz) δ 9.57 (s, 1H), 8.77–8.82 (m, 1H), 8.59–8.65 (m, 1H), 8.18 (d, 1H, $J = 8.3$ Hz), 7.95 (dd, 1H, $J = 8.1, 1.5$ Hz), 7.72–7.84 (m, 1H), 7.52–7.66 (m, 2H), 7.31–7.43 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.0 (d, $J_{C-F} = 261.3$ Hz), 150.3 (d, $J_{C-F} = 6.6$ Hz), 148.0, 145.8 (d, $J_{C-F} = 5.1$ Hz), 143.6 (d, $J_{C-F} = 11.0$ Hz), 136.0 (d, $J_{C-F} = 7.0$ Hz), 130.2, 129.3, 128.6, 128.2 (d, $J_{C-F} = 5.9$ Hz), 127.5, 126.9, 124.3 (d, $J_{C-F} = 16.8$ Hz), 124.1 (d, $J_{C-F} = 4.0$ Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ -122.3; IR ν 3061, 3038, 1595, 1410, 1344, 1113 cm^{-1} ; MS, m/z (%) 224 (100) [M] $^+$, 223 (45), 205 (10), 122 (10), 76 (10), 50 (14); HRMS (EI) m/z [M] $^+$ calcd for $C_{14}H_8FN_2$ 224.0750; found 224.0739.

3-Fluoro-2-(3-thienyl)pyridine (3as). Compound **3as** was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 3-bromothiophene **2s** (168 mg, 1.0 mmol). **3as** was isolated (SiO_2 , cyclohexane/ethyl acetate = 9/1) as a colorless oil (50 mg, 56%); 1H NMR ($CDCl_3$, 200 MHz) δ 8.46 (dt, 1H, $J_d = 4.5$ Hz, $J_t = 1.6$ Hz), 8.04–8.12 (m, 1H), 7.86 (dt, 1H, $J_d = 5.1$ Hz, $J_t = 1.3$ Hz), 7.36–7.53 (m, 2H), 7.14–7.25 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.8 (d, $J_{C-F} = 260.5$ Hz), 145.1 (d, $J_{C-F} = 4.8$ Hz), 142.1 (d, $J_{C-F} = 11.0$ Hz), 136.9 (d, $J_{C-F} = 6.2$ Hz), 127.6 (d, $J_{C-F} = 4.8$ Hz), 126.2 (d, $J_{C-F} = 11.0$ Hz), 125.3 (d, $J_{C-F} = 1.5$ Hz), 123.7 (d, $J_{C-F} = 20.5$ Hz), 122.7 (d, $J_{C-F} = 4.0$ Hz); ^{19}F NMR ($CDCl_3$, 377 MHz) δ -121.4; IR ν 3113, 3065, 3021, 1597, 1454, 1440, 1206, 1099 cm^{-1} ; MS, m/z (%) 179 (100) [M] $^+$, 178 (26), 160 (37), 135 (10), 107 (10), 45 (11); HRMS (EI) m/z [M] $^+$ calcd for C_9H_6FNS 179.0205; found 179.0208.

3-Fluoro-2-(2-thienyl)pyridine (3at). Compound **3at** was prepared following method A from potassium 3-fluoropyridinecarboxylate **1a** (90.5 mg, 0.50 mmol) and 2-bromothiophene **2t** (166 mg, 1.0 mmol). **3at** was isolated (SiO_2 , cyclohexane/ethyl acetate = 9/1) as a colorless solid (56 mg, 63%); mp 43–44 °C; 1H NMR ($CDCl_3$, 200

MHz) δ 8.41 (dt, 1H, $J_d = 4.9$ Hz, $J_t = 1.6$ Hz), 7.80–7.86 (m, 1H), 7.38–7.53 (m, 2H), 7.12–7.23 (m, 2H); ¹³C NMR (CDCl₃, 50 MHz) δ 155.7 (d, $J_{C-F} = 263.1$ Hz), 145.0 (d, $J_{C-F} = 4.8$ Hz), 141.3 (d, $J_{C-F} = 11.3$ Hz), 139.8 (d, $J_{C-F} = 7.7$ Hz), 128.2 (d, $J_{C-F} = 2.2$ Hz), 128.1 (d, $J_{C-F} = 5.5$ Hz), 127.9 (d, $J_{C-F} = 7.3$ Hz), 123.6 (d, $J_{C-F} = 19.4$ Hz), 122.6 (d, $J_{C-F} = 4.0$ Hz); ¹⁹F NMR (CDCl₃, 377 MHz) δ -120.7; IR ν 3123, 3082, 1597, 1449, 1362, 1260, 1204, 1101 cm⁻¹; MS, *m/z* (%) 179 (100) [M]⁺, 178 (13), 135 (17), 134 (8), 107 (10), 45 (14); HRMS (EI) *m/z* [M]⁺ calcd for C₉H₈FNS 179.0205; found 179.0200.

1-(5-(3-Fluoro-2-pyridinyl)-2-thienyl)ethanone (3au). Compound 3au was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate 1a (90.5 mg, 0.50 mmol) and 1-(5-bromo-2-thienyl)ethanone 2u (207 mg, 1.0 mmol). 3au was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a yellow solid (34 mg, 31%): mp 146–147 °C; ¹H NMR (CDCl₃, 200 MHz) δ 8.44 (dt, 1H, $J_d = 4.5$ Hz, $J_t = 1.6$ Hz), 7.76–7.82 (m, 1H), 7.69–7.74 (m, 1H), 7.43–7.55 (m, 1H), 7.22–7.32 (m, 1H), 2.59 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 190.7, 156.4 (d, $J_{C-F} = 262.6$ Hz), 147.0 (d, $J_{C-F} = 7.7$ Hz), 145.4 (d, $J_{C-F} = 5.0$ Hz), 144.9 (d, $J_{C-F} = 3.3$ Hz), 140.1 (d, $J_{C-F} = 11.1$ Hz), 133.0 (d, $J_{C-F} = 2.2$ Hz), 128.3 (d, $J_{C-F} = 12.2$ Hz), 124.3 (d, $J_{C-F} = 3.3$ Hz), 124.1 (d, $J_{C-F} = 18.2$ Hz), 26.9; ¹⁹F NMR (CDCl₃, 377 MHz) δ -119.4; IR ν 3121, 3063, 2920, 2850, 1646, 1425, 1273, 1259 cm⁻¹; MS, *m/z* (%) 221 (42) [M]⁺, 207 (14), 206 (100), 178 (23), 134 (17), 107 (9); HRMS (EI) *m/z* [M]⁺ calcd for C₁₁H₈FNOS 221.0311; found 221.0304.

3-Fuoro-2-(5-benzofuranyl)pyridine (3av). Compound 3av was prepared following method A from potassium 3-fluoro-2-pyridinecarboxylate 1a (90.5 mg, 0.50 mmol) and 5-bromobenzofuran 2v (203 mg, 1.0 mmol). 3av was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a yellow solid (54 mg, 51%): mp 81–82 °C; ¹H NMR (CDCl₃, 200 MHz) δ 8.50–8.58 (m, 1H), 8.23 (t, 1H, $J = 1.5$ Hz), 7.91–8.00 (m, 1H), 7.44–7.70 (m, 3H), 7.21–7.32 (m, 1H), 6.86 (dd, 1H, $J = 2.3, 1.0$ Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 157.4 (d, $J_{C-F} = 259.8$ Hz), 155.4, 146.5 (d, $J_{C-F} = 10.5$ Hz), 145.6, 145.3 (d, $J_{C-F} = 5.5$ Hz), 130.3 (d, $J_{C-F} = 5.5$ Hz), 127.6, 125.3 (d, $J_{C-F} = 5.5$ Hz), 124.1 (d, $J_{C-F} = 20.5$ Hz), 123.0 (d, $J_{C-F} = 3.9$ Hz), 122.0 (d, $J_{C-F} = 6.1$ Hz), 111.3, 107.0; ¹⁹F NMR (CDCl₃, 41 MHz) δ -120.7; IR ν 3156, 3125, 3042, 3013, 1597, 1443, 1192, 1024 cm⁻¹; MS, *m/z* (%) 213 (100) [M]⁺, 212 (14), 185 (17), 184 (13); HRMS (EI) *m/z* [M]⁺ calcd for C₁₃H₈FNO 213.0590; found 213.0585.

1-(2-(4-Fluorophenyl)-3-pyridinyl)ethanone (3ba) [CAS: 280573-47-9]. Compound 3ba was prepared following method A from potassium 3-acetyl-2-pyridinecarboxylate 1b (102 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene 2a (177 mg, 1.1 μ L, 1.0 mmol). 3ba was isolated (SiO₂, cyclohexane/ethyl acetate = 2/1) as an orange oil (56 mg, 52%): ¹H NMR (CDCl₃, 250 MHz) δ 8.75 (dd, 1H, $J = 4.8, 1.7$ Hz), 7.86 (dd, 1H, $J = 7.7, 1.7$ Hz), 7.51–7.61 (m, 2H), 7.35 (dd, 1H, $J = 7.7, 4.9$ Hz), 7.11–7.22 (m, 2H), 2.11 (s, 3H); ¹³C NMR (CDCl₃, 63 MHz) δ 203.3, 163.6 (d, $J_{C-F} = 250.0$ Hz), 156.0, 150.9, 136.2, 136.2, 135.8 (d, $J_{C-F} = 3.7$ Hz), 131.0 (d, $J_{C-F} = 8.3$ Hz), 122.0, 115.8 (d, $J_{C-F} = 22.1$ Hz), 30.2; ¹⁹F NMR (CDCl₃, 235 MHz) δ -111.7; IR ν 3046, 2922, 2853, 1686, 1510, 1425, 1221, 843 cm⁻¹; MS, *m/z* (%) 215 (42) [M]⁺, 214 (26), 200 (100), 172 (45), 145 (20), 43 (43); HRMS (EI) *m/z* [M]⁺ calcd for C₁₃H₁₀FNO 215.0746; found 215.0742.

3-(1-Piperidinyl)-2-(4-fluorophenyl)pyridine (3ca). Compound 3ca was prepared following method A from potassium 3-(1-piperidinyl)-2-pyridinecarboxylate 1c (122 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene 2a (177 mg, 1.1 μ L, 1.0 mmol). 3ca was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a brown oil (22 mg, 17%): ¹H NMR (CDCl₃, 200 MHz) δ 8.30 (dd, 1H, $J = 4.5, 1.5$ Hz), 7.95–8.08 (m, 2H), 7.34 (dd, 1H, $J = 8.3, 1.5$ Hz), 7.04–7.21 (m, 3H), 2.78 (m, 4H), 1.44–1.64 (m, 6H); ¹³C NMR (CDCl₃, 50 MHz) δ 162.5 (d, $J_{C-F} = 246.6$ Hz), 151.3, 147.9, 142.7, 136.6 (d, $J_{C-F} = 3.7$ Hz), 130.3 (d, $J_{C-F} = 8.1$ Hz), 126.0, 122.5, 114.9 (d, $J_{C-F} = 21.2$ Hz), 52.3, 25.9, 23.9; ¹⁹F NMR (CDCl₃, 41 MHz) δ -114.4; IR ν 3060, 2935, 2854, 1602, 1573, 1507, 1432, 1219 cm⁻¹; MS, *m/z* (%) 256 (100) [M]⁺, 255 (39), 199 (15), 160 (17), 159 (7), 145 (8); HRMS (EI) *m/z* [M]⁺ calcd for C₁₆H₁₇FN₂ 256.1376; found 256.1365.

3-Chloro-2-(4-fluorophenyl)pyridine (3da) [CAS: 847226-00-0].

Compound 3da was prepared following method A from potassium 3-chloro-2-pyridinecarboxylate 1d (97.8 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene 2a (177 mg, 1.1 μ L, 1.0 mmol) in the presence of Ag₂CO₃ (6.96 mg, 25 μ mol, 5 mol %) instead of Cu₂O. 3da was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless solid (63 mg, 49%): mp 80–81 °C; ¹H NMR (CDCl₃, 300 MHz) δ 8.59 (dd, 1H, $J = 4.7, 1.6$ Hz), 7.71–7.83 (m, 3H), 7.12–7.26 (m, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ 163.1 (d, $J_{C-F} = 248.1$ Hz), 155.5, 147.6, 138.2, 134.2 (d, $J_{C-F} = 3.3$ Hz), 131.3 (d, $J_{C-F} = 8.4$ Hz), 130.1, 123.1, 115.0 (d, $J_{C-F} = 22.0$ Hz); ¹⁹F NMR (CDCl₃, 41 MHz) δ -112.6; IR ν 3044, 1599, 1574, 1513, 1432, 1402, 1161, 848 cm⁻¹; MS, *m/z* (%) 209 (30) [M]⁺, 208 (12), 207 (73) [M]⁺, 173 (12), 172 (100), 145 (20), 43 (20); HRMS (EI) *m/z* [M]⁺ calcd for C₁₁H₇³⁵ClFN 207.0251; found 207.0237; [M]⁺ calcd for C₁₁H₇³⁷ClFN 209.0222; found 209.0211.

2-(4-Fluorophenyl)-3-methoxypyridine (3ea) [CAS: 1214324-71-6]. Compound 3ea was prepared following method B from potassium 3-methoxy-2-pyridinecarboxylate 1e (95.6 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene 2a (177 mg, 1.1 μ L, 1.0 mmol). 3ea was isolated (SiO₂, cyclohexane/ethyl acetate = 6/1) as a colorless oil (71 mg, 70%): ¹H NMR (CDCl₃, 400 MHz) δ 8.31 (dd, 1H, $J = 4.6, 1.4$ Hz), 7.90–7.97 (m, 2H), 7.28–7.32 (m, 1H), 7.22–7.26 (m, 1H), 7.09–7.17 (m, 2H), 3.88 (s, 3H); ¹³C NMR (CDCl₃, 101 MHz) δ 162.8 (d, $J_{C-F} = 247.0$ Hz), 153.4, 147.0, 141.3, 133.7 (d, $J_{C-F} = 2.7$ Hz), 131.2 (d, $J_{C-F} = 8.2$ Hz), 122.9, 118.5, 114.8 (d, $J_{C-F} = 20.9$ Hz), 55.4; ¹⁹F NMR (CDCl₃, 377 MHz) δ -113.7; IR ν 3061, 3006, 2942, 2839, 1601, 1508, 1430, 1266, 1220, 1196, 1158, 1125, 1013 cm⁻¹; MS *m/z* (%) 203 (71) [M]⁺, 202 (100), 174 (14), 173 (18), 172 (32), 133 (28), 50 (12); HRMS (EI) *m/z* [M]⁺ calcd for C₁₂H₁₀FNO 203.0746; found 203.0744.

2-(4-Fluorophenyl)-pyridine (3fa) [CAS: 58861-53-3]. Compound 3fa was prepared following method A in NMP/mesitylene (2 mL, 1/1) at 190 °C from potassium 2-pyridinecarboxylate 1f (81.4 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene 2a (177 mg, 1.1 μ L, 1.0 mmol). 3fa was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless solid (32 mg, 37%): mp 39–40 °C; ¹H NMR (CDCl₃, 300 MHz) δ 8.73–8.63 (m, 1H), 8.06–7.94 (m, 2H), 7.81–7.65 (m, 2H), 7.26–7.12 (m, 3H); ¹³C NMR (CDCl₃, 101 MHz) δ 163.5 (d, $J_{C-F} = 248.5$ Hz), 156.5, 149.7, 136.8, 135.6 (d, $J_{C-F} = 3.3$ Hz), 128.7 (d, $J_{C-F} = 8.4$ Hz), 122.0, 120.2, 115.6 (d, $J_{C-F} = 21.6$ Hz); ¹⁹F NMR (CDCl₃, 41 MHz) δ -112.0; IR ν 3055, 3011, 1600, 1584, 1509, 1464, 1433, 1219, 1099 cm⁻¹; MS *m/z* (%) 173 (100) [M]⁺, 146 (9), 51 (11); HRMS (EI) *m/z* [M]⁺ calcd for C₁₁H₈FN 173.0641; found 173.0640.

2-Phenylpyridine (3fb) [CAS: 1008-89-5].^{35,55} Compound 3fb was prepared following method A in NMP/mesitylene (2 mL, 1/1) at 190 °C from potassium 2-pyridinecarboxylate 1f (81.4 mg, 0.50 mmol) and bromobenzene 2b (159 mg, 1.06 μ L, 1.0 mmol). 3fb was isolated (SiO₂, cyclohexane/ethyl acetate = 9/1) as a colorless liquid (31 mg, 40%): ¹H NMR (CDCl₃, 200 MHz) δ 8.72 (dt, 1H, $J_d = 4.8, J_t = 1.4$ Hz), 8.06–7.95 (m, 2H), 7.83–7.70 (m, 2H), 7.55–7.37 (m, 3H), 7.30–7.21 (m, 1H); ¹³C NMR (CDCl₃, 50 MHz) δ 157.5, 149.6, 139.4, 136.8, 129.0, 128.7, 126.9, 122.1, 120.6; MS *m/z* (%) 155 (100) [M]⁺.

2-(4-Methoxyphenyl)-pyridine (3fd) [CAS: 5957-90-4].^{35,56} Compound 3fd was prepared following method A in NMP/mesitylene (2 mL, 1/1) at 190 °C from potassium 2-pyridinecarboxylate 1f (81.4 mg, 0.50 mmol) and bromo-4-methoxybenzene 2d (187 mg, 1.26 μ L, 1.0 mmol). 3fd was isolated (SiO₂, cyclohexane/ethyl acetate = 4/1) as a colorless oil (26 mg, 28%): ¹H NMR (CDCl₃, 200 MHz) δ 8.67 (dt, 1H, $J_d = 4.7$ Hz, $J_t = 1.5$ Hz), 8.01–7.92 (m, 2H), 7.78–7.63 (m, 2H), 7.19 (ddd, 1H, $J = 6.6, 4.9, 1.9$ Hz), 7.06–6.96 (m, 2H), 3.88 (s, 3H); ¹³C NMR (CDCl₃, 50 MHz) δ 160.5, 157.1, 149.4, 136.7, 131.9, 128.2, 121.4, 119.8, 114.1, 55.3; MS *m/z* (%) 185 (100) [M]⁺.

5-(4-Fluorophenyl)-1-methyl-1H-pyrazole (3ga) [CAS: 689251-78-3]. Compound 3ga was prepared following method B from potassium 1-methyl-1H-pyrazole-5-carboxylate 1g (82.1 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene 2a (177 mg, 1.1 μ L, 1.0 mmol). 3ga was isolated (SiO₂, cyclohexane/ethyl acetate = 6/1) as a colorless liquid (56 mg, 64%): ¹H NMR (CDCl₃, 250 MHz) δ 7.51 (d,

1H, $J = 1.9$ Hz), 7.34–7.44 (m, 2H), 7.08–7.21 (m, 2H), 6.28 (d, 1H, $J = 1.9$ Hz), 3.87 (s, 3H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 162.8 (d, $J_{\text{C-F}} = 248.1$ Hz), 142.5, 138.5, 130.6 (d, $J_{\text{C-F}} = 3.7$ Hz), 126.9 (d, $J_{\text{C-F}} = 8.1$ Hz), 115.7 (d, $J_{\text{C-F}} = 22.0$ Hz), 106.1, 37.3; ^{19}F NMR (CDCl_3 , 235 MHz) δ -112.8; IR ν 3103, 3063, 2947, 1605, 1545, 1493, 1223, 839 cm^{-1} ; MS, m/z (%) 176 (100) $[\text{M}]^+$, 175 (39), 148 (16), 133 (13), 121 (16), 109 (9); HRMS (EI) m/z $[\text{M}]^+$ calcd for $\text{C}_{10}\text{H}_9\text{FN}_2$ 176.0750; found 176.0740.

5-(4-Fluorophenyl)-4-methylthiazole (3ha) [CAS: 623577-48-0]. Compound **3ha** was prepared following methods A and B, respectively, from potassium 4-methyl-5-thiazolecarboxylate **1h** (90.6 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene **2a** (177 mg, 1.11 μL , 1.0 mmol). **3ha** was isolated (SiO_2 , cyclohexane/ethyl acetate = 6/1) as a yellow solid (35 mg, 36% (method A); 72 mg, 75% (method B)): mp 35–36 °C; ^1H NMR (CDCl_3 , 250 MHz) δ 8.68 (s, 1H), 7.35–7.46 (m, 2H), 7.05–7.18 (m, 2H), 2.51 (s, 3H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 162.4 (d, $J_{\text{C-F}} = 248.5$ Hz), 150.2, 148.6 (d, $J_{\text{C-F}} = 0.7$ Hz), 131.0 (d, $J_{\text{C-F}} = 8.0$ Hz), 130.8, 127.9 (d, $J_{\text{C-F}} = 3.3$ Hz), 115.7 (d, $J_{\text{C-F}} = 22.0$ Hz), 15.9; ^{19}F NMR (CDCl_3 , 235 MHz) δ -113.5; IR ν 3096, 3042, 2922, 1603, 1497, 1240, 831 cm^{-1} ; MS, m/z (%) 193 (100) $[\text{M}]^+$, 192 (9), 166 (24), 165 (24), 133 (19), 122 (11); HRMS (EI) m/z $[\text{M}]^+$ calcd for $\text{C}_{10}\text{H}_9\text{FNS}$ 193.0361; found 193.0352.

2-(4-Fluorophenyl)-benzo[b]thiophene (3ia) [CAS: 936734-96-2]. Compound **3ia** was prepared following method B from potassium benzo[b]thiophene-2-carboxylate **1i** (108 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene **2a** (177 mg, 1.11 μL , 1.0 mmol). **3ia** was isolated (SiO_2 , cyclohexane) as a colorless solid (24 mg, 21%): mp 181–182 °C; ^1H NMR (CDCl_3 , 250 MHz) δ 7.75–7.89 (m, 2H), 7.63–7.75 (m, 2H), 7.48 (s, 1H), 7.28–7.43 (m, 2H), 7.06–7.21 (m, 2H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 162.8 (d, $J_{\text{C-F}} = 248.1$ Hz), 143.1, 140.7, 139.5, 130.6, 128.2 (d, $J_{\text{C-F}} = 8.1$ Hz), 124.6, 124.4, 123.5, 122.2, 119.4 (d, $J_{\text{C-F}} = 1.5$ Hz), 115.9 (d, $J_{\text{C-F}} = 21.6$ Hz); ^{19}F NMR (CDCl_3 , 235 MHz) δ -113.4; IR ν 3061, 1593, 1431, 1233, 818 cm^{-1} ; MS, m/z (%) 228 (100) $[\text{M}]^+$, 196 (8), 183 (12), 40 (9); HRMS (EI) m/z $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_9\text{FS}$ 228.0409; found 228.0397.

Synthesis of 3-Methoxy-2-phenylpyridine (4) [CAS: 53698-49-0].⁵⁷ To a solution of methanol (17.6 mg, 22 μL , 0.55 mmol) and **3ab** (86.6 mg, 0.5 mmol) in dry DMF (5 mL) at 0 °C was added dropwise dry KHMDS (0.5 M in toluene, 1.1 mL, 0.55 mmol). The reaction was allowed to warm to rt overnight and then quenched with saturated aqueous NaHCO_3 (10 mL). The aqueous layer was extracted with ethyl acetate (3 \times 20 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2 , cyclohexane/ethyl acetate = 6/1), yielding **4** as colorless oil (86 mg, 93%): ^1H NMR (CDCl_3 , 200 MHz) δ 8.33 (dd, 1H, $J = 4.3, 1.8$ Hz), 7.96–7.86 (m, 2H), 7.51–7.32 (m, 3H), 7.30–7.19 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 153.6, 148.2, 141.3, 137.7, 129.4, 128.3, 128.0, 122.9, 118.5, 55.5; MS, m/z (%) 185 (61) $[\text{M}]^+$, 184 (100), 154 (33).

Synthesis of 2-Phenyl-2-(3-(2-phenyl)pyridyl)acetonitrile (6). A 20 mL microwave vessel was charged with **3ab** (86.6 mg, 0.5 mmol) and potassium *tert*-butoxide (318 mg, 2.75 mmol). NMP (1 mL) and benzyliyanide **5** (293 mg, 290 μL , 2.5 mmol) were added, and the mixture was heated at 100 °C in the microwave for 5 min. The mixture was allowed to cool to rt, washed with distilled water (20 mL), and extracted with ethyl acetate (3 \times 20 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2 , *n*-pentane/diethyl ether = 2/3), yielding compound **6** as colorless oil (120 mg, 89%): ^1H NMR (CDCl_3 , 200 MHz) δ 8.69 (dd, 1H, $J = 4.8, 1.5$ Hz), 7.85 (dd, 1H, $J = 8.0, 1.6$ Hz), 7.53–7.42 (m, 5H), 7.41–7.28 (m, 4H), 7.18–7.06 (m, 2H), 5.44 (s, 1H); ^{13}C NMR (CDCl_3 , 50 MHz) δ 158.5, 149.3, 138.7, 137.3, 135.2, 130.1, 129.2, 128.9, 128.8, 128.7, 128.3, 127.4, 123.1, 119.4, 38.9; IR ν 3051, 2910, 2241, 1564, 1492, 1435 cm^{-1} ; MS, m/z (%) 270.15 (89) $[\text{M}]^+$, 269.15 (100); HRMS (EI) m/z $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{14}\text{N}_2$ 270.1157; found 270.1146.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00046.

Full optimization table and copies of ^1H , ^{13}C , and ^{19}F NMR spectra of all products (PDF)

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Notes

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5.5 Rhodium-catalyzed *ortho*-Arylation of (hetero)aromatic Acids

Obwohl decarboxylierende Kreuzkupplungen und *ortho*-Funktionalisierungen aromatischer Carbonsäuren zwecks Biarylsynthese bisher ausgiebig studiert wurden, gibt es immer noch viele Carbonsäuren, die mit den bisher veröffentlichten Methoden nicht oder nur unzureichend umgesetzt werden können. Während der Zusammenarbeit mit *Pfizer* fielen uns diverse Pyridincarbonsäuren auf, vor allem Nicotinsäurederivate, auf die dies zutrifft. Larrosa *et al.* konnten zu dieser Zeit ein Protokoll präsentieren, welches Nicotinsäuren und Isonicotinsäuren mit Arylbromiden und -chloriden selektiv in C3- bzw. C4-Position arylieren konnte.²⁶⁷ Obwohl die Selektivität oftmals sehr gut war, ist die Anwendungsbreite nicht sonderlich groß und viele Beispiele kommen nicht über moderate Ausbeuten hinaus. Wir testeten mit diesem System die Umsetzung von 2-Methoxynicotinsäure und erhielten nur 14% Ausbeute. Ein in unserer Gruppe entwickeltes Protokoll mit Ruthenium war selbst bei höheren Temperaturen nicht in der Lage diese Carbonsäure umzusetzen.²⁶⁸ Aufgrund der teils explosiven Reaktivität von Pyridinen mit Aryldiazoniumsalzen, ist das in unserer Gruppe entwickelte Iridium-katalysierte Protokoll ebenfalls keine Alternative.²⁶⁹

Während Literaturrecherchen sind uns die Arbeiten von Bergman und Ellman sowie Chang aufgefallen.^{270–272} Diese konnten mit Hilfe von Rhodium und Arylbromiden Pyridine in C2- bzw. Chinoline in C8-Position arylieren. Als wir simples $\text{Rh}_2(\text{OAc})_4$ unter ähnlichen Bedingungen wie dem des Ruthenium-Protokolls mit 2-Methoxynicotinsäure reagieren ließen, wurde die C2-Selektivität des Pyridins überstimmt und durch die Säuregruppe selektiv mit einer Ausbeute von 77% in C4-Position dirigiert. Begeistert von den guten Resultaten und der Reaktivität von Rhodium beschlossen wir, dieses Protokoll bestmöglich zu optimieren und dem Mechanismus auf die Spur zu kommen. Da wir ein Rhodium-Dimer als Intermediat vermuteten bestand die Möglichkeit mit dem Exzellenzcluster 3MET zu interagieren.

Ich führte die ersten Experimente durch, welche zur Entdeckung der Reaktion führten und optimierte das Reaktionsprotokoll. In Zusammenarbeit mit Herrn Enis Yalcinkaya konnte die Anwendungsbreite der Reaktion demonstriert werden. Die Protodecarboxylierungsexperimente wurden von Herrn Yalcinkaya durchgeführt, wobei ich ihn unterstützte. Der Großteil der mechanistischen Untersuchungen wurde von mir und Herrn Christian Rank mit der Unterstützung von Herr Prof. Dr. Gooßen und Herr Prof. Dr. Frederic W. Patureau geplant, ausgeführt und ausgewertet. Zudem war ich zuständig für die Synthese von $\text{Rh}_2(\text{ortho-Toluolsäure})_4$ während Frau Laura Schneider die Bestimmung der Molekülmasse übernahm. Die DFT-Berechnungen wurden von Herrn Marco Dyga mit Unterstützung von Herrn Tim van

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Rhodium-catalyzed *ortho*-Arylation of (Hetero)aromatic Acids

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Abstract: Rhodium acetate effectively promotes the carboxylate-directed *ortho*-arylation of (hetero) aromatic carboxylates with aryl bromides. The main advantage of this phosphine-free, redox-neutral method arises from its efficiency in assembling biologically meaningful electron-rich arylpyridines, which are problematic substrates in known C–H arylations using Pd, Ru, and Ir catalysts.

Keywords: rhodium; aryl bromides; benzoic acids; biaryls; heteroarenes; C–H arylation

with aryl (pseudo)halides, Ullmann reactions, or decarboxylative couplings.^[6–11] In the case of pyridines, most preformed organometallic reagents are unstable, C–H arylations are particular advantageous for the construction of heteroaryl skeletons.^[12] The arylation can be directed into specific positions by various donor groups, and even by the heteroatom of heteroarenes. In this context, Bergman and Ellman demonstrated that pyridines can be arylated selectively at the C-2 position of the pyridine ring (Scheme 1, top).^[13–16] This directing effect of the heterocyclic nitrogen can be overridden by other ring substituents, for example by carboxylates. Larrosa showed that in the presence of a sophisticated Pd catalyst, nicotinic acid derivatives are

Arylated pyridines represent a key motif in various pharmaceutically active substances,^[1–3] and expedient synthetic entries to this substructure are constantly sought (Figure 1).

Known methods for the arylation of (hetero)arenes include cross-couplings of organometallic reagents

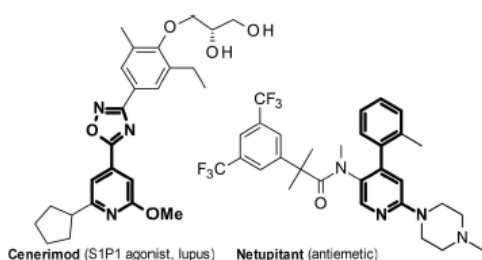
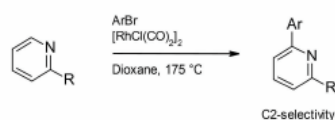
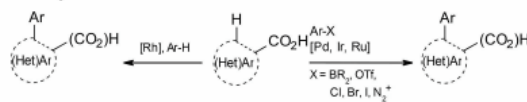


Figure 1. Pharmaceuticals containing heteroaromatic biaryl motifs.^[4,5]

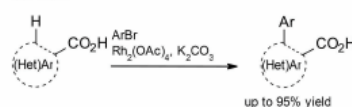
Bergman and Ellman *et al.*



ortho-Arylations of Benzoic Acids



our work



Scheme 1. C–H Arylations directed by neighboring atoms and *o*-carboxylates.

arylated in the position *ortho* to the carboxylate rather than the nitrogen atom.^[17]

The use of carboxylates as directing groups is particularly advantageous for heterocyclic substrates, because they are often present as leftovers from the construction of the heterocycle skeleton.^[18] Following the arylation step, they can either be removed tracelessly, or reused as leaving groups in decarboxylative couplings.^[19,20] Carboxylate-directed C–H arylations are effectively promoted by Pd,^[21–29] Ir,^[30] or Ru^[31–34] systems. Rh systems, and Cp*Rh in particular, are at the heart of modern C–H functionalization chemistry.^[35–40] Su and You have used Rh in carboxylate-directed oxidative (decarboxylative) arylation processes, e. g. thiophenes (Scheme 1).^[41–43]

In the context of a planned synthesis of 2-alkoxy-4-arylpyridines, we identified 2-alkoxynicotinic acids as the optimal starting materials. Based on the work by Larrosa, one would expect it to undergo selective arylation at the 4-position. Thereafter, the carboxylate group could subsequently be removed by protodecarboxylation or converted to halides, alkoxides, amines, etc. However, the known Pd and Ru systems gave unsatisfactory yields for our model reaction, the coupling of 2-alkoxynicotinic acid with 4-bromotoluene (Table 1, entries 1, 2), and all our attempts to develop effective protocols based on the above catalysts failed.

In search for alternative catalysts, we identified dirhodium tetraacetate as a promising candidate. Aryl

phosphines have been reported to react with this dinuclear Rh^{II} complex, liberating acetic acid and forming a carbometalated dinuclear aryl-Rh species in which the phosphine coordinates to one of the Rh nuclei, and the C-2 carbon binds to the other Rh.^[44,45] Considering the proverbial affinity of Rh^{II} to carboxylates, we reasoned that a similar base-assisted cyclometallation deprotonation (CMD) mechanism might be possible with a carboxylate rather than a phosphine as *ortho*-directing group. This would open up the catalytic cycle sketched out in Scheme 2. It starts with a directed CMD reaction furnishing cyclometallated Rh^{II} carboxylate **II**, which has a structure analogous to that observed in the reaction with aryl phosphines. It reacts with an aryl bromide to give the diaryl Rh^{III} complex **III**, along with stable Rh^{III} carboxylate **VI**. The intermediacy of **III** seems in line with literature reports on Rh-catalyzed arylations.^[41,43] The desired biaryl product is then formed by reductive elimination and released by salt metathesis with fresh carboxylate substrate. The coordinatively unsaturated Rh^I species **V** could be stabilized by comproportionation with **VI** regenerating Rh^{II} carboxylate **I**.

When probing Rh₂(OAc)₂ in our model reaction, it gave good results in combination with the simple base K₂CO₃ (Table 1, Entry 3). The C–H arylation was directed exclusively *ortho* to the carboxylate group rather than the pyridine nitrogen.

Systematic studies revealed that aprotic polar solvents are beneficial with best results obtained in

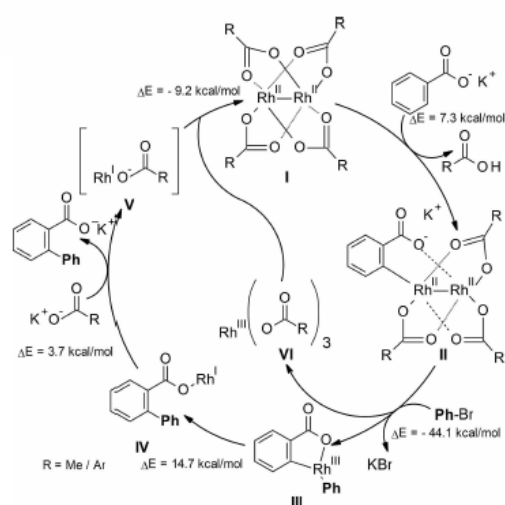
Table 1. Screening of the reaction conditions.^[a]

Entry	mol% cat	equiv. Base	Solvent	Yield 3ka ^[b] [%]
1	5.0 cataCXium A–Pd–G3	2.2 Cs ₂ CO ₃	DMF	14
2	4.0 [(<i>p</i> -cym)RuCl ₂] ₂ + 8 PEt ₃ ·HBF ₄	1.1 K ₂ CO ₃	NMP	0
3	4.0 Rh ₂ (OAc) ₄	1.0 K ₂ CO ₃	“	77
4	“	“	DMF	79
5	“	“	DMSO	23
6	“	“	mes	5
7	“	–	DMF	1
8	“	0.5 K ₂ CO ₃	“	24
9	“	1.5 K ₂ CO ₃	“	87
10	“	2.0 K ₂ CO ₃	“	33
11 ^[b]	“	1.5 K ₂ CO ₃	“	7
12 ^[c]	0.25 Rh ₂ (OAc) ₄	“	“	91

^[a] Reactions conditions: **1k** (0.5 mmol), **2a** (0.75 mmol), cat, base, solvent (2 mL), 140 °C, 18 h. Yields of the corresponding methyl esters determined by GC analysis after esterification with K₂CO₃ (2 equiv.) and MeI (5 equiv.) in NMP using *n*-tetradecane as internal standard.

^[b] 130 °C.

^[c] 6 h. DMF: dimethylformamide, NMP: *N*-methylpyrrolidone, mes: mesitylene, DMSO: dimethylsulfoxide.

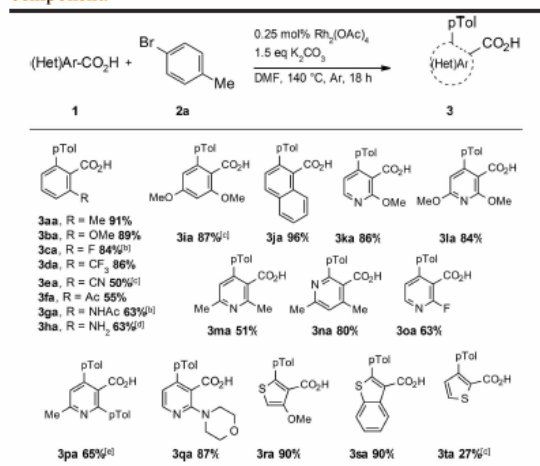

 Scheme 2. Mechanistic blueprint for a Rh^{II} catalysed arylation.

DMF. The catalyst loading can be reduced to 0.5 mol% Rh (Table 1, Entry 12), and only a slight excess of the base is required. A temperature of 140 °C is optimal, below that, the yields drop markedly (Table 1, Entry 11). Further studies revealed that many rhodium (III) salts showed similar activity in this transformation (Supporting Information), which can be rationalized with their swift conversion to Rh^{II} carboxylates when heated in the presence of carboxylates.^[46]

In order to probe the general applicability of our new protocol, we investigated its scope with regard to both coupling partners (Tables 2, 3, and S10). As can be seen in Table 2, benzoic acids bearing electron-donating or -withdrawing substituents were smoothly coupled with 4-bromotoluene (**2a**), among them even unprotected anthranilic acid (**1h**). Various heterocyclic acids gave good results, including our targeted nicotinates bearing *ortho*-amino or *ortho*-methoxy groups. Similarly to other directed *ortho*-arylations, competing diarylation was observed when two *ortho*-positions were accessible, e.g. for **1p**. While most acids were converted with a low Rh-loading of 0.5 mol %, a few examples like 2-fluorobenzoic acid **1c** or 2-cyanobenzoic acid **1e** need larger amounts of Rh.

The coupling is broadly applicable with regard to the aryl bromide (Table 3). Various functional groups including esters, ketones were tolerated, and even 4-bromophenol **2t** was coupled in excellent yield. Arylated phenols are structural components of several drug precursors.^[47]

Removal of the carboxylate group by protodecarboxylation was possible in situ by heating the reaction mixture in the presence of Cu^I/tetrameth-

 Table 2. Substrate scope with regard to the carboxylate component.^[a]


^[a] Reactions conditions: **1** (0.5 mmol), **2a** (0.75 mmol), 0.25 mol% Rh₂(OAc)₄, K₂CO₃ (1.5 equiv.), DMF (2 mL), 140 °C, 18 h. Yields of the corresponding methyl esters after esterification with K₂CO₃ (2 equiv.) and MeI (5 equiv.) in NMP.

^[b] 1 mol% Rh₂(OAc)₄.

^[c] 4 mol% Rh₂(OAc)₄.

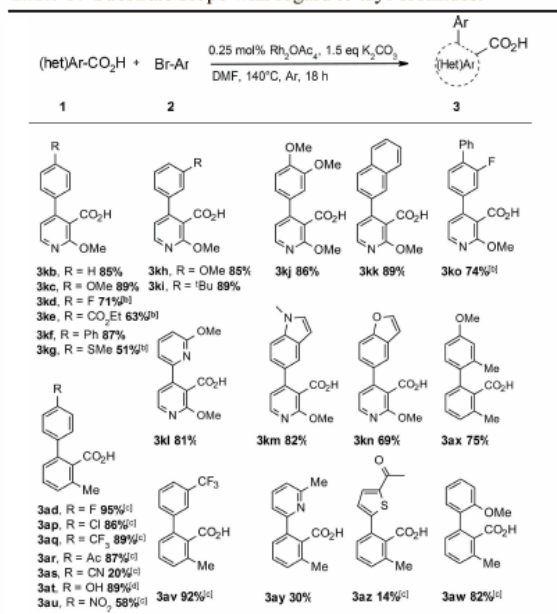
^[d] Isolated as the corresponding dimethyl amine.

^[e] **2a** (1.25 mmol).

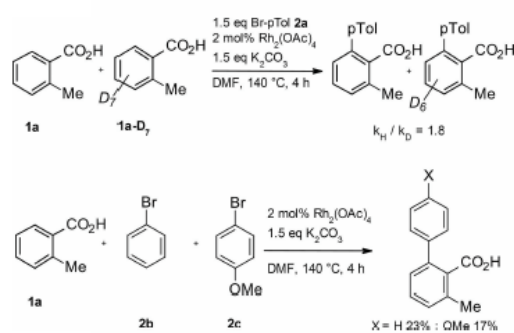
ylphenanthroline and quinoline (see the supporting information).^[48]

To probe the validity of our mechanistic blueprint, a series of control experiments, kinetic investigations and DFT calculations were performed (see the supporting information). Heating *o*-toluic acid in deuterated methanol in the presence of rhodium acetate led to selective *ortho*-deuteration.^[49] In contrast, rhodium acetate did not promote halogen exchange between aryl iodide and potassium bromide.^[50] The findings support our hypothesis that the reaction is initiated by a reversible *ortho*-metallation step. A competition experiment of deuterated and non-deuterated *ortho*-toluic acid with 4-bromotoluene showed only a moderate kinetic isotope effect, suggesting that this step is not alone rate-determining (Scheme 3, top). ESI-MS analysis of reaction mixtures of *ortho*-toluic acid under catalytic conditions, both in the presence and absence of 4-bromotoluene, display several dinuclear Rh fragments carrying the 2-methylbenzoate fragments, suggesting that the reaction is indeed initiated by carboxylate coordination. We additionally synthesized dirhodium tetra-*ortho*-toluate (**5**) and found it to effectively catalyse the reaction and quantitatively form the product if coupled with 4-bromotoluene and without Rh₂(OAc)₄ (Table S9).

Table 3. Substrate scope with regard to aryl bromides.



- [a] Reactions conditions: **1** (0.5 mmol), **2** (0.75 mmol), 4 mol% Rh₂(OAc)₄, K₂CO₃ (1.5 equiv.), DMF (2 mL), 140 °C, 18 h. Yields of the corresponding methyl esters after esterification with K₂CO₃ (2 equiv.) and MeI (5 equiv.) in NMP.
- [b] 1 mol% Rh₂(OAc)₄.
- [c] 4 mol% Rh₂(OAc)₄.
- [d] 1 mol% Rh₂(OAc)₄. Isolated as the free carboxylic acid.



Scheme 3. Selected mechanistic experiments (see SI for conditions).

In a competition experiment, *ortho*-toluic acid was allowed to react with a mixture of bromobenzene and electron-rich 4-methoxyaryl bromide, furnishing similar quantities of both arylation products. This indicates that oxidative addition is not rate-determining, either (Scheme 3, bottom), so that the overall rate seems to be mostly limited by the C–C bond-forming step.

The initial reaction rates for the arylation of **1k** with **2a** were determined after 1 h for catalyst loadings between 0.5 and 2.0 mol%. The results point to almost first-order kinetics (1.2 ± 0.2) with regard to Rh dimer. This is in agreement with our mechanism in which the rate-determining steps involve a mononuclear Rh complex. For these experiments we chose **1k** over *ortho*-toluic acid **1a**, because **1a** has an induction period over several hours before the product formation quickly increases. The addition of strongly coordinating pyridine helps breaking up the dirhodium tetracarboxylate structure and strongly reduces the induction period. Further kinetic studies conducted at a 0.5 mol% Rh dimer loading revealed that the reaction follows almost zero-order kinetics with regard to 4-bromotoluene, which is in line with the findings of the competition experiment. Interestingly, the initial kinetic order of the carboxylate **1k** is negative (-2.6 ± 0.2) indicating a poisoning effect, possibly through a competing pyridyl-rhodium coordination.

The DFT-calculations of the reaction steps support the proposed mechanism. All intermediates have been verified to be stable minima on the potential energy surface. The calculated energies (ΔE_i) of all steps of the catalytic cycles are within a feasible range. Notably, the disproportionation of intermediate **II** to **III** and **VI** was calculated to be a favorable process. In a dilute solution, species **V** is likely to enter a new catalytic cycle directly. However, its alternative recombination with Rh^(III) carboxylate (**VI**) with formation of the Rh^(II) dimer (**I**) is clearly exothermic. This is consistent with the proposed role of the Rh^(II)-carboxylate dimer as a catalyst reservoir. For a more detailed scheme with the calculated structures including solvent molecules see the supporting information (Scheme S5).

In conclusion, low loadings of simple rhodium acetate catalyze the *ortho*-C–H arylation of various aromatic and heteroaromatic carboxylic acids with a broad range of aryl bromides. The new protocol is well-suited to the synthesis of functionalized aryl pyridines, which are of special interest in pharmaceutical research. Dinuclear Rh₂(OAc)₂ was found to be particularly suited for *ortho*-C–H bond activation of benzoic acids opening up further opportunities for directed functionalizations.

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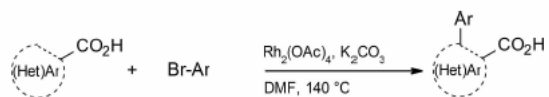
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COMMUNICATIONS

Rhodium-catalyzed *ortho*-Arylation of (Hetero)aromatic Acids

Adv. Synth. Catal. **2019**, *361*, 1–6

 P. Weber, C. K. Rank, E. Yalcinkaya, M. Dyga, T. van Lingen, R. Schmid*, F. W. Patureau*, L. J. Gooßen*



5.6 Regiospecific *ortho*-C-H Allylation of Benzoic Acids

Allylierte Benzolderivate stellen eine wichtige Unterstruktur in der Kosmetik sowie der Pharmabranche dar. Zur Herstellung dieser Moleküle werden oftmals dirigierende Gruppen verwendet welche häufig entweder schwer zu installieren oder schwer zu entfernen sind. Wie in Kapitel 3.3.7.2 erwähnt würden sich aromatische Carbonsäuren als gute Alternative anbieten, da diese sehr einfach zu installieren und zu entfernen sind. Bisher ist ein Rhenium-katalysiertes Protokoll von Takai bekannt, welches die Allylgruppe von Allylbenzoaten mit einem Überschuss an Allylacetat in die *ortho*-Position verschieben kann, wobei eine *ortho*-Allylbenzoesäure entsteht.²⁶⁰ Mit dem Wissen im Hinterkopf, dass in unserer Gruppe bereits Ruthenium-katalysierte Protokolle entwickelt wurden, welche aromatische Carbonsäuren erfolgreich mit Alkinen hydroarylieren können, waren wir davon überzeugt, dass Allylierungen ebenfalls erfolgreich sein sollten.²⁷³

Frau A. Stefania Trita war für den Großteil der Reaktionsoptimierung und der mechanistischen Untersuchungen zuständig, wobei Herr Dr. Martin Pichette-Drapeau unterstützend mitwirkte. Herr Agostino Biafora hat daraufhin zur Entwicklung des Protokolls beigetragen. Die Demonstration der Anwendungsbreite sowie die Auswertung der analytischen Daten isolierter Produkte wurden gemeinschaftlich von Frau Trita und mir durchgeführt. Während ich die Entwicklung der darauffolgenden Protodecarboxylierung übernahm, optimierte Frau Trita die darauffolgende Lactonisierung. Frau Trita übernahm auch die Verfassung des Manuskriptes, wobei Herr Biafora sie unterstützte und Herr Prof. Goßen die finalen Korrekturen durchführte. Die Ergebnisse wurden 2018 in der Zeitschrift *Angewandte Chemie* bzw. in *Angewandte Chemie International Edition* veröffentlicht. Eine angepasste Kopie des Manuskripts wurde mit Erlaubnis von John Wiley & Sons nachfolgend beigefügt:

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 Regiospecific *ortho*-C–H Alkylation of Benzoic Acids

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 Lukas J. Gooßen*

Abstract: A carboxylate-directed *ortho*-C–H functionalization has been developed and it allows the regiospecific introduction of allyl residues to benzoic acids. In the presence of a [Ru(*p*-cymene)Cl₂]₂ and K₃PO₄, benzoic acids react with allyl acetates at only 50°C to give the corresponding *ortho*-allylbenzoic acids. The protocol is generally applicable to both electron-rich and electron-poor benzoic acids in combination with linear and branched allyl acetates. The products can be further functionalized *in situ*, for example, by double-bond migration, lactonization, or decarboxylation.

Allylarenes are common structural motifs widely encountered in the flavor and fragrance industry, pharmaceuticals, natural products, and functional materials (Figure 1).^[1] Traditionally, allylarenes are accessed by Friedel–Crafts allylations^[2] or various cross-couplings of electrophiles with organometallic reagents.^[3] However, these approaches either suffer from poor regioselectivity or require prefunctionalized arene derivatives, and generate substantial amounts of salt waste.

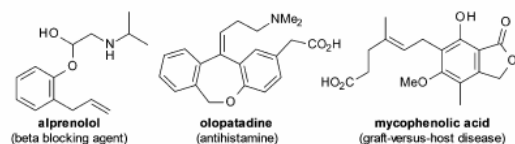


Figure 1. Selected examples of allyl-containing bioactive molecules.

tionally, allylarenes are accessed by Friedel–Crafts allylations^[2] or various cross-couplings of electrophiles with organometallic reagents.^[3] However, these approaches either suffer from poor regioselectivity or require prefunctionalized arene derivatives, and generate substantial amounts of salt waste.

These limitations may be overcome by using catalytic C–H allylations. Only a few specialized substrates, such as polyfluorinated arenes, intrinsically give high stereoselectivities in direct allylations.^[4] In most cases, regioselectivity of the allylation process is ensured by strongly coordinating nitrogen-based directing groups^[5] in combination with Ir,^[6] Rh,^[7] Ru,^[8] Co,^[9] Ni,^[10] Fe,^[11] or Mn catalysts.^[12] The inherent drawback of these first-generation directing groups is that their installation and removal are labor- and waste-intensive.^[13]

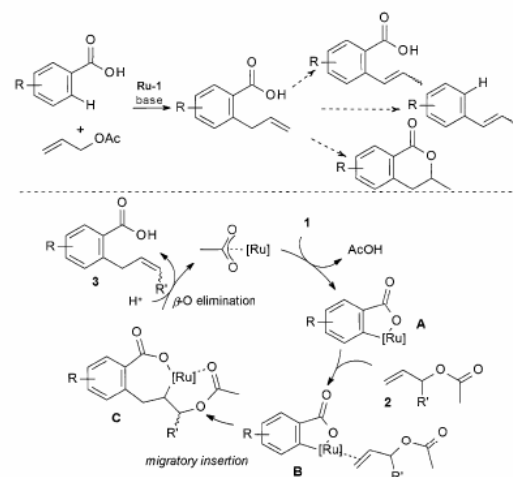
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Currently, the focus in the field of C–H activation is shifting towards the use of simple, abundant functionalities as directing groups. In this context, carboxylates have many advantages. Benzoic acids are widely available at low cost and in great structural diversity. Following regiospecific *ortho*-C–H functionalization, the carboxylate moiety can be tracelessly removed by protodecarboxylation,^[14] or used as an anchor point for decarboxylative cross-couplings.^[15] However, the weak coordinating ability, compared to (bidentate) nitrogen donors, increases the hurdles encountered in catalytic reaction development.^[16] Still, efficient protocols have been disclosed for carboxylate-directed *ortho*-C–H arylations,^[17] alkenylations,^[18] acylations,^[19] alkoxylation,^[20] halogenations,^[21] and C–N bond formations,^[22] often using Pd, Rh, Ir, or Ru catalysts.

Catalytic *ortho*-C–H allylations of benzoates are equally desirable transformations, but even harder to accomplish (Scheme 1). The initiating step in directed C–H functionalizations would have to be an *ortho*-C–H activation of the benzoate, and allyl electrophiles tend to interfere with this step. They may esterify the benzoates,^[23] thus complicating formation of the cyclometallated species **A**. Many metals preferentially undergo oxidative insertion into allyl–X bonds, thus leading to intermediates that are inactive towards C–H insertion.^[24] We are aware of only one catalytic C–H allylation of benzoates. Takai et al. reported a rhenium-catalyzed rearrangement of allyl benzoates to *ortho*-allylbenzoic acids by intramolecular C–H functionalization.^[25] This



Scheme 1. Mechanistic blueprint for a carboxylate-directed *ortho*-C–H allylation of arenes.

pioneering contribution has several drawbacks, such as the necessity to preform the allyl benzoate and to use additional allyl acetate, the relatively high reaction temperatures, and an in situ saponification step.

In the course of our work on carboxylate-directed hydroarylations,^[18d,g] we noticed the remarkable ease with which ruthenium inserts into an *ortho*-C–H bond with formation of ruthenacycles, and the preference of this metal for additions across multiple bonds over oxidative insertion processes. We reasoned that this reactivity might support the catalytic cycle for carboxylate allylations outlined in Scheme 1. The reaction is initiated with a carboxylate-directed, base-assisted *ortho*-C–H activation of the benzoate. If the resulting ruthenacycle **A** adds across the double bond of an allyl acetate, an alkylruthenium species (**C**) will form with ruthenium in the α position to the acetate. The challenge is now to open up a new pathway that liberates the desired allylated benzoate by elimination of ruthenium acetate, and to retard classical pathways such as Heck-type reaction by β -hydride elimination, or hydroarylation by reductive C–H elimination. We saw a good chance that this could be achieved, since reductive carboxylate eliminations have literature precedent, for example, in allylations of either benzamides or aromatic ketoximes catalyzed by rhodium or ruthenium.^[7a,c,8c,e]

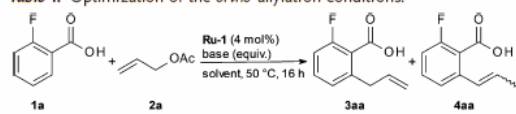
To probe the feasibility of the desired ruthenium-catalyzed *ortho*-allylation of benzoates, we chose the reaction of 2-fluorobenzoic acid (**1a**) with allyl acetate (**2a**) as a model and investigated various catalysts and conditions (Table 1). We were delighted to find that the desired product forms in

encouraging yields at 50 °C when using the inexpensive [Ru(*p*-cymene)Cl₂]₂ (**Ru-1**) as the catalyst and K₂CO₃ as the base in NMP (entry 1). Systematic screening of the reaction conditions revealed that the solvent system is the most critical reaction parameter.^[26] Most aprotic solvents, both polar and nonpolar, were ineffective (entries 2 and 3). However, protic, alcoholic solvents greatly increased the yields. The best results were obtained with 2,2,2-trichloroethanol ($pK_a = 12.24$ ^[27]; entry 4). Less acidic ethanol ($pK_a = 15.9$ ^[28]) and more acidic hexafluoroisopropanol ($pK_a = 9.3$ ^[28]) or acetic acid ($pK_a = 4.76$ ^[28]) gave lower conversion (entries 5–7). 2,2,2-Trifluoroethanol ($pK_a = 12.37$ ^[27]) was effective, but led to partial isomerization to **4aa** (entry 8). The reaction is also sensitive to the nature and amount of base (entries 9–11). The best results were obtained when the medium was buffered with 0.7 equivalents of potassium phosphate (entry 12). The reaction is best performed in concentrated solution (entry 13). The reaction temperature of 50 °C is remarkably low for a C–H functionalization process. Under the optimized reaction conditions, the allyl benzoate **7a** (for structure see Scheme 3) was not observed. At higher temperatures, the thermodynamically favored isomerization product (**4aa**) starts to form in significant amounts (entry 14). Performing the reaction at 100 °C in TFE can be exploited to access the vinylic product **4aa** in good yield and an *E/Z* ratio of 30:1 (entry 15).

The optimized protocol (0.5 mmol benzoic acid **1**, 1.5 equiv allyl acetate **2**, 4 mol % **Ru-1**, 0.7 equiv K₃PO₄, 0.5 mL TCE, 50 °C, 16 h) proved to be applicable to a wide range of aromatic and heteroaromatic carboxylates in combination with linear or branched allyl acetates (Table 2). Various functionalities, such as ether, nitro, sulfonyl, keto, amide, or halo groups were tolerated. Only free amino or hydroxy groups were found to be incompatible. The tolerance of the bromo groups makes this transformation orthogonal to traditional cross-couplings, and that of amides orthogonal to other directed C–H functionalization reactions. On gram-scale, the reaction gave the product **3da** in 62 % yield without any further adjustments. Moreover, the allyl product **3ba** is an intermediate in Fürstner's synthesis of salicylhalamides **A** and **B**, which are natural products presenting cytotoxic properties.^[29] Selective monofunctionalization was observed not only for *ortho*-, but also for *meta*-substituted benzoic acids. For nonsubstituted benzoic acid, competing diallylation was observed. α,β -Unsaturated carboxylic acids reacted only sluggishly. Starting from 1-cyclohexene-1-carboxylic acid, the allylated product was detected in 10 % yield by using ¹H NMR spectroscopy. The regioselectivity for the allylarenes was high throughout (> 30:1). The complementary protocol (0.5 mmol benzoic acid **1**, 1.5 equiv allyl acetate **2a**, 4 mol % **Ru-1**, 0.5 equiv K₃PO₄, 0.5 mL TFE, 100 °C, 16 h) afforded 2-propenylarenes, with stereoselectivities ranging from 2.7:1 to 30:1.

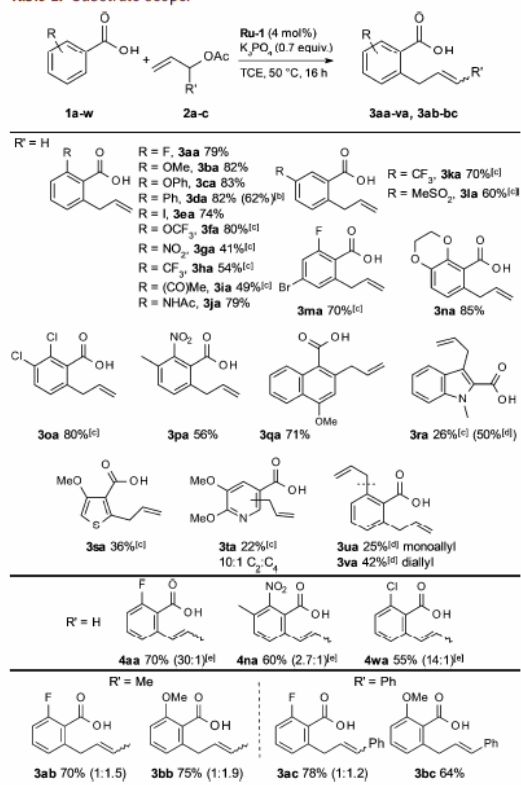
Besides allyl acetate, α -substituted derivatives were successfully converted. However, no substituents were tolerated at the double bond, and is in agreement with reports for ruthenium-catalyzed allylations of either benzamides or ketoximes.^[8c,e] α,α -Dimethyl allyl acetate gave no conversion, thus indicating that steric crowding is an issue in this reaction. Linear products were exclusively obtained, with *E/Z* selectiv-

Table 1: Optimization of the *ortho* allylation conditions.^[a]



Entry ^[a]	Base (equiv)	Solvent	Yield [%]	
			3aa	4aa
1	K ₂ CO ₃ (0.5)	NMP	18	3
2	K ₂ CO ₃ (0.5)	1,4-dioxane	5	–
3	K ₂ CO ₃ (0.5)	toluene	trace	–
4	K ₂ CO ₃ (0.5)	TCE	60	trace
5	K ₂ CO ₃ (0.5)	EtOH	28	trace
6	K ₂ CO ₃ (0.5)	HFIP	15	13
7	K ₂ CO ₃ (0.5)	AcOH	–	–
8	K ₂ CO ₃ (0.5)	TFE	60	5
9	KOAc (0.5)	TCE	20	–
10	K ₃ PO ₄ (0.5)	TCE	69	trace
11	Li ₃ PO ₄ (0.5)	TCE	–	–
12	K ₃ PO ₄ (0.7)	TCE	75	trace
13 ^[b]	K ₃ PO ₄ (0.7)	TCE	81	trace
14 ^[b,c]	K ₃ PO ₄ (0.7)	TCE	81	8
15 ^[b,d]	K ₃ PO ₄ (0.5)	TFE	7	72 (30:1)

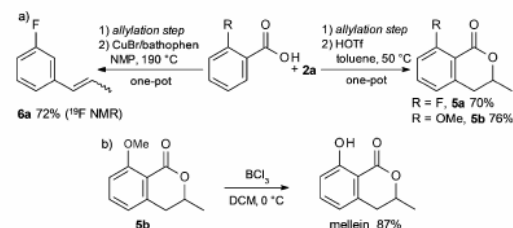
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), **Ru-1** (4 mol%), base, solvent (1 mL), 50 °C, 16 h. Yields determined by ¹⁹F NMR spectroscopy using benzotrifluoride as an internal standard. *E/Z* ratios are given within parentheses. [b] Solvent (0.5 mL). [c] 60 °C. [d] 100 °C. **Ru-1** = [Ru(*p*-cymene)Cl₂]₂. HFIP = hexafluoro-2-propanol, NMP = *N*-methyl-2-pyrrolidone, TCE = 2,2,2-trichloroethanol, TFE = 2,2,2-trifluoroethanol.

Table 2: Substrate scope.^[a]


[a] Reaction conditions: **1 a–w** (0.5 mmol), **2 a** (0.75 mmol), **Ru-1** (4 mol%), K_3PO_4 (0.7 equiv), TCE (0.5 mL), 50 °C, 16 h. Yields are those of isolated products. [b] 10 mmol scale. [c] 60 °C. [d] 1H NMR yields. [e] K_3PO_4 (0.5 equiv), TFE (0.5 mL), 100 °C, *E/Z* ratios are given within parentheses.

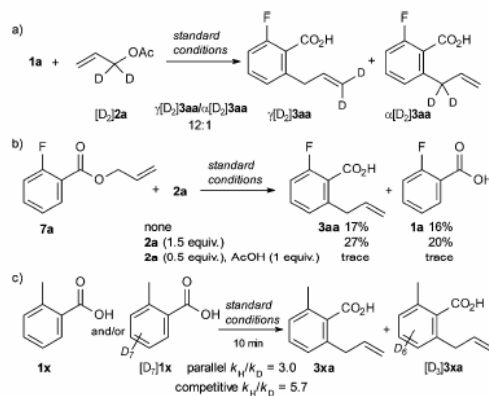
ities ranging from 1.2:1 to more than 30:1 for the *E*-configured product. The *E/Z* ratios were found not to change over the course of the reactions. The reason for the unique selectivity in the case of **3bc** is unclear.

The C–H allylation can be combined with in situ derivatization steps (Scheme 2). Intramolecular hydroacylox-


Scheme 2. Optional derivatization reactions. Tf = trifluoromethanesulfonyl.

ylation occurs when acidifying the reaction mixture with trifluoromethanesulfonic acid (HOTf).^[31] Protodecarboxylation of the allylated benzoates occurs when adding a copper catalyst and increasing the temperature to 190 °C. The product **5b**, itself a natural product,^[31] can be subsequently converted into (–)-mellein, an antifungal natural product (Scheme 2 b).^[32]

All observations made in the course of this study agree with the proposed catalytic cycle in Scheme 1. When α , α -dideuteroallyl acetate (**[D₂]2a**) was employed, a 12:1 mixture of γ -**[D₂]3aa**/ α -**[D₂]3aa** was observed, thus confirming the high selectivity for *S_N2'*-type products predicted by the proposed hydroarylation mechanism (Scheme 3 a). If allylu-


Scheme 3. Mechanistic investigations and control experiments.

thenium intermediates were involved, one would have expected to see higher deuterium incorporation at the α -position, and linear/branched product mixtures when starting from unsymmetrical substrates. It also explains the low reactivity of γ -substituted, in comparison to α -substituted, allyl acetates. Control experiments revealed that **7a** can be converted into the allylated product **3aa**, but this intramolecular version was less efficient than the reaction starting from the benzoic acid **1a**, which speaks for an intermolecular pathway (Scheme 3 b). Had **7a** been an intermediate, yields of **3aa** should have been comparable to that of entry 13 in Table 1. A kinetic isotope effect (KIE) of $k_H/k_D = 5.7$ was observed in competition experiments with non- and perdeuterated arene substrates. In the corresponding parallel experiments, the KIE was 3.0, which confirms that C–H cleavage is the rate-determining step (Scheme 3 c).

In conclusion, an inexpensive dimeric ruthenium complex was found to efficiently and selectively catalyze the carboxylate-directed *ortho*-allylation of benzoic acids under remarkably mild conditions. The reaction is based on widely available, structurally diverse (hetero)aromatic carboxylate substrates. Its synthetic utility is further extended by follow-up isomerization, hydroacyloxylation, or protodecarboxylation steps.

Experimental Section

An oven-dried 20 mL vial was charged with [Ru(*p*-cymene)Cl₂]₂ (12.2 mg, 0.02 mmol), K₃PO₄ (76.6 mg, 0.35 mmol) and a benzoic acid (0.50 mmol), and closed with a septum cap. Under exclusion of air and water, 2,2,2-trichloroethanol (0.5 mL) and an allyl acetate (0.75 mmol) were added by syringe. The resulting mixture was stirred at 50 °C for 16 h. After the reaction was complete, it was diluted with EtOAc (10 mL) and extracted with aq. K₂CO₃ solution (3 × 10 mL). The combined aqueous phases were acidified with 2 M HCl (pH 1–2), then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂, ethyl acetate/cyclohexane gradient, 1% HCO₂H), yielding the corresponding *ortho* allylated benzoic acid.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allylation · C–H activation · carboxylic acids · reaction mechanisms · ruthenium

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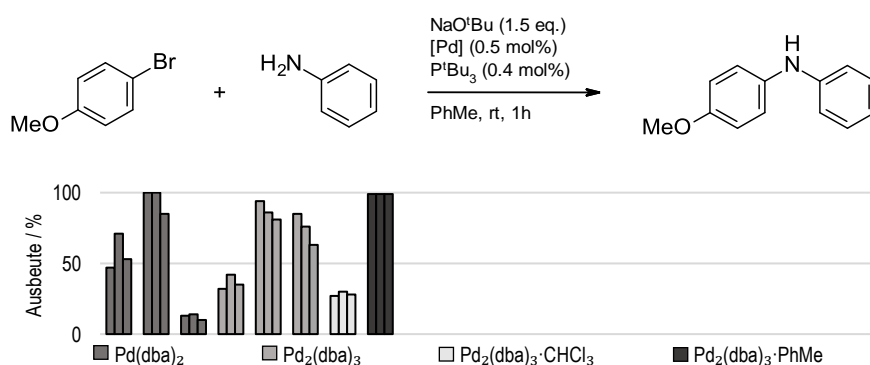
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6. Zusammenfassung und Ausblick

Im Rahmen dieser Doktorarbeit wurden neue Katalysatoren und Liganden zur C-C und C-Heteroatom-Bindungsknüpfung entwickelt und angewendet. Zum einen konnten bekannte Palladium-katalysierte Kreuzkupplungsreaktionen effizient bei Raumtemperatur durchgeführt werden. Zum anderen wurden Funktionalisierungen (hetero)aromatischer Carbonsäuren neu entdeckt (Allylierung) oder die Anwendungsbreite bekannter Reaktionen erhöht (Biarylsynthesen).

Um neuen Liganden für Palladium-katalysierte Reaktionen mit bestmöglichen Grundvoraussetzungen zu begegnen und Reproduzierbarkeitsprobleme mit Katalysatorvorläufern bereits vorab zu vermeiden, wurden die in meiner Diplomarbeit begonnenen Studien mit Pd-dba zu Ende geführt. Mit der Buchwald-Hartwig-Aminierung von 4-Bromanisol mit Anilin konnte eine schnelle Testreaktion identifiziert werden, um die katalytische Aktivität einer Pd-dba-Probe zu überprüfen (Schema 37).

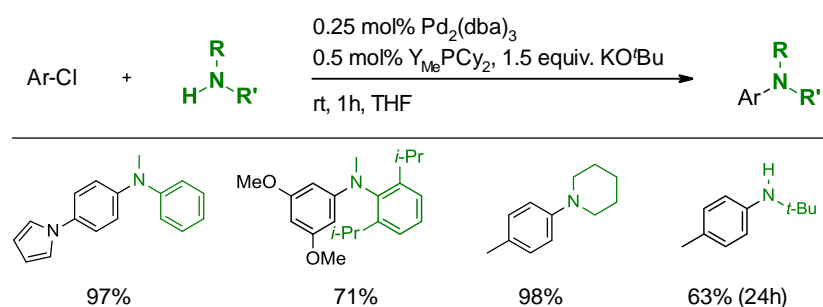


Schema 37. Testung der katalytischen Aktivität diverser Pd-dba-Proben (je Probe wurden drei Versuche durchgeführt).

Anhand von REM- und EDX-Aufnahmen konnte nachgewiesen werden, dass viele Proben eine sehr unterschiedliche Verteilung von komplexiertem (katalytisch aktiven) und unkomplexiertem (inaktivem) Palladium enthalten. Zudem konnte aufgezeigt werden, dass die kommerziell erhältlichen Chloroform-Addukte in Wirklichkeit keine reinen Addukte sind. Die Chloratome wurden oftmals außerhalb der Kristallmatrix oder gar nicht detektiert. Mittels einer langsamen Kristallisation in Toluol zum entsprechenden Toluol-Addukt konnten katalytisch weniger aktive Proben aufgewertet und eine sehr aktive und lagerstabile Spezies hergestellt werden. Initiale Versuche haben gezeigt, dass eine langsame Kristallisation essentiell für ein katalytisch aktives und stabiles Produkt ist und kürzere Kristallisationszeiten (oder Direktsynthesen) schlechtere Ergebnisse erzielen. Es könnte ein lohnendes Ziel sein, das

Addukt im industriellen Maßstab und in höheren Ausbeuten herzustellen. Ebenfalls könnte nach weiteren Testreaktionen geforscht werden (Suzuki, Heck, allgemein heterogen katalysierte Reaktionen), um zu ergründen, ob die Trends aus der Buchwald-Hartwig-Aminierung auch bei anderen Reaktionstypen auftreten.

Mit den gewonnenen Erfahrungen in Bezug auf Pd-dba konnte mit dem in der Gruppe von Prof. Dr. Däschlein-Gessner entwickelten YPhos-Liganden $Y_{Me}PCy_2$ eine sehr effiziente Methode zur Aminierung von Arylchloriden entwickelt werden. Hierbei konnte gezeigt werden, dass YPhos-Palladium-Komplexe den üblicherweise verwendeten Phosphan- oder NHC-Liganden bei Raumtemperatur überlegen sind (Schema 38).

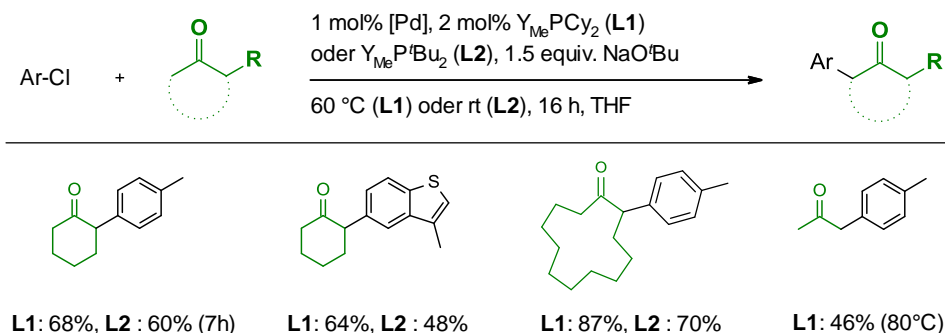


Schema 38. Palladium-katalysierte Aminierung von Arylchloriden mit YPhos.

Der hohe synthetische Nutzen konnte anhand der Herstellung diverser Arylamine in sehr guten Ausbeuten demonstriert werden. Die erhaltenen Ergebnisse sind ein vielversprechender Startpunkt für weitere Untersuchungen. Beispielsweise könnten chirale Amine verwendet werden, dabei müsste sichergestellt sein, dass diese nach erfolgreicher Umsetzung nicht racemisieren. Durch sperrige Gruppen (wie beispielsweise einem Adamantyl-Rest) am YPhos-Liganden könnte zudem versucht werden Ammoniak selektiv zu monoarylieren. Erste Versuche mit dem sperrigeren Liganden $Y_{Me}P^tBu_2$ konnten zumindest die Triarylierung unterbinden und schon bei milden Bedingungen das diarylierte Produkt in guten Ausbeuten erzeugen.

Im anschließenden YPhos-Projekt konnte eine Palladium-katalysierte Methode zur selektiven α -Arylierung von Ketonen mit Arylchloriden entwickelt werden. Mit $Y_{Me}PCy_2$ waren wir in der Lage selbst schwierige Ketone wie Cyclohexanon bei milden 60 °C in guten Ausbeuten zu erhalten. $Y_{Me}P^tBu_2$ erwies sich zwar als weniger robust, konnte dafür aber erstmals Cyclohexanon bei Raumtemperatur in guten Ausbeuten umsetzen (Schema 39).

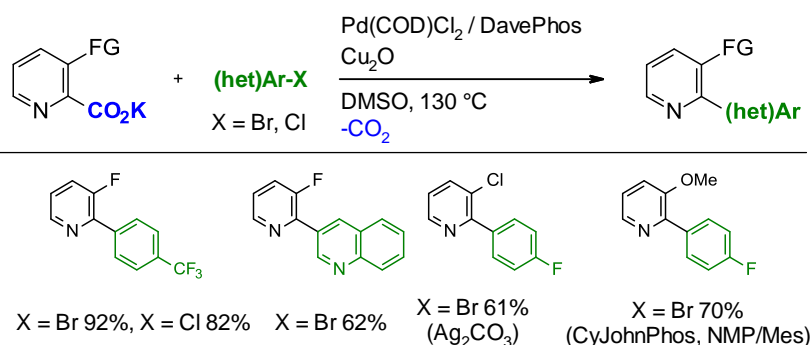
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Schema 39. *YPhos-Palladiumkatalysierte selektive Monoarylierung von Ketonen mit Arylchloriden.*

Mit der selektiven Monoarylierung zahlreicher Ketone sowie von Umsetzungen im Gramm-Maßstab und einer Nachfolgereaktion zum ϵ -Caprolakton konnte der hohe synthetische Nutzen demonstriert werden. Weiterhin kann versucht werden Einschränkungen bekannter Suzuki- oder Kumada-Kupplungen mit YPhos entgegenzutreten. Die Chancen könnten sich erhöhen, wenn andere Metalle (außer Palladium) wie zum Beispiel Nickel verwendet werden.

Im weiteren Verlauf dieser Arbeit wurde sich mit der decarboxylierenden Kreuzkupplung von Picolinsäuren beschäftigt. Zwar konnte die Effizienz der Umsetzung einfacher Picolinsäure gegenüber bekannten Protokollen nicht deutlich gesteigert werden, jedoch zeigte sich, dass elektronenziehende Substituenten (insbesondere Fluor) in C3-Position die decarboxylierende Kreuzkupplung mit Arylbromiden und -chloriden deutlich begünstigen. Im Vergleich zu anderen Protokollen konnte die Reaktionstemperatur deutlich auf 130 °C gesenkt werden (Schema 40).

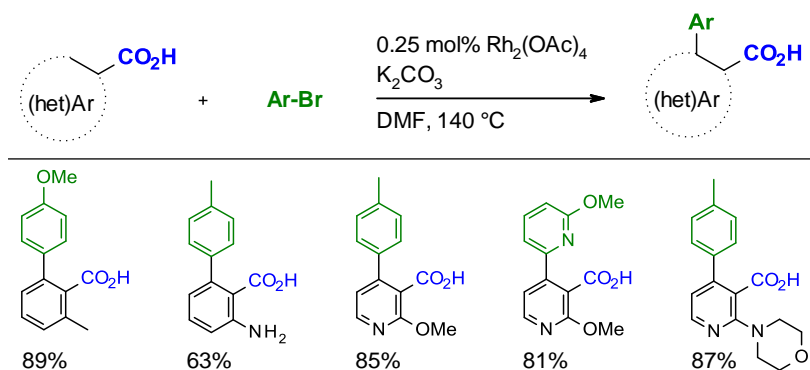


Schema 40. *Decarboxylierende Kreuzkupplung von 3-substituierten Picolinsäuren mit Arylbromiden und -chloriden.*

Mit dieser Methode konnten zahlreiche Heterobiaryle synthetisiert und in einer nachfolgenden nukleophilen aromatischen Substitution weiterfunktionalisiert werden. Erst kürzlich erschien ein Protokoll von Willis *et al.*, in dem heterozyklische Allylsulfone mit (Hetero)Arylbromiden durch Palladiumkatalyse in sehr guten Ausbeuten gekuppelt werden konnten.²⁷⁴ Zwar sind die Ausgangsstoffe weniger gut zugänglich und das freigesetzte SO₂ ist im Gegensatz zu CO₂

toxisch, dennoch kann dieses Protokoll als Startpunkt für tiefere Untersuchungen dienen.

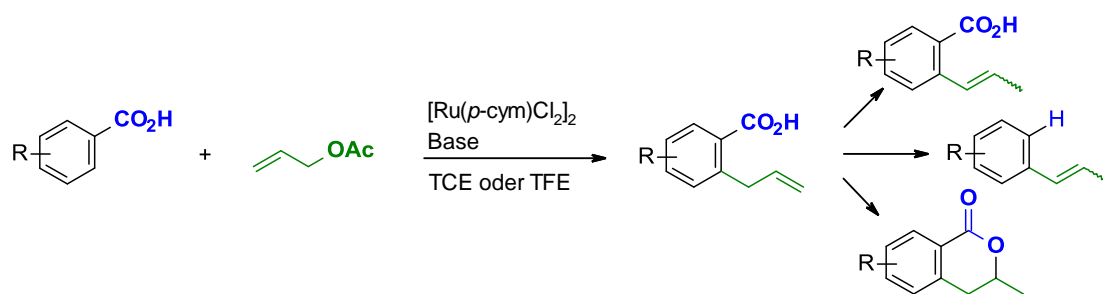
In dieser Arbeit konnte ebenfalls ein Rhodium-katalysiertes Protokoll entwickelt werden, welches erstmals Carbonsäuren wie Anthranilsäure oder 2-Methoxynicotinsäure in sehr guten Ausbeuten in *ortho*-Position arylieren konnte (Schema 41).



Schema 41. Rhodium-katalysierte *ortho*-Arylierung (hetero)aromatischer Carbonsäuren mit Arylbromiden.

Zudem konnte nach umfangreichen Untersuchungen ein plausibler Reaktionsmechanismus postuliert werden. $\text{Rh}_2(\text{OAc})_4$ könnte, nach Austausch eines Acetats mit mindestens einem Benzoat, durch eine dirigierte CMD-Reaktion ein cyclometalliertes $\text{Rh}(\text{II})$ -Carboxylat bilden. Das Dimer könnte nach Reaktion mit einem Arylbromid zu einem monomeren $\text{Rh}(\text{III})$ -Carboxylat gespalten und somit in den Katalysezyklus eingeführt werden. Der synthetische Nutzen konnte anhand der Herstellung zahlreicher *ortho*-arylierter (hetero)aromatischer Carbonsäuren sowie einer nachfolgenden Protodecarboxylierung demonstriert werden. Oftmals waren niedrige Katalysatorbeladungen (0.5 mol%) und Reaktionszeiten (1-2 Stunden) ausreichend. Die Erkenntnis, dass auch simple Rhodiumsalze für *ortho*-Arylierungen von Benzoensäuren geeignet sind, bietet Spielraum für weitere dirigierende Funktionalisierungen. Durch den Verzicht auf das deutlich teurere $[\text{RhCp}^*\text{Cl}_2]_2$ können auch andere, ähnliche Reaktionen kostengünstiger gestaltet werden.

Im letzten Teilprojekt dieser Arbeit wurde eine Ruthenium-katalysierte Methode zur *ortho*-Allylierung von Benzoensäuren mit Allylacetat entwickelt. Dieses Reaktionsprotokoll ist derart effizient, dass die Reaktionstemperatur $< 60^\circ\text{C}$ gehalten werden kann und dadurch eine Umlagerung der Allyl-Doppelbindung unterbunden wird. Der synthetische Nutzen wurde anhand der Kupplung vieler Benzoensäurederivate und einiger Allylacetatderivate, sowie einer nachfolgenden Protodecarboxylierung oder Lactonisierung demonstriert (Schema 42).



Schema 42. Ruthenium-katalysierte ortho-Allylierung von Benzoesäuren mit Allylacetat.

Basierend auf diesem Protokoll konnten in unserer Gruppe zwei weitere Ruthenium-katalysierte Allylierungen von Benzoesäuren mit Allylaminen sowie Allylalkoholen oder -estern entwickelt werden.^{275,276} Auch hier sind halogenierte Lösungsmittel (Trichlorethanol und Trifluorethanol) nötig, um bestmögliche Ausbeuten zu erhalten. Man kann zuversichtlich sein, dass ökologischere Alternativen für diese Prozesse gefunden werden können.

7. Experimenteller Teil

7.1 Struktur und Inhalt des Experimentellen Teils

Insofern die experimentellen Daten nicht schon in den jeweiligen Manuskripten in Form eines „Full-Papers“ dargestellt wurden, wurden diese zum größten Teil aus der entsprechenden „Supporting Information“ entnommen. Da diese der Originalversion entsprechen wurden sie auf Englisch verfasst.

7.2 Allgemeine Methoden

7.2.1 Chemikalien und Lösungsmittel

Kommerziell erhältliche Chemikalien und Lösungsmittel wurden bei einer Reinheit von ≥ 95 % direkt eingesetzt oder andererseits nach Standardverfahren aufgereinigt.²⁷⁷ Luft- und feuchtigkeitsempfindliche Substanzen wurden mit Standard-Schlenktechniken unter Stickstoff- oder Argonatmosphäre gelagert und gehandhabt. Die verwendeten Lösungsmittel wurden dabei nach Standardverfahren getrocknet²⁷⁷ und unter Stickstoff- oder Argonatmosphäre über Molekularsieben (3 oder 4 Å) gelagert, welche zuvor im Mikrowellenofen (2 x 2 min, 600 W) erhitzt und im Vakuum (10^{-3} mbar) bis auf Raumtemperatur abgekühlt wurden. Flüssige Reaktanden und Lösungsmittel wurden, soweit nicht anders angegeben, vor der Reaktion mittels Durchleiten von Argon von Sauerstoff befreit. Feststoffe wurden, wenn nicht in einer „Glovebox“, unter Luft eingewogen und im Vakuum (10^{-3} mbar) von Luft und Feuchtigkeit befreit.

7.2.2 Durchführung von Parallelreaktionen

Bis zu 10 parallele Reaktionen wurden in 20 mL Headspace-Vials für die Gaschromatographie durchgeführt und mit Aluminium-Bördelkappen mit Teflon-beschichteten Butylgummisepten verschlossen. Die Temperierung erfolgte in 8 cm hohen und 7 cm tiefen (Löcher) Aluminiumblöcken, welche zehn zylindrische Bohrungen, deren Durchmesser (etwa 2.27 cm) auf die Reaktionsgefäße angepasst wurde, enthalten. Feststoffe wurden unter Luft eingewogen. Die Reaktionsgefäße wurden mit einem Magnetrührkern (20 mm Länge) ausgestattet und mit einer Septumkappe luftdicht verschlossen. Luft- und feuchtigkeitsempfindliche Substanzen wurden in einer Glovebox unter Stickstoffatmosphäre eingewogen. Die Reaktionsgefäße wurden in die Bohrungen der Aluminiumblöcke gesetzt und über Kanülen mit einem Vakuumverteiler verbunden, welcher wiederum an eine Schlenkapparatur mit Ölpumpe

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verbunden wurde. Danach wurden die Reaktionsgefäße dreimal hintereinander evakuiert und mit Stickstoff oder Argon befüllt. Gerührt wurde mit etwa 300 Umdrehungen pro Minute. Reaktionen in der Mikrowelle wurden mit einem *Initiator Mikrowellenreaktor* der Firma *Biotage* durchgeführt. Nach beendeter Reaktion wurde, je nach Analysemethode (Gaschromatographie, ^{19}F -NMR oder ^1H -NMR), ein interner Standard zugegeben. Bei der Ausbeutebestimmung via NMR wurden der Probe 0.5 mL entnommen, über Celite gefiltert und direkt vermessen. Für die Ausbeutenbestimmung via GC-Analyse wurde die Reaktionsmischung mit Ethylacetat (4 mL) verdünnt und durchmischt. Mit einer Einwegpipette wurden etwa 0.25 mL der Reaktionsmischung in 10 mL Rollrandgefäße überführt, in welche vorher ein wässriges Extraktionsmedium (2 mL destilliertes Wasser, bei Verwendung von DMF oder NMP eine 1M Lösung LiCl) und Ethylacetat (3 mL) gegeben wurde. Die Phasen wurden durchmischt und nach der Phasentrennung wurden etwa 1.5 mL der organischen Phase durch Celite und Magnesiumsulfat gefiltert. Als Filter dienten Glaspipetten die mit einem Wattepfropfen versehen wurden. Die Probe wurde gaschromatographisch untersucht und die Ausbeute durch Integration des Produktsignals im Vergleich mit dem des internen Standards bestimmt. Responsefaktoren des gewünschten Produktes wurden in Bezug auf den internen Standard experimentell durch Analyse bekannter Produktmengen bestimmt.

7.2.3 Analytische Methoden

7.2.3.1 Dünnschichtchromatographie

Es wurden Platten der Firma *Macherey-Nagel* (Polygram[®] SIL G/UV) mit 0.2 mm Kieselgel 60 F254 auf Aluminiumfolie verwendet. Zur Detektion der Substanzen wurde eine UV-Lampe mit einer Wellenlänge von 254 nm eingesetzt.

7.2.3.2 Säulenchromatographie

Zur Isolierung der Produkte wurde mit dem Combi Flash Companion-Chromatographie-System der Firma *Isco-Systems* oder dem Reveleris X2-Chromatographie-System der Firma *Grace* gearbeitet. Als Säulen wurden die Reveleris Silica-Säulen der Größe 12 g der Firma *Grace* verwendet.

7.2.3.3 Schmelzpunkte

Die Schmelzpunkte wurden mit einem Digimelt MPA161 der Firma *Stanford Research Systems* oder einem *Mettler FP 61* mit optischem Sensor automatisch bestimmt.

7.2.3.4 Elementaranalyse

Die Elementaranalysen wurden an einem *Elemental Analyzer Vario Micro Cube* gemessen.

7.2.3.5 Gaschromatographie

Die GC-Analysen wurden mit ein *Hewlett Packard 6890* Gaschromatograph in Kombination mit einer HP-5-Säule mit 5 % Phenyl-Methyl-Siloxan (30 m x 320 µm x 0.25 µm) der Firma *Agilent* verwendet. Als Trägergas diente Stickstoff mit einer Flussrate von 55 ml (0.64 bar Druck). Die Injektionstemperatur betrug 220 °C bei einem Split-Verhältnis von 1:20. Das Temperaturprogramm begann bei 60 °C (2 min), dann kam es zu einem linearen Temperaturanstieg von 30 °C/min bis auf 300 °C (3 min halten). Dabei wurde ein Flammenionisationsdetektor mit einer Detektortemperatur von 330 °C verwendet.

7.2.3.6 Massenspektrometrie

Die Massenspektren wurden zum einen an einem GC-MS *Saturn 2100 T* der Firma *Varian* aufgenommen. Weiterhin wurden Massenspektren an einem GC-MS 5977B MSD der Firma *Agilent* aufgenommen. Hier erfolgte die Ionisation per Elektrosprayionisation. Die angegebenen Intensitäten der Signale beziehen sich auf das Verhältnis zum intensivsten Peak. Für Fragmente mit einer Isotopenverteilung ist jeweils nur der intensivste Peak eines Isotopomers aufgeführt. Die hochauflösenden Massenspektren wurden zum einen in der Analytikabteilung des Fachbereichs Chemie der Technischen Universität Kaiserslautern an einem *GCT Premier* der Firma *Waters* gemessen. Zum anderen wurden hochauflösenden Massenspektren an einem *Waters GCT Premier CAB162* mit einem TOF-Analysator gemessen. In beiden Fällen erfolgte die Ionisation per Elektronenstoßionisation.

7.2.3.7 Infrarotspektroskopie

Die Infrarot-Schwingungsspektren wurden entweder an einem *Spectrum 100 ATR-FTIR* der Firma *Perkin Elmer* oder einem *Vertex 70* Spektrometer der Firma *Bruker* gemessen. Alle Messungen erfolgten gegen Luft als Hintergrund in einem Bereich von 4000 bis 400 Wellenzahlen. Die Angabe der Schwingungsbanden erfolgt in Wellenzahlen (cm⁻¹).

7.2.3.8 NMR-Spektroskopie

¹H-NMR-, breitbandenkoppelte ¹³C-NMR-, ¹⁹F-NMR- und ³¹P-NMR-Spektren wurden bei Raumtemperatur größtenteils am FT-NMR-Spektrometer *Avance 400* der Fa. *Bruker* aufgenommen. Einzelne Messungen erfolgten weiterhin an den Geräten *Avance 200*, *Avance 300*, *Avance 600*, *DPX 200* und *DPX 250* der Firma *Bruker* sowie am *Spinsolve*

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Benchtop-NMR der Firma *Magritek*. ^{19}F -NMR-Messungen zur Ausbeutenbestimmung wurden am *Spinsolve* Benchtop-NMR mit einer Fluorresonanz bei 41 MHz durchgeführt. ^{13}C -MAS-Spektren wurden bei Raumtemperatur mit einem AVANCE III 500 Solid State NMR der Firma *Bruker* aufgenommen. Die chemischen Verschiebungen der Signale sind in ppm bezüglich der δ -Skala angegeben. Für die Multiplizität der Signale wurden folgende Abkürzungen verwendet: s = Singulett, d = Duplett, t = Triplett, m = Multipllett. Die Kopplungskonstanten J der Signale wurden in Hertz [Hz] angegeben. Zur Auswertung der Spektren wurde ACD/Labs 12.0 der Firma *Advanced Chemistry Development Inc.* verwendet. Die graphische Darstellung der ^{13}C -MAS-Spektren erfolgte mit Origin 8 der Firma *Originlab*.

7.2.3.9 XRD-Spektroskopie

Die Pulverdiffraktogramme wurden mit einem *Siemens* Röntgen-Pulverdiffraktometer D 5005 unter Verwendung von $\text{CuK}\alpha$ -Strahlung (Wellenlänge 0.15406 nm, Beschleunigungsspannung 40 kV, Stromstärke 30 mA) im Messbereich von $1^\circ < 2\Theta < 100^\circ$ aufgenommen. Die graphische Darstellung erfolgte mit Origin 8 der Firma *Originlab*.

7.2.3.10 Mikroskopaufnahmen

Es wurde mit dem Digitalmikroskop VHX-500F der Firma *Keyence* gearbeitet. Die Probe wurde auf einem Objektträger platziert und entweder von oben oder unten beleuchtet. Die Fotos wurden aufgenommen und digital bearbeitet.

7.2.3.11 Röntgenstrukturanalyse

Die Röntgenstrukturanalyse erfolgte am Diffraktometer Oxford Diffraction Gemini S Ultra bei 150 K unter Verwendung von $\text{MoK}\alpha$ -Strahlung oder $\text{CuK}\alpha$ -Strahlung.

7.3 A comparative study of dibenzylideneacetone palladium complexes in catalysis

7.3.1 Allgemeine Informationen

Da einige experimentelle Daten bereits in vorherigen Arbeiten veröffentlicht wurden,¹ wurde auf die Abbildung der Elementaranalysen, Schmelzpunkte, Mikroskopbilder, Infrarotspektren, ¹H-NMR-Spektren, ¹³C-NMR-Spektren, und XRD-Spektren verzichtet. Diese Daten, die detaillierte Kristallstruktur des Toluol-Adduktes sowie eine genaue Auswertung der REM- und EDX-Aufnahmen ist kostenfrei in der „Supporting Information“ unter <https://doi.org/10.1021/acs.oprd.9b00214> zu finden.

7.3.2 Properties of crystals and Pd nanoparticles

Tabelle 24. Properties of crystals and Pd nanoparticles (from the SEM pictures).

Sample	Particle form	Pd distribution	Particle size / nm	Particle distribution
1A	needles	inhomogeneous - homogeneous	2, 4, 10, 15, 500	Little on the surface, much inside crystal matrix
1B ₁	amorphous	Inhomogeneous	5, 10, 25, 100, 2500, 3800	Much on the surface, almost exclusively agglomerates of Pd nanoparticles
1B ₂	amorphous	very inhomogeneous	5	On the surface, little agglomerates
1C ₁	cubic	very homogeneous	2, 20	All inside the crystal matrix
1C ₂	distorted hexagonal	very homogeneous	none	-
1D	round	inhomogeneous - homogeneous	3, 5, 1500, 6000, 12000	On the surface, arranged linearly, agglomerates
1E	amorphous	inhomogeneous	12, 500, 1000	On the surface, many small agglomerates
2A	amorphous	homogeneous	5, 10, 20	On the surface and inside the crystal matrix
2B ₁	amorphous	very inhomogeneous	1, 2, 5, 10, 40, 100, 2000	Agglomerates and Pd-nanoparticles on the surface
2B ₂	distorted cubic	inhomogeneous - homogeneous	2, 5, 4000	Agglomerates linearly inside the crystal matrix, nanoparticles equally distributed inside the crystal matrix
2C	amorphous	very homogeneous	none	-
2D	distorted hexagonal	inhomogeneous - homogeneous	3, 5, 1500, 6000, 12000	Agglomerates all outside the crystal matrix
2E	distorted hexagonal	homogeneous	12, 500, 1000	Agglomerates on the surface and inside the crystal matrix
2F	round	inhomogeneous	5, 10, 50, 1500, 2000, 8000	Braid of Pd nanoparticles
3A	needles with distorted hexagonal base	inhomogeneous - homogeneous	2, 5, 10, 20, 1500, 2500, 3500, 4000	In agglomerates and inside the crystal matrix

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3D	needles with distorted hexagonal base	inhomogeneous - homogeneous	3, 5, 1000, 2000, 4000, 6000, 15000	In agglomerates and on the surface
3E	cubic distorted	homogeneous	2, 4, 5, 10, 15, 20, 5000	Inside the crystal matrix

7.3.3 Catalytic test reactions

Tabelle 25. Results Buchwald-Hartwig-Amination of 4-Bromoanisole with Aniline.

Sample	Yield / %
	80
1A	100
	100
	47
1B ₁	71
	53
	100
1C ₁	100
	85
	94
1C ₂	94
	71
	38
1B ₂	51
	46
	13
1D	14
	10
	64
1E	30
	28
	91
2A	91
	73
	32
2B ₁	42
	35
	94
2C	86
	81
	70
2C after storing under air for 14 months	68
	40
	63
2B ₂	68
	80
	64
2D	70
	66
	100

2E	88
	99
2F	85
	76
3A	63
	39
3D	46
	35
3E	27
	30
	28
	46
	43
	49

[a] **5** (1.0 mmol), **6** (1.0 mmol), NaO^tBu (1.5 mmol), Pd_x(dba)_y (0.5 mol% Pd, calculated from the Pd content reported by the supplier) and P^tBu₃ (0.4 mol%) in toluene (2 mL), room temperature, 1h. Yields were determined by GC analysis using *n*-dodecane as internal standard.

Table 26. Results Buchwald-Hartwig-Amination of 4-Bromoanisole with Aniline using Pd₂(dba)₃ and Pd black as the Pd-source.

Amount Pd ₂ (dba) ₃	Amount Pd black	Yield / %
-	0.5 mol%	0
-	1.0 mol%	0
0.5 mol% [Pd] ^b	-	71
„	0.5 mg	84
„	1.0 mg	74
0.5 mol% [Pd] ^c	-	60
0.25 mol% [Pd] ^c	0.25 mol%	28

[a] **5** (1.0 mmol), **6** (1.0 mmol), NaO^tBu (1.5 mmol), [Pd] (0.5 mol%) and P^tBu₃ (0.4 mol%) in toluene (2 mL), room temperature, 1h. Yields were determined by GC analysis using *n*-dodecane as internal standard. [b] 2nd batch Pd₂dba₃ by Supplier F (15.62% Palladium). [c] 3rd batch Pd₂dba₃ by Supplier F (14.82% Palladium).

Table 27. Results Buchwald-Hartwig-Amination of 4-Bromoanisole with Aniline using a Pd₂(dba)₃ sample by Supplier F (15.31% Pd) under different storing conditions after 6 months.

Storing condition	Yield / % ^[a]	Average Yield / %
Reference (before storing)	83	86
	89	
	86	
Air, PE, dark, 4 °C	99	96
	90	
	99	
Air, PE, dark, 40 °C	90	92
	93	
	92	
Air, PE, dark, rt	90	91
	95	
	88	
Air, PE, light, rt	85	87
	86	
	90	

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	93	
Air, glass, light, rt	87	91
	93	
	75	
Air, glass, dark, rt	91	85
	88	
	93	
Air, glass, dark, 40 °C	89	88
	82	
	94	
Air, glass, dark, 4 °C	77	86
	88	
	91	
Argon, glass, dark, 4 °C	90	89
	87	
	91	
Argon, glass, dark, 40 °C	86	91
	95	
	80	
Argon, glass, dark, rt	89	87
	91	
	88	
Argon, glass, light, rt	85	86
	85	

[a] 1 mmol Aniline, 1 mmol 4-Bromoanisole, 1.5 eq. NaO^tBu, 0.5 mol% Pd(0), 0.4 mol% P^tBu₃, 2 ml toluene, rt, 60 min. Yields determined via GC using n-tetradecane as internal standard. Stored in a glass or PE (Polyethylene) vessel, under air or argon, light or dark, under different temperatures. Δ Displays the deviation from the average of the three parallel reactions.

7.3.4 X-ray analysis

Tabelle 28. Crystal data and structure refinement for the toluene adduct.

Identification code	shelx	
Empirical formula	C ₅₈ H ₅₀ O ₃ Pd ₂	
Formula weight	1007.78	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 13.6937(4) Å	α = 90°.
	b = 23.4684(4) Å	β = 113.752(3)°.
	c = 15.3166(4) Å	γ = 90°.
Volume	4505.4(2) Å ³	
Z	4	
Density (calculated)	1.486 Mg/m ³	
Absorption coefficient	0.845 mm ⁻¹	

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F(000)	2056
Crystal size	0.3243 x 0.2271 x 0.1197 mm ³
Theta range for data collection	2.722 to 29.000°.
Index ranges	-18<=h<=13, -32<=k<=31, -17<=l<=20
Reflections collected	27847
Independent reflections	11970 [R(int) = 0.0439]
Completeness to theta = 25.242°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.97523
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	11970 / 128 / 953
Goodness-of-fit on F ²	1.041
Final R indices [I>2sigma(I)]	R1 = 0.0429, wR2 = 0.0832
R indices (all data)	R1 = 0.0724, wR2 = 0.0940
Extinction coefficient	n/a
Largest diff. peak and hole	1.509 and -0.835 e.Å ⁻³

7.4 A Highly Active Ylide-Functionalized Phosphine for Palladium-Catalyzed Aminations of Aryl Chlorides

7.4.1 Preparation of the catalyst stock solution

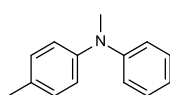
Inside a globevox containing inert gas atmosphere, an oven-dried 20 mL vial was charged with Pd₂dba₃ (0.025 mmol per mL THF), YPhos (0.05 mmol per mL THF) and THF. The resulting mixture was stirred at room temperature for 0.5 h.

7.4.2 General procedure for the amination

Inside a globevox containing inert gas atmosphere, an oven-dried 20 mL vial was charged with KO^tBu (187 mg, 1.50 mmol), dry THF (2mL), an aryl chloride (1.00 mmol), an amine (1.10 mmol) and catalyst stock solution (0.1 mL) and closed with a septum cap. The resulting mixture was stirred at room temperature or, whenever stated, at 60 °C for 1 h or, whenever stated, for 4 h and 24 h. After the reaction was complete, it was diluted with EtOAc (10 mL) and washed with brine (3×20 mL), then the aqueous phases were extracted with EtOAc (3×20 mL). The combined organic phases were dried over MgSO₄, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂, ethyl acetate/cyclohexane gradient), yielding the corresponding amine.

7.4.3 Synthesis and characterization of products

Synthesis of N-4-dimethyl-N-phenyl-Benzenamine 3aa



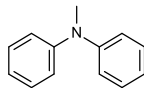
[CAS: 38158-65-5]

Compound **3aa** was prepared following the general procedure for the amination of 4-chlorotoluene (127 mg, 1.00 mmol) with *N*-methylaniline (119 mg, 1.10 mmol) and isolated as colorless oil (179 mg, 0.905 mmol, 91%).

¹H NMR (400 MHz, CDCl₃) δ = 7.21 - 7.31 (m, 2 H), 7.14 (d, *J* = 8.3 Hz, 2 H), 6.99 - 7.07 (m, 2 H), 6.94 (dd, *J* = 8.8, 1.0 Hz, 2 H), 6.84 - 6.92 (m, 1 H), 3.31 (s, 3 H), 2.34 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ = 149.4 (s) 146.6 (s) 132.0 (s) 129.9 (s) 129.0 (s) 122.5 (s) 119.8 (s) 118.2 (s) 40.3 (s) 20.7 (s) ppm. MS (EI, 70 eV) *m/z* (%): 197.0 (100) [M⁺], 196.0 (69), 104.0 (15), 90.9 (18), 76.9 (23), 51.0 (16), 49.9 (13). IR: $\tilde{\nu}$ = 3025 (w), 2864 (w), 2808 (w), 1594 (m), 1494 (s), 1338 (m), 1251 (m), 1129 (m), 867 (m), 748 (s), 693 (s) cm⁻¹. CHN: Calculated: C:

85.24, H: 7.66, N: 7.10. Measured: C: 84.87, H: 7.26, N: 7.56. The analytical Data (NMR) matched those reported in the literature.²⁷⁸

Synthesis of N-methyl-N-phenyl-Benzenamine 3ab

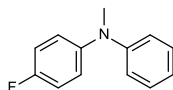


[CAS: 552-82-9]

Compound **3ab** was prepared following the general procedure for the amination of chlorobenzene (113 mg, 1.00 mmol) with *N*-methylaniline (119 mg, 1.10 mmol) and isolated as yellow oil (168 mg, 0.918 mmol, 92%).

¹H NMR (300 MHz, CDCl₃) δ = 7.19 - 7.33 (m, 4 H), 6.99 - 7.07 (m, 4 H), 6.91 - 6.99 (m, 2 H), 3.31 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ = 149.0 (s) 129.2 (s) 121.2 (s) 120.4 (s) 40.2 (s) ppm. MS (EI, 70 eV) *m/z* (%): 182.9 (100) [M⁺], 182.0 (63), 167.0 (9), 104.0 (17), 76.9 (17), 51.0 (14), 50.0 (9). IR: $\tilde{\nu}$ = 3035 (w), 2877 (w), 2809 (w), 1584 (m), 1492 (s), 1339 (m), 1250 (m), 1129 (m), 746 (s), 690 (s) cm⁻¹. The analytical Data (NMR) matched those reported in the literature.²⁷⁹

Synthesis of 4-fluoro-N-methyl-N-phenyl-Benzenamine 3ac



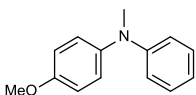
[CAS: 902781-07-1]

Compound **3ac** was prepared following the general procedure for the amination of 1-chloro-4-fluorobenzene (131 mg, 1.00 mmol) with *N*-methylaniline (119 mg, 1.10 mmol) and isolated as colorless oil (168 mg, 0.832 mmol, 83%).

¹H NMR (300 MHz, CDCl₃) δ = 7.19 - 7.29 (m, 2 H), 6.94 - 7.09 (m, 4 H), 6.83 - 6.94 (m, 3 H), 3.28 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ = 158.7 (d), 149.3 (s), 145.2 (s), 129.1 (s), 124.2 (d), 120.0 (s), 118.0 (s), 116.0 (d), 40.5 (s) ppm. ¹⁹F NMR (235 MHz, CDCl₃) δ = -120.69 ppm. MS (EI, 70 eV) *m/z* (%): 201.0 (100) [M⁺], 200.0 (61), 183.0 (19), 121.9 (19), 104.0 (18), 76.9 (18), 51.0 (15). IR: $\tilde{\nu}$ = 3039 (w), 3005 (w), 2946 (w), 2879 (w), 2811 (w), 1594 (m), 1494 (s), 1340 (m), 1214 (s), 804 (m), 750 (m), 639 (m) cm⁻¹. CHN: Calculated: C: 77.59, H: 6.01, N: 6.96. Measured: C: 77.42, H: 5.98, N: 7.43.

Synthesis of 4-methoxy-N-methyl-N-phenyl- Benzenamine 3ad

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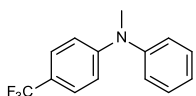


[CAS: 55251-46-2]

Compound **3ad** was prepared following the general procedure for the amination of 4-chloroanisole (145 mg, 1.00 mmol) with *N*-methylaniline (119 mg, 1.10 mmol) and isolated as orange oil (192 mg, 0.901 mmol, 90%).

^1H NMR (300 MHz, CDCl_3) δ = 7.22 - 7.33 (m, 2 H), 7.12 - 7.21 (m, 2 H), 6.92 - 7.01 (m, 2 H), 6.79 - 6.90 (m, 3 H), 3.88 (s, 3 H), 3.33 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ = 156.2 (s), 149.6 (s), 142.1 (s), 128.8 (s), 126.1 (s), 118.3 (s), 115.7 (s), 114.7 (s), 55.3 (s), 40.3 (s) ppm. MS (EI, 70 eV) m/z (%): 212.9 (85) [M^+], 198.0 (100), 154.0 (11). IR: $\tilde{\nu}$ = 3036 (w), 2933 (w), 2833 (w), 1595 (m), 1494 (s), 1341 (m), 1237 (s), 1130 (m), 1031 (s), 868 (m), 748 (s), 692 (s) cm^{-1} . CHN: Calculated: C: 78.84, H: 7.09, N: 6.57. Measured: C: 78.80, H: 6.98, N: 6.83. The analytical Data (NMR) matched those reported in the literature.²⁷⁸

Synthesis of *N*-methyl-*N*-phenyl-4-(trifluoromethyl)-Benzeneamine **3ae**

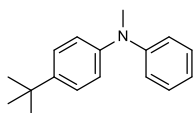


[CAS: 189065-46-1]

Compound **3ae** was prepared following the general procedure for the amination of 1-chloro-4-(trifluoromethyl)benzene (181 mg, 1.00 mmol) with *N*-methylaniline (119 mg, 1.10 mmol) and isolated as orange oil (246 mg, 0.978 mmol, 98%).

^1H NMR (400 MHz, CDCl_3) δ = 7.19 - 7.43 (m, 4 H), 6.93 - 7.19 (m, 3 H), 6.71 (d, J = 9.1 Hz, 2 H), 3.20 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ = 151.5 (s), 147.7 (s), 129.8 (s), 126.7 (s), 126.2 (q), 125.3 (s), 124.9 (s), 119.9 (d), 114.8 (s), 40.2 (s) ppm. ^{19}F NMR (41 MHz, CDCl_3) δ = -59.16 ppm. MS (EI, 70 eV) m/z (%): 251.0 (100) [M^+], 250.1 (64), 232.1 (9), 182.0 (8), 76.9 (7). IR: $\tilde{\nu}$ = 3039 (w), 2946 (w), 1616 (m), 1594 (m), 1521 (m), 1496 (m), 1320 (s), 1161 (m), 1103 (s), 1060 (s), 825 (m), 697 (m) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁸⁰

Synthesis of 4-(1,1-dimethylethyl)-*N*-methyl-*N*-phenyl-Benzenamine **3af**

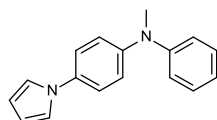


[CAS: 196213-26-0]

Compound **3af** was prepared following the general procedure for the amination of 1-*tert*-butyl-4-chlorobenzene (172 mg, 1.00 mmol) with *N*-methylaniline (119 mg, 1.10 mmol) and isolated as yellow oil (234 mg, 0.977 mmol, 98%).

^1H NMR (300 MHz, CDCl_3) δ = 7.22 - 7.37 (m, 4 H), 6.96 - 7.08 (m, 4 H), 6.87 - 6.96 (m, 1 H), 3.33 (s, 3 H), 1.35 (s, 9 H) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ = 149.2 (s) 146.4 (s) 144.8 (s) 129.0 (s) 126.0 (s) 121.2 (s) 120.2 (s) 119.0 (s) 40.2 (s) 34.2 (s) 31.4 (s) ppm. MS (EI, 70 eV) m/z (%): 239.0 (51) [M^+], 224.0 (100). IR: $\tilde{\nu}$ = 3034 (w), 2959 (m), 2866 (w), 1594 (s), 1494 (s), 1340 (m), 1254 (m), 1132 (m), 870 (m), 745 (s), 693 (s) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁸¹

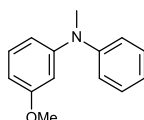
Synthesis of 4-(1H-pyrrol-1-yl) N-methyl-N-phenyl-Benzenamine 3ag



Compound **3ag** was prepared following the general procedure for the amination of 1-(4-chlorophenyl)-1H-pyrrole (181 mg, 1.00 mmol) with *N*-methylaniline (119 mg, 1.10 mmol) and isolated as orange solid (241 mg, 0.972 mmol, 97%).

m.p.: 96-97 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.27 - 7.36 (m, 4 H), 6.97 - 7.12 (m, 7 H), 6.34 (t, J = 2.1 Hz, 2 H), 3.36 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ = 148.8 (s), 146.9 (s), 134.8 (s), 129.3 (s), 121.8 (s), 121.7 (s), 121.1 (s), 120.6 (s), 119.5 (s), 109.9 (s), 40.4 (s) ppm. MS (EI, 70 eV) m/z (%): 248.0 (100) [M^+], 247.0 (14), 233.1 (12). HRMS-ESI (m/z): [$\text{M}+\text{H}^+$] calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{H}^+$: 249.1392; found 249.1392. IR: $\tilde{\nu}$ = 3039 (w), 2935 (w), 1593 (m), 1520 (m), 1492 (m), 1322 (m), 823 (m), 725 (s) cm^{-1} . CHN: Calculated: C: 82.22, H: 6.49, N: 11.28. Measured: C: 82.52, H: 6.40, N: 11.25.

Synthesis of 3-methoxy-N-methyl-N-phenyl-Benzenamine 3ah



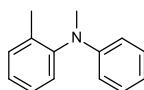
[CAS: 54263-65-9]

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Compound **3ah** was prepared following the general procedure for the amination of 3-chloroanisole (145 mg, 1.00 mmol) with *N*-methylaniline (119 mg, 1.10 mmol) and isolated as orange oil (200 mg, 0.938 mmol, 94%).

^1H NMR (300 MHz, CDCl_3) δ = 7.21 - 7.32 (m, 2 H), 7.14 (t, J = 8.2 Hz, 1 H), 7.01 - 7.08 (m, 2 H), 6.93 - 7.01 (m, 1 H), 6.42 - 6.60 (m, 3 H), 3.74 (s, 3 H), 3.29 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ = 160.5 (s) 150.4 (s) 148.8 (s) 129.7 (s) 129.2 (s) 122.0 (s) 121.6 (s) 112.2 (s) 105.9 (s) 105.6 (s) 55.2 (s) 40.3 (s) ppm. MS (EI, 70 eV) m/z (%): 213.1 (100), 212.0 (28). IR: $\tilde{\nu}$ = 3034 (w), 2937 (w), 1584 (s), 1488 (s), 1345 (m), 1271 (m), 1210 (m), 1167 (m), 1124 (m), 1043 (m), 751 (s), 689 (s). CHN: Calculated: C: 78.84, H: 7.09, N: 6.57. Measured: C: 79.03, H: 7.07, N: 7.06. The analytical Data (NMR) matched those reported in the literature.²⁸²

Synthesis of *N*-2-dimethyl-*N*-phenyl-Benzenamine **3ai**

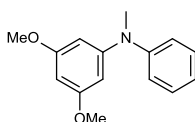


[CAS: 6590-44-9]

Compound **3ai** was prepared following the general procedure for the amination of 2-chlorotoluene (128 mg, 1.00 mmol) with *N*-methylaniline (119 mg, 1.10 mmol) and isolated as yellow oil (110 mg, 0.559 mmol, 56%).

^1H NMR (300 MHz, CDCl_3) δ = 7.28 - 7.35 (m, 1 H), 7.13 - 7.28 (m, 5 H), 6.73 (td, J = 7.2, 1.1 Hz, 1 H), 6.51 - 6.60 (m, 2 H), 3.23 - 3.26 (m, 3 H), 2.17 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ = 149.1 (s), 146.8 (s), 136.8 (s), 131.3 (s), 128.9 (s), 128.3 (s), 127.5 (s), 126.4 (s), 116.8 (s), 112.8 (s), 39.0 (s), 17.8 (s) ppm. MS (EI, 70 eV) m/z (%): 213.1 (100) [M^+], 212.0 (28). IR: $\tilde{\nu}$ = 3023 (w), 2922 (w), 1593 (m), 1491 (s), 1340 (m), 1253 (m), 1112 (m), 746 (s), 726 (s), 691 (s) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁸⁰

Synthesis of 3,5-dimethoxy-*N*-methyl-*N*-phenyl-Benzenamine **3aj**



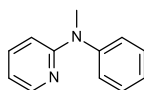
[CAS: 247940-07-4]

Compound **3aj** was prepared following the general procedure for the amination of 5-chloro-1,3-dimethoxybenzene (178 mg, 1.00 mmol) with *N*-methylaniline (119 mg, 1.10 mmol) and isolated as orange oil (241 mg, 0.989 mmol, 99%).

^1H NMR (300 MHz, CDCl_3) δ = 7.20 - 7.32 (m, 2 H), 7.07 (dd, J = 8.7, 1.2 Hz, 2 H), 6.95 - 7.03 (m, 1 H), 6.10 (d, J = 2.0 Hz, 2 H), 6.01 - 6.06 (m, 1 H), 3.70 (s, 6 H), 3.27 (s, 3 H) ppm.

^{13}C NMR (101 MHz, CDCl_3) δ = 161.3 (s), 150.9 (s), 148.7 (s), 129.2 (s), 122.4 (s), 122.4 (s), 97.6 (s), 92.5 (s), 55.2 (s), 40.3 (s) ppm. MS (EI, 70 eV) m/z (%): 243.0 (100) [M^+], 242.2 (20), 214.0 (7). IR: $\tilde{\nu}$ = 3060 (w), 2997 (w), 2936 (w), 1584 (s), 1495 (m), 1478 (m), 1448 (m), 1291 (m), 1202 (s), 1149 (s), 812 (m), 752 (m), 692 (m) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁸³

Synthesis of *N*-methyl-*N*-phenyl-2-Pyridinamine **3ak**

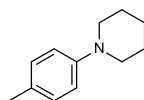


[CAS: 62093-17-8]

Compound **3ak** was prepared following the general procedure for the amination of 2-chloropyridine (115 mg, 1.00 mmol) with *N*-methylaniline (119 mg, 1.10 mmol) and isolated as orange oil (102 mg, 0.553 mmol, 55%). Yield at 60 °C stirring for 4 h: 180 mg, 0.979 mmol, 98 %.

^1H NMR (300 MHz, CDCl_3) δ = 8.19 - 8.29 (m, 1 H), 7.36 - 7.47 (m, 2 H), 7.16 - 7.36 (m, 4 H), 6.62 (ddd, J = 7.1, 5.0, 0.9 Hz, 1 H), 6.54 (dt, J = 8.6, 0.9 Hz, 1 H), 3.49 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ = 158.8 (s) 147.7 (s) 146.8 (s) 136.6 (s) 129.7 (s) 126.3 (s) 125.4 (s) 113.1 (s) 109.2 (s) 38.4 (s) ppm. MS (EI, 70 eV) m/z (%): 185.0 (38), 183.1 (100), 106.0 (7), 76.9 (10), 51.0 (15), 50.0 (8). IR: $\tilde{\nu}$ = 3004 (w), 2934 (w), 1602 (s), 1476 (s), 1361 (m), 1152 (m), 980 (m), 763 (s), 696 (s) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁸⁴

Synthesis of 1-(4-methylphenyl)-Piperidine **3ba**



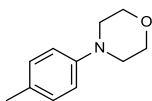
[CAS: 31053-03-9]

Compound **3ba** was prepared following the general procedure for the amination of 4-chlorotoluene (127 mg, 1.00 mmol) with piperidine (94.6 mg, 1.10 mmol) and isolated as yellow oil (171 mg, 0.976 mmol, 98%).

EXPERIMENTELLER TEIL

^1H NMR (400 MHz, CDCl_3) δ = 7.07 (d, J = 8.3 Hz, 2 H), 6.88 (d, J = 8.6 Hz, 2 H), 3.02 - 3.18 (m, 4 H), 2.28 (s, 3 H), 1.73 (quin, J = 5.7 Hz, 4 H), 1.49 - 1.64 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ = 150.2 (s), 129.5 (s), 128.8 (s), 117.0 (s), 51.3 (s), 25.9 (s), 24.3 (s), 20.4 (s) ppm. MS (EI, 70 eV) m/z (%): 175.1 (70) [M^+], 174.1 (100), 119.05 (27), 118.0 (18), 91.0 (22). IR: $\tilde{\nu}$ = 3025 (w), 2932 (m), 2853 (m), 2791 (m), 1618 (m), 1513 (s), 1452 (m), 1382 (m), 1236 (s), 1130 (m), 919 (m), 808 (s), 526 (m) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁸⁵

Synthesis of 4-(4-methylphenyl)-Morpholine **3ca**

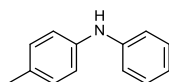


[CAS: 3077-16-5]

Compound **3ca** was prepared following the general procedure for the amination of 4-chlorotoluene (127 mg, 1.00 mmol) with morpholine (96.8 mg, 1.10 mmol) and isolated as yellow solid (176 mg, 0.993 mmol, 99%).

m.p.: 50°C. ^1H NMR (300 MHz, CDCl_3) δ = 7.11 (d, J = 8.8 Hz, 2 H), 6.85 (d, J = 8.4 Hz, 2 H), 3.83 - 3.91 (m, 4 H), 3.08 - 3.16 (m, 4 H), 2.29 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ = 149.2 (s), 129.7 (s), 129.5 (s), 116.0 (s), 67.0 (s), 49.9 (s), 20.4 (s) ppm. MS (EI, 70 eV) m/z (%): 176.9 (100) [M^+], 175.9 (12), 118.9 (93), 118.0 (45), 90.9 (65), 65.0 (22), 51.0 (9). IR: $\tilde{\nu}$ = 3028 (w), 2977 (w), 2956 (m), 2852 (m), 1725 (w), 1511 (m), 1227 (m), 1115 (s), 921 (s), 818 (s), 607 (m), 500 (m) cm^{-1} . CHN:Calculated: C: 74.54, H: 8.53, N: 7.90. Measured: C: 74.63, H: 8.35, N: 7.86. The analytical Data (NMR) matched those reported in the literature.²⁷⁹

Synthesis of 4-methyl-N-phenyl-Benzenamine **3da**



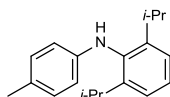
[CAS: 620-84-8]

Compound **3da** was prepared following the general procedure for the amination of 4-chlorotoluene (127 mg, 1.00 mmol) with aniline (103 mg, 1.10 mmol) and isolated as yellow solid (32.8 mg, 0.179 mmol, 18%). Yield after stirring for 4 h: 154 mg, 0.843 mmol, 84%.

m.p.: 85-86 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.17 - 7.34 (m, 3 H), 6.95 - 7.16 (m, 5 H), 6.83 - 6.95 (m, 1 H), 5.78 (br. s., 1 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ = 143.9 (s),

140.3 (s), 130.9 (s), 129.8 (s), 129.3 (s), 120.3 (s), 118.9 (s), 116.8 (s), 20.7 (s) ppm. MS (EI, 70 eV) m/z (%): 182.9 (100) [M^+], 182.0 (66), 167.0 (14), 90.9 (19), 76.9 (25), 64.9 (12), 51.0 (17). IR: $\tilde{\nu}$ = 3393 (m), 3028 (w), 2920 (w), 1593 (s), 1496 (s), 1269 (s), 1162 (m), 743 (s), 692 (s), 503 (m) cm^{-1} . CHN: Calculated: C: 85.21, H: 7.15, N: 7.64. Measured: C: 85.10, H: 7.02, N: 7.49. The analytical Data (NMR) matched those reported in the literature.²⁸⁶

Synthesis of 2,6-bis(1-methylethyl)-N-(4-methylphenyl)-Benzenamine 3ea

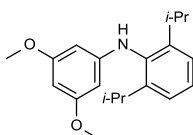


[CAS: 384344-08-5]

Compound **3ea** was prepared following the general procedure for the amination of 4-chlorotoluene (127 mg, 1.00 mmol) with 2,6-diisopropylaniline (217 mg, 1.10 mmol) and isolated as orange oil (114 mg, 0.424 mmol, 42%). Yield after stirring for 4 h: 215 mg, 0.804 mmol, 80%).

^1H NMR (300 MHz, CDCl_3) δ = 7.28 - 7.51 (m, 3 H), 6.97 - 7.19 (m, 2 H), 6.40 - 6.68 (m, 2 H), 5.16 (s, 1 H), 3.11 - 3.52 (m, 2 H), 2.32 - 2.41 (m, 3 H), 1.07 - 1.47 (m, 12 H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ = 147.3 (s), 145.8 (s), 135.5 (s), 129.7 (s), 126.9 (s), 126.7 (s), 123.7 (s), 113.0 (s), 28.1 (s), 23.8 (s), 20.4 (s) ppm. MS (EI, 70 eV) m/z (%): 267.15 (100) [M^+], 252.15 (82), 222.1 (22), 210.1 (18), 194.05 (39), 162.05 (18), 160.05 (34). IR: $\tilde{\nu}$ = 3397 (m), 3016 (w), 2961 (m), 2866 (m), 1616 (m), 1511 (s), 1464 (m), 1295 (m), 803 (m), 503 (m) cm^{-1} . CHN: Calculated: C: 85.34, H: 9.42, N: 5.24. Measured: C: 86.42, H: 8.97, N: 5.61. The analytical Data (NMR) matched those reported in the literature.²⁸⁴

Synthesis of N-[2,6-bis(1-methylethyl)phenyl]-3,5-dimethoxy-Benzenamine 3ej



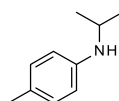
Compound **3ej** was prepared following the general procedure for the amination of 5-chloro-1,3-dimethoxybenzene (178 mg, 1.00 mmol) with 2,6-diisopropylaniline (217 mg, 1.10 mmol) and isolated as red oil (223 mg, 0.711 mmol, 71%).

^1H NMR (300 MHz, CDCl_3) δ = 7.25 - 7.33 (m, 1 H), 7.18 - 7.24 (m, 2 H), 5.90 (t, J = 2.2 Hz, 1 H), 5.69 (d, J = 2.0 Hz, 2 H), 5.13 (br. s., 1 H), 3.71 (s, 6 H), 3.09 - 3.33 (m, 2 H), 1.17 (d, J = 7.0 Hz, 12 H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ = 161.7 (s), 150.2 (s), 147.6 (s), 134.8

EXPERIMENTELLER TEIL

(s), 127.4 (s), 123.8 (s), 91.9 (s), 90.1 (s), 55.1 (s), 28.2 (s), 23.9 (s) ppm. MS (EI, 70 eV) m/z (%): 312.8 (100) [M+], 298.0 (43), 269.9 (46), 255.9 (17), 228.0 (65), 186.0 (28), 162.0 (46). HRMS-ESI (m/z): [M+H⁺] calcd. for C₂₀H₂₇NO₂H⁺: 314.2120; found 314.2214. IR: $\tilde{\nu}$ = 3384 (m), 3067 (w), 2960 (m), 2867 (w), 1595 (s), 1455 (m), 1202 (m), 1148 (s), 1058 (m), 804 (m) cm⁻¹.

Synthesis of 4-methyl-N-(1-methylethyl)- Benzenamine **3fa**

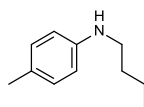


[CAS: 10436-75-6]

Compound **3fa** was prepared following the general procedure (stirring for 24 h) for the amination of 4-chlorotoluene (127 mg, 1.00 mmol) with isopropylamine (65.7 mg, 1.10 mmol) and isolated as yellow oil (16.7 mg, 0.112 mmol, 11%). Yield with 2 mol% catalyst after stirring for 24 h: 71.1 mg, 0.476 mmol, 48%.

¹H NMR (300 MHz, CDCl₃) δ = 7.00 (dd, J = 8.5, 0.6 Hz, 2 H), 6.43 - 6.64 (m, 2 H), 3.44 - 3.78 (m, 1 H), 3.15 (br. s., 1 H), 2.25 (s, 3 H), 1.22 (d, J = 6.2 Hz, 6 H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ = 145.2 (s), 129.7 (s), 126.2 (s), 113.6 (s), 44.5 (s), 23.0 (s), 20.3 (s) ppm. MS (EI, 70 eV) m/z (%): 148.9 (25) [M+], 135.0 (12), 134.0 (100), 106.0 (13), 90.9 (20), 76.9 (17), 65.0 (10). IR: $\tilde{\nu}$ = 3384 (w), 3096 (w), 2923 (m), 2854 (w), 1715 (m), 1599 (m), 1340 (s), 1176 (m), 813 (m), 738 (m), 699 (m) cm⁻¹. The analytical Data (NMR) matched those reported in the literature.²⁸⁷

Synthesis of N-butyl-4-methyl-Benzenamine **3ga**



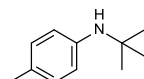
[CAS: 10387-24-3]

Compound **3ga** was prepared following the general procedure for the amination of 4-chlorotoluene (127 mg, 1.00 mmol) with n-butylamine (80.9 mg, 1.10 mmol) and isolated as yellow oil (45.4 mg, 0.278 mmol, 28%). Yield with 1 mol% catalyst after stirring for 24 h: 92.6 mg, 0.567 mmol, 57%.

¹H NMR (400 MHz, CDCl₃) δ = 7.00 (d, J = 8.3 Hz, 2 H), 6.48 - 6.63 (m, 2 H), 3.47 (br. s., 1 H), 3.11 (t, J = 7.1 Hz, 2 H), 2.25 (s, 3 H), 1.54 - 1.69 (m, 2 H), 1.35 - 1.53 (m, 2 H), 0.97 (t,

$J = 7.3$ Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3) $\delta = 146.3$ (s), 129.7 (s), 126.3 (s), 112.9 (s), 44.1 (s), 31.7 (s), 20.3 (s), 20.3 (s), 13.9 (s) ppm. MS (EI, 70 eV) m/z (%): 163.8 (100), 162.9 (58) $[\text{M}^+]$, 120.0 (64), 90.9 (10). IR: $\tilde{\nu} = 3406$ (w), 3017 (w), 2957 (m), 2861 (m), 1618 (m), 1519 (s), 1317 (m), 1181 (m), 804 (s), 506 (m) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁸⁸

Synthesis of N-(1,1-dimethylethyl)-4-Benzenamine 3ha

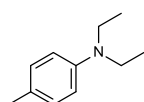


[CAS: 10219-31-5]

Compound **3ha** was prepared following the general procedure for the amination of 4-chlorotoluene (127 mg, 1.00 mmol) with *tert*-butylamine (82.1 mg, 1.10 mmol) and isolated as yellow oil (9.70 mg, 0.059 mmol, 6%). Yield after stirring for 24 h: 103 mg, 0.630 mmol, 63%.

^1H NMR (300 MHz, CDCl_3) $\delta = 6.91 - 7.09$ (m, 2 H), 6.63 - 6.80 (m, 2 H), 3.17 (br. s., 1 H), 2.28 (s, 3 H), 1.32 (s, 9 H) ppm. ^{13}C NMR (75 MHz, CDCl_3) $\delta = 144.1$ (s), 129.3 (s), 128.5 (s), 119.1 (s), 51.7 (s), 30.1 (s), 20.4 (s) ppm. MS (EI, 70 eV) m/z (%): 162.9 (41) $[\text{M}^+]$, 148.0 (100), 106.0 (47), 90.9 (9), 78.9 (8), 76.9 (13), 40.9 (7). IR: $\tilde{\nu} = 3409$ (w), 3020 (w), 2969 (m), 2867 (w), 1616 (m), 1513 (s), 1363 (m), 1217 (s), 807 (s) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁸⁹

Synthesis of N,N-diethyl-4-methyl-Benzenamine 3ia



[CAS: 613-48-9]

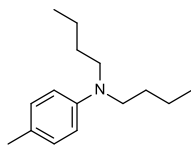
Compound **3ia** was prepared following the general procedure (stirring for 24 h) for the amination of 4-chlorotoluene (127 mg, 1.00 mmol) with diethylamine (80.9 mg, 1.10 mmol) and isolated as orange oil (33.9 mg, 0.208 mmol, 21%). Yield with 2 mol% catalyst after stirring for 24 h: 96.5 mg, 0.591 mmol, 59%.

^1H NMR (300 MHz, CDCl_3) $\delta = 7.08$ (d, $J = 8.4$ Hz, 2 H), 6.59 - 6.76 (m, 2 H), 3.36 (q, $J = 7.0$ Hz, 4 H), 2.29 (s, 3 H), 1.18 (t, $J = 7.1$ Hz, 6 H) ppm. ^{13}C NMR (75 MHz, CDCl_3) $\delta = 145.8$ (s), 129.7 (s), 124.8 (s), 112.6 (s), 44.5 (s), 20.1 (s), 12.5 (s) ppm. MS (EI, 70 eV) m/z (%): 162.9 (19) $[\text{M}^+]$, 148.9 (10), 148.0 (100), 120.0 (45), 118.0 (16), 90.9 (39), 65.0 (12). IR: $\tilde{\nu} =$

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3013 (w), 2968 (m), 2928 (w), 1619 (m), 1510 (s), 1263 (m), 800 (s) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁹⁰

Synthesis of N,N-dibutyl-4-methyl-Benzenamine 3ja



[CAS: 31144-33-9]

Compound **3ja** was prepared following the general procedure for the amination of 4-chlorotoluene (127 mg, 1.00 mmol) with di-n-butylamine (143 mg, 1.10 mmol) and isolated as yellow oil (48.0 mg, 0.219 mmol, 22%). Yield after stirring for 4 h: 141 mg, 0.643 mmol, 64%.

^1H NMR (300 MHz, CDCl_3) δ = 7.02 - 7.10 (m, 2 H), 6.60 - 6.68 (m, 2 H), 3.23 - 3.33 (m, 4 H), 2.29 (s, 3 H), 1.54 - 1.66 (m, 4 H), 1.31 - 1.47 (m, 4 H), 1.00 (t, $J=7.3$ Hz, 5 H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ = 146.2 (s), 129.7 (s), 124.3 (s), 112.2 (s), 51.0 (s), 29.4 (s), 20.4 (s), 20.1 (s), 14.0 (s) ppm. MS (EI, 70 eV) m/z (%): 219.15 (29) [M^+], 176.1 (100), 134.05 (69), 120.05 (40). IR: $\tilde{\nu}$ = 3007 (w), 2956 (m), 2861 (m), 1619 (m), 1519 (s), 1366 (m), 1187 (m), 798 (s), 507 (m) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.^[283]

7.5 A Highly Electron-Rich Ylide Functionalized Phosphine for Selective Monoarylation of Alkyl Ketones with Aryl Chlorides

7.5.1 General Methods

All reactions were performed in oven-dried glassware containing a Teflon-coated stirring bar and dry septum under argon atmosphere. Optimization reactions were monitored by GC analysis using *n*-tetradecane as internal standard. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded on Avance-III-300 spectrometers at 25 °C if not stated otherwise. $^{19}\text{F}\{^1\text{H}\}$ NMR spectra were recorded on Spinsolve Benchtop NMR (MAGRITTEK) spectrometers at 25 °C. All values of the chemical shift are in ppm regarding the δ -scale. GC analyses were carried out using an HP-5 capillary column (Phenyl methyl siloxane, 30 m \times 320 \times 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 on a Reveleris X2 (BÜCHI) Flash Chromatography-System using Reveleris packed columns (12 g). Mass spectrometric data were acquired on a GC-MS Agilent 5977B MSD. HRMS analyses and mass spectral data were acquired on a Waters GCT Premier CAB163 with a TOF mass analyzer. The MS ionization was achieved by EI+. Infrared spectra were recorded on Bruker Vertex 70 Spectrometer with Universal ATR Sampling Accessory. Melting points were measured on a Mettler Toledo MP70. Commercial substrates were used as received unless otherwise stated. Solvents were purchased (puriss p.A.) from commercial suppliers and dried by standard procedures.²⁹¹ All solvents and liquid reactants were degassed by Argon purge prior to use. Sodium and potassium hydroxide were dried by heating at 100 °C under high vacuum. Pd₂dba₃ was donated by Umicore. Pd(COD)Cl₂ was purchased from Sigma Aldrich. Ligand **L1** was synthesized as described in the literature.²⁹²

7.5.2 Preparation of catalyst stock solution

Inside a glovebox containing inert gas atmosphere, an oven-dried 20 mL vial was charged with the palladium precursor (0.1 mmol Pd per mL THF), the YPhos-ligand (0.2 mmol per mL THF) and THF. The resulting mixture was stirred at room temperature for 0.5 h (1.5 h for L2).

7.5.3 General procedure for the arylation

General procedure A (standard). Inside a glovebox containing inert gas atmosphere, an oven-dried 20 mL vial was charged with NaO^tBu (147 mg, 1.50 mmol), dry THF (2mL), an aryl chloride (1.00 mmol), a ketone (2.00 mmol) and catalyst stock solution with Pd(COD)Cl₂ and L1 (0.1 mL) and closed with a septum cap. The resulting mixture was stirred at 60 °C for 16 h.

EXPERIMENTELLER TEIL

After the reaction was complete, it was diluted with EtOAc (10 mL) and washed with brine (3×20 mL), then the aqueous phases were extracted with EtOAc (3×20 mL). The combined organic phases were dried over MgSO₄, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂, ethyl acetate/cyclohexane gradient), yielding the corresponding arylated ketone.

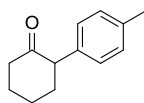
General procedure B (standard). Inside a glovebox containing inert gas atmosphere, an oven-dried 20 mL vial was charged with NaO^tBu (147 mg, 1.50 mmol), dry THF (2mL), an aryl chloride (1.00 mmol), a ketone (2.00 mmol) and catalyst stock solution with Pd₂dba₃ and L2 (0.1 mL) and closed with a septum cap. The resulting mixture was stirred at 60 °C for 16 h. After the reaction was complete, it was diluted with EtOAc (10 mL) and washed with brine (3×20 mL), then the aqueous phases were extracted with EtOAc (3×20 mL). The combined organic phases were dried over MgSO₄, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂, ethyl acetate/cyclohexane gradient), yielding the corresponding arylated ketone.

General procedure C (coupling of phenyl ethyl ketone). Inside a glovebox containing inert gas atmosphere, an oven-dried 20 mL vial was charged with NaO^tBu (147 mg, 1.50 mmol), dry THF (2mL), an aryl chloride (1.00 mmol), phenyl ethyl ketone (201 mg, 2.00 mmol) and catalyst stock solution with Pd(COD)Cl₂ and L1 (0.05 mL) and closed with a septum cap. The resulting mixture was stirred at room temperature for 16 h. After the reaction was complete, it was diluted with EtOAc (10 mL) and washed with brine (3×20 mL), then the aqueous phases were extracted with EtOAc (3×20 mL). The combined organic phases were dried over MgSO₄, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂, ethyl acetate/cyclohexane gradient), yielding the corresponding arylated ketone.

General procedure D (coupling of acetone). Inside a glovebox containing inert gas atmosphere, an oven-dried 20 mL vial was charged with LiO^tBu (121 mg, 1.50 mmol), dry THF (2mL), 4-chlorotoluene (1.00 mmol), acetone (581 mg, 10.00 mmol) and catalyst stock solution with Pd₂dba₃ (0.1 mL) and closed with a septum cap. The resulting mixture was stirred at 80 °C for 16 h. After the reaction was complete, it was diluted with EtOAc (10 mL) and washed with brine (3×20 mL), then the aqueous phases were extracted with EtOAc (3×20 mL). The combined organic phases were dried over MgSO₄, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂, ethyl acetate/cyclohexane gradient), yielding the corresponding arylated ketone.

7.5.4 Synthesis and characterization of products

Synthesis of 2-(4-methylphenyl)cyclohexanone 3aa



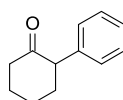
[CAS: 52776-14-4]

Compound **3aa** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a colorless solid (128 mg, 0.68 mmol, 68%).

Compound **3aa** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a colorless solid (113 mg, 0.60 mmol, 60%) after 7 h.

m.p.: 48 – 50 °C. ¹H NMR (300 MHz, CDCl₃) δ = 7.17 (d, *J* = 7.9 Hz, 2 H), 7.05 (d, *J* = 7.9 Hz, 2 H), 3.65 - 3.52 (m, 1 H), 2.60 - 2.38 (m, 2 H), 2.35 (s, 3 H), 2.32 - 2.22 (m, 1 H), 2.19 - 2.10 (m, 1 H), 2.09 - 1.91 (m, 2 H), 1.89 - 1.72 (m, 2 H) ppm. ¹³C {¹H} NMR (75 MHz, CDCl₃) δ = 210.5, 136.4, 135.7, 129.1, 128.3, 57.0, 42.1, 35.1, 27.8, 25.3, 21.1 ppm. IR: ν̄ = 3027 (w), 2937 (m), 2858 (m), 1700 (s), 1517 (m), 1423 (m), 1122 (m), 804 (s), 539 (s) cm⁻¹. MS (EI-TOF) *m/z* (%) 187.8 (59) [M⁺], 144.9 (50), 144.0 (100), 131.1 (89), 129.0 (45), 117.1 (55), 91.0 (57). HRMS (EI-TOF): [M + H]⁺ calcd. for C₁₃H₁₇O: 189.1279; found: 189.1275. The analytical data (NMR) matched those reported in the literature.²⁹³

Synthesis of 2-phenylcyclohexanone 3ab



[CAS: 1444-65-1]

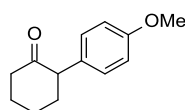
Compound **3ab** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with chlorobenzene (113 mg, 1.00 mmol) and isolated as a colorless solid (112 mg, 0.64 mmol, 64%).

Compound **3ab** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with chlorobenzene (113 mg, 1.00 mmol) and isolated as a colorless solid (93 mg, 0.53 mmol, 53%) after 7 h.

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m.p.: 57 – 59 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.39 - 7.31 (m, 2 H), 7.30 - 7.23 (m, 1 H), 7.18 - 7.12 (m, 2 H), 3.67 - 3.57 (m, 1 H), 2.61 - 2.40 (m, 2 H), 2.35 - 2.23 (m, 1 H), 2.23 - 2.10 (m, 1 H), 2.10 - 1.95 (m, 2 H), 1.93 - 1.78 (m, 2 H) ppm. ^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 210.2, 138.7, 128.5, 128.3, 126.9, 57.4, 42.2, 35.1, 27.8, 25.3 ppm. IR: $\tilde{\nu}$ = 3030 (w), 2947 (m), 2930 (m), 2868 (w), 1696 (s), 1445 (m), 1124 (m), 756 (s), 699 (s), 544 (s) cm^{-1} . MS (EI-TOF) m/z (%) 174.1 (45) [M^+], 131.0 (15), 130.05 (100), 117.05 (50), 115.05 (22), 104.1 (31), 91.05 (30). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{12}\text{H}_{15}\text{O}$: 175.1117; found: 175.1123. The analytical data (NMR) matched those reported in the literature.²⁹⁴

Synthesis of 2-(4-methoxyphenyl)cyclohexanone **3ac**



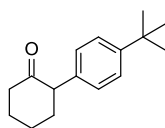
[CAS: 37087-68-6]

Compound **3ac** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 4-chloroanisole (143 mg, 1.00 mmol) and isolated as a light yellow solid (110 mg, 0.54 mmol, 54 %).

Compound **3ac** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 4-chloroanisole (143 mg, 1.00 mmol) and isolated as a light yellow solid (103 mg, 0.50 mmol, 50 %) after 7 h.

m.p.: 85 – 86 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.12 - 7.03 (m, 2 H), 6.93 - 6.85 (m, 2 H), 3.81 (s, 3 H), 3.57 (dd, J = 5.6, 12.0 Hz, 1 H), 2.59 - 2.39 (m, 2 H), 2.36 - 2.09 (m, 2 H), 2.09 - 1.93 (m, 2 H), 1.91 - 1.77 (m, 2 H) ppm. ^{13}C $\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 210.6, 158.4, 130.9, 129.4, 113.8, 56.6, 55.2, 42.2, 35.3, 27.8, 25.4 ppm. IR: $\tilde{\nu}$ = 3008 (w), 2948 (m), 2925 (m), 2858 (w), 1702 (s), 1614 (m), 1447 (s), 1249 (s), 1178 (s), 1066 (s), 809 (s), 543 (s) cm^{-1} . MS (EI-TOF) m/z (%) 204.1 (66) [M^+], 176.1 (18), 160.05 (15), 147.05 (100), 134.05 (27), 121.05 (33), 91.05 (21). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{13}\text{H}_{17}\text{O}_2$: 205.1223; found: 205.1222. The analytical data (NMR) matched those reported in the literature.²⁹⁵

Synthesis of 2-[4-(1,1-dimethylethyl)phenyl]cyclohexanone **3ad**



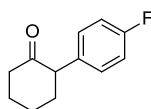
[CAS: 119046-91-2]

Compound **3ad** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 1-*tert*-butyl-4-chlorobenzene (169 mg, 1.00 mmol) and isolated as a light yellow solid (143 mg, 0.62 mmol, 62%).

Compound **3ad** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 1-*tert*-butyl-4-chlorobenzene (169 mg, 1.00 mmol) and isolated as a light yellow solid (151 mg, 0.65 mmol, 65%) after 7 h.

m.p.: 83 – 85 °C. ¹H NMR (300 MHz, CDCl₃) δ = 7.40 - 7.32 (m, 2 H), 7.13 - 7.04 (m, 2 H), 3.60 (dd, *J* = 11.7, 5.5 Hz, 1 H), 2.62 - 2.39 (m, 2 H), 2.26 (s, 1 H), 2.15 (d, *J* = 2.4 Hz, 1 H), 2.09 - 1.95 (m, 2 H), 1.89 - 1.77 (m, 2 H), 1.32 (s, 9 H) ppm. ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 210.6, 149.5, 135.6, 128.1, 125.3, 56.9, 42.2, 35.1, 34.4, 31.4, 27.8, 25.3 ppm. IR: $\tilde{\nu}$ = 3028 (w), 2952 (m), 2862 (w), 1699 (s), 1462 (w), 1268 (w), 1110 (m), 1024 (w), 828 (m), 578 (m) cm⁻¹. MS (EI-TOF) *m/z* (%) 230.2 (48) [M⁺], 216.15 (18), 215.15 (100), 187.15 (86), 186.15 (17), 129.05 (27), 91.05 (18). HRMS (EI-TOF): [M + H]⁺ calcd. for C₁₆H₂₃O: 231.1743; found: 231.1745. The analytical data (NMR) matched those reported in the literature.²⁹⁶

Synthesis of 2-(4-fluorophenyl)cyclohexanone **3ae**



[CAS: 59227-02-0]

Compound **3ae** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 1-chloro-4-fluorobenzene (131 mg, 1.00 mmol) and isolated as a light yellow solid (105 mg, 0.55 mmol, 55 %).

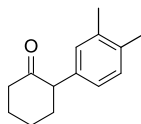
Compound **3ae** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 1-chloro-4-fluorobenzene (131 mg, 1.00 mmol) and isolated as a light yellow solid (39 mg, 0.20 mmol, 20 %).

m.p.: 54 – 57 °C. ¹H NMR (300 MHz, CDCl₃) δ = 7.16 - 7.07 (m, 2 H), 7.07 - 6.98 (m, 2 H), 3.61 (dd, *J* = 5.4, 11.7 Hz, 1 H), 2.59 - 2.38 (m, 2 H), 2.34 - 2.22 (m, 1 H), 2.22 - 2.11 (m, 1 H), 2.08 - 1.92 (m, 2 H), 1.91 - 1.76 (m, 2 H) ppm. ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 210.0, 161.8 (d, *J*_{C-F} = 244.9 Hz), 134.4 (d, *J*_{C-F} = 3.3 Hz), 130.0 (d, *J*_{C-F} = 7.7 Hz), 115.2 (d, *J*_{C-F} = 21.0 Hz), 56.7, 42.2, 35.4, 27.8, 25.4 ppm. ¹⁹F NMR (41 MHz, CDCl₃) δ = -114.17 ppm. IR: $\tilde{\nu}$ = 3044 (w), 2936 (m), 2936 (m), 2858 (w), 1702 (s), 1601 (m), 1510 (s), 1162 (m), 820 (s), 539 (s), 504 (s) cm⁻¹. MS (EI-TOF) *m/z* (%) 192.05 (42) [M⁺], 148.05 (100), 147.05 (14), 135.05 (70), 133.05 (15), 122.05 (43), 109.05 (32). HRMS (EI-TOF): [M + H]⁺ calcd. for

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C₁₂H₁₄O: 193.1023; found: 193.1024. The analytical data (NMR) matched those reported in the literature.²⁹⁵

Synthesis of 2-(3,4-dimethylphenyl)cyclohexanone 3af



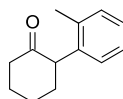
[CAS: 854717-86-5]

Compound **3af** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 4-chloro-1,2-dimethylbenzene (143 mg, 1.00 mmol) and isolated as a yellow oil (142 mg, 0.70 mmol, 70%).

Compound **3af** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 4-chloro-1,2-dimethylbenzene (143 mg, 1.00 mmol) and isolated as a yellow oil (130 mg, 0.64 mmol, 64%) after 7 h.

¹H NMR (300 MHz, CDCl₃) δ = 7.12 (d, J = 7.7 Hz, 1 H), 6.97 - 6.84 (m, 2 H), 3.64 - 3.48 (m, 1 H), 2.61 - 2.37 (m, 2 H), 2.33 - 2.10 (m, 8 H), 2.10 - 1.93 (m, 2 H), 1.93 - 1.73 (m, 2 H) ppm. ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 210.6, 136.4, 136.2, 135.1, 129.8, 129.6, 125.8, 57.0, 42.1, 35.0, 27.8, 25.3, 19.8, 19.4 ppm. IR: $\tilde{\nu}$ = 3006 (w), 2933 (m), 2860 (m), 1709 (s), 1505 (m), 1447 (m), 1123 (m), 1067 (m), 812 (m), 584 (m) cm⁻¹. MS (EI-TOF) m/z (%) 202.15 (100) [M⁺], 159.1 (80), 158.1 (65), 145.1 (80), 143.05 (48), 132.1 (29), 105.05 (33). HRMS (EI-TOF): [M + H]⁺ calcd. for C₁₄H₁₉O: 203.1430; found: 203.1432. The analytical data (NMR) matched those reported in the literature.²⁹⁷

Synthesis of 2-(2-methylphenyl)cyclohexanone 3ag



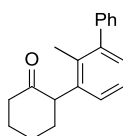
[CAS: 63882-42-8]

Compound **3ag** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 2-chlorotoluene (127 mg, 1.00 mmol) and isolated as a light yellow solid (138 mg, 0.73 mmol, 73%).

Compound **3ag** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 2-chlorotoluene (127 mg, 1.00 mmol) and isolated as a light yellow solid (94 mg, 0.50 mmol, 50%).

m.p.: 53 – 54 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.26 - 7.10 (m, 4 H), 3.80 (dd, J = 12.6, 5.2 Hz, 1 H), 2.67 - 2.44 (m, J = 2.3, 1.4 Hz, 2 H), 2.36 - 2.16 (m, 5 H), 2.14 - 1.98 (m, 2 H), 1.95 - 1.74 (m, 2 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 210.0, 136.1, 130.3, 127.6, 126.8, 126.0, 53.8, 42.5, 34.2, 27.8, 25.9, 19.7 ppm. IR: $\tilde{\nu}$ = 3017 (w), 2963 (w), 2935 (m), 2861 (w), 1696 (s), 1493 (w), 1303 (w), 1129 (m), 1072 (w), 756 (m), 562 (m) cm^{-1} . MS (EI-TOF) m/z (%) 188.15 (100) [M^+], 145.1 (43), 144.1 (61), 131.1 (66), 129.1 (64), 117.1 (60), 91.05 (43). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{13}\text{H}_{17}\text{O}$: 189.1274; found: 189.1275. The analytical data (NMR) matched those reported in the literature.²⁹⁸

*Synthesis of 2-(2-methyl[1,1'-biphenyl]-3-yl)cyclohexanone **3ah***

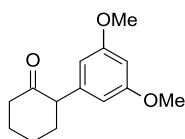


Compound **3ah** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 3-chloro-2-methylbiphenyl (211 mg, 1.00 mmol) and isolated as a light yellow solid (234 mg, 0.89 mmol, 89%).

Compound **3ah** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 3-chloro-2-methylbiphenyl (211 mg, 1.00 mmol) and isolated as a light yellow solid (138 mg, 0.52 mmol, 52%).

m.p.: 99 – 100 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.49 - 7.26 (m, 6 H), 7.23 - 7.14 (m, 2 H), 4.04 - 3.83 (m, 1 H), 2.68 - 2.49 (m, 2 H), 2.43 - 2.11 (m, 4 H), 2.11 (s, 3 H), 1.99 - 1.81 (m, 2 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 210.1, 142.7, 142.6, 138.0, 133.5, 129.4, 128.7, 127.9, 126.8, 126.6, 125.3, 54.2, 42.6, 34.6, 27.8, 25.9, 16.8 ppm. IR: $\tilde{\nu}$ = 3047 (w), 2968 (w), 2936 (m), 2861 (w), 1705 (s), 1447 (m), 1298 (m), 1195 (m), 1131 (m), 793 (s), 764 8 (s), 731 (s) cm^{-1} . MS (EI-TOF) m/z (%) 264.15 (100) [M^+], 221.1 (24), 205.1 (30), 179.05 (28), 178.05 (30), 167.05 (32), 165.05 (44). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{19}\text{H}_{21}\text{O}$: 265.1587; found: 265.1584.

*Synthesis of 2-(3,5-dimethoxyphenyl)cyclohexanone **3ai***



[CAS: 89261-31-4]

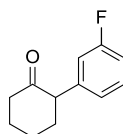
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Compound **3ai** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 5-chloro-1,3-dimethoxybenzene (178 mg, 1.00 mmol) and isolated as a yellow solid (140 mg, 0.60 mmol, 60%).

Compound **3ai** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 5-chloro-1,3-dimethoxybenzene (178 mg, 1.00 mmol) and isolated as a yellow solid (141 mg, 0.60 mmol, 60%).

m.p.: 48 – 49 °C. ^1H NMR (300 MHz, CDCl_3) δ = 6.39 - 6.36 (m, 1 H), 6.31 (d, J = 2.2 Hz, 2 H), 3.78 (s, 6 H), 3.61 - 3.51 (m, 1 H), 2.59 - 2.40 (m, 2 H), 2.25 (d, J = 2.0 Hz, 1 H), 2.18 - 2.09 (m, 1 H), 2.08 - 1.96 (m, 2 H), 1.88 - 1.76 (m, 2 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 210.1, 160.6, 141.0, 106.7, 98.8, 57.5, 55.2, 42.1, 34.7, 27.7, 25.1 ppm. IR: $\tilde{\nu}$ = 3092 (w), 2998 (w), 2861 (w), 1707 (s), 1593 (s), 1458 (m), 1203 (s), 1149 (s), 1058 (s), 829 (s), 693 (m) cm^{-1} . MS (EI-TOF) m/z (%) 234.1 (100) [M^+], 191.1 (20), 178.1 (30), 177.05 (33), 165.1 (77), 152.05 (28), 91.05 (18). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{14}\text{H}_{19}\text{O}_3$: 235.1329; found: 235.1330. The analytical data (NMR) matched those reported in the literature.²⁹⁹

Synthesis of 2-(3-fluorophenyl)cyclohexanone 3aj



[CAS: 857872-72-1]

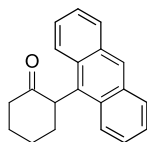
Compound **3aj** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 1-chloro-3-fluorobenzene (132 mg, 1.00 mmol) and isolated as a yellow solid (100 mg, 0.52 mmol, 52%).

Compound **3aj** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 1-chloro-3-fluorobenzene (132 mg, 1.00 mmol) and isolated as a yellow solid (45 mg, 0.23 mmol, 23%).

m.p.: 38 – 40 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.34 - 7.27 (m, 1 H), 7.00 - 6.83 (m, 3 H), 3.62 (dd, J = 11.9, 5.9 Hz, 1 H), 2.60 - 2.40 (m, 2 H), 2.35 - 2.23 (m, 1 H), 2.23 - 2.10 (m, 1 H), 2.09 - 1.93 (m, 2 H), 1.93 - 1.74 (m, 2 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 209.5, 164.4 (d, $J_{\text{C-F}}$ = 254.9 Hz), 141.2 (d, $J_{\text{C-F}}$ = 7.7 Hz), 129.7 (d, $J_{\text{C-F}}$ = 8.3 Hz), 124.2 (d, $J_{\text{C-F}}$ = 2.8 Hz), 115.5 (d, $J_{\text{C-F}}$ = 21.6 Hz), 113.7 (d, $J_{\text{C-F}}$ = 21.0 Hz), 57.0, 42.1, 35.0, 27.7, 25.2 ppm. ^{19}F NMR (41 MHz, CDCl_3) δ = -114.20 ppm. IR: $\tilde{\nu}$ = 3060 (w), 2941 (m), 2861 (w), 1700 (s), 1588 (s), 1446 (s), 1143 (m), 1125 (m), 769 (s), 693 (s), 526 (s) cm^{-1} . MS (EI-TOF) m/z (%) 192.1

(46) $[M^+]$, 148.1 (100), 147.1 (26), 135.05 (39), 133.05 (18), 122.05 (38), 109.05 (27). HRMS (EI-TOF): $[M + H]^+$ calcd. for $C_{12}H_{14}FO$: 193.1023; found: 193.1023. The analytical data (NMR) matched those reported in the literature.³⁰⁰

*Synthesis of 2-(9-anthracenyl)cyclohexanone **3ak***

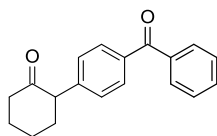


[CAS: 111189-53-8]

Compound **3ak** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 9-chloroanthracene (222 mg, 1.00 mmol) and isolated as a yellow solid (110 mg, 0.40 mmol, 40%).

m.p.: 184 – 186 °C. 1H NMR (300 MHz, $CDCl_3$) δ = 8.43 (s, 1 H), 8.10 - 7.99 (m, 2 H), 7.99 - 7.83 (m, 2 H), 7.53 - 7.40 (m, 4 H), 4.95 - 4.84 (m, 1 H), 2.98 - 2.83 (m, 1 H), 2.78 - 2.47 (m, 2 H), 2.42 - 2.29 (m, 2 H), 2.27 - 2.11 (m, 2 H), 2.09 - 1.90 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ = 209.2, 132.4, 131.9, 129.6, 129.3, 127.5, 125.4, 124.6, 51.3, 41.8, 33.4, 25.6, 25.4 ppm. IR: $\tilde{\nu}$ = 3053 (w), 2943 (m), 2890 (w), 2860 (w), 1697 (s), 1446 (m), 1120 (m), 889 (s), 787 (m), 734 (s), 505 (s) cm^{-1} . MS (EI-TOF) m/z (%) 275.1 (22), 274.1 (100) $[M^+]$, 217.1 (24), 215.1 (27), 203.05 (28), 202.05 (41), 178.05 (81). HRMS (EI-TOF): $[M + H]^+$ calcd. for $C_{20}H_{19}O$: 275.1430; found: 275.1430. The analytical data (NMR) matched those reported in the literature.³⁰¹

*Synthesis of 2-(4-benzoylphenyl)cyclohexanone **3al***



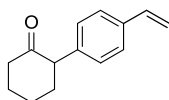
Compound **3al** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 4-chlorobenzophenone (219 mg, 1.00 mmol) and isolated as a yellow solid (128 mg, 0.46 mmol, 46%).

Compound **3al** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 4-chlorobenzophenone (219 mg, 1.00 mmol) and isolated as a yellow solid (138 mg, 0.50 mmol, 50%).

EXPERIMENTELLER TEIL

m.p.: 115 – 117 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.87 - 7.77 (m, 4 H), 7.63 - 7.55 (m, 1 H), 7.52 - 7.44 (m, 2 H), 7.30 - 7.24 (m, 2 H), 3.71 (dd, J = 12.2, 5.8 Hz, 1 H), 2.63 - 2.44 (m, 2 H), 2.38 - 2.26 (m, 1 H), 2.26 - 2.14 (m, 1 H), 2.13 - 1.97 (m, 2 H), 1.95 - 1.76 (m, 2 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 209.5, 196.3, 143.7, 137.7, 136.1, 132.2, 130.2, 130.0, 128.6, 128.2, 57.4, 42.2, 35.2, 27.7, 25.3 ppm. IR: $\tilde{\nu}$ = 3060 (w), 2931 (m), 2861 (w), 1705 (s), 1646 (s), 1446 (m), 1313 (m), 1279 (s), 1126 (m), 926 (s), 699 (s), 646 (s) cm^{-1} . MS (EI-TOF) m/z (%) 278.1 (91) [M^+], 234.1 (47), 233.1 (28), 173.05 (49), 129.05 (26), 105.0 (100), 77.0 (44). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{19}\text{H}_{19}\text{O}_2$: 279.1380; found: 279.1377.

*Synthesis of 2-(4-ethenylphenyl)cyclohexanone **3am***



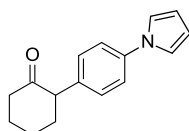
[CAS: 1391245-63-8]

Compound **3am** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 4-chlorostyrene (143 mg, 1.00 mmol) and isolated as a beige solid (139 mg, 0.69 mmol, 69%).

Compound **3am** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 4-chlorostyrene (143 mg, 1.00 mmol) and isolated as a beige solid (96 mg, 0.48 mmol, 48%).

m.p.: 53 – 54 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.44 - 7.33 (m, 2 H), 7.18 - 7.05 (m, 2 H), 6.71 (dd, J = 17.6, 10.8 Hz, 1 H), 5.73 (dd, J = 17.6, 1.1 Hz, 1 H), 5.35 - 5.07 (m, 1 H), 3.74 - 3.50 (m, 1 H), 2.62 - 2.38 (m, 2 H), 2.35 - 2.10 (m, 2 H), 2.09 - 1.93 (m, 2 H), 1.93 - 1.72 (m, 2 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 210.2, 138.4, 136.6, 136.3, 128.7, 126.2, 113.5, 57.1, 42.2, 35.0, 27.8, 25.3 ppm. IR: $\tilde{\nu}$ = 3082 (w), 3003 (w), 2935 (m), 2859 (m), 1700 (s), 1514 (m), 1447 (m), 1122 (s), 903 (s), 865 (s), 822 (s), 539 (s) cm^{-1} . MS (EI-TOF) m/z (%) 200.1 (100) [M^+], 156.1 (79), 143.05 (59), 130.05 (52), 129.05 (36), 128.05 (73), 115.05 (47). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{14}\text{H}_{17}\text{O}$: 201.1274; found: 201.1276.

*Synthesis of 2-[4-(1H-pyrrol-1-yl)phenyl]cyclohexanone **3an***



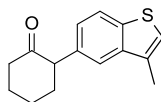
[CAS: 1391338-84-3]

Compound **3an** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 1-(4-chlorophenyl)-1*H*-pyrrole (181 mg, 1.00 mmol) and isolated as a beige solid (142 mg, 0.59 mmol, 59%).

Compound **3an** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 1-(4-chlorophenyl)-1*H*-pyrrole (181 mg, 1.00 mmol) and isolated as a beige solid (110 mg, 0.46 mmol, 46%).

m.p.: 108 – 110 °C. ¹H NMR (300 MHz, CDCl₃) δ = 7.41 - 7.34 (m, 2 H), 7.26 - 7.17 (m, 2 H), 7.08 (t, *J* = 2.2 Hz, 2 H), 6.35 (t, *J* = 2.2 Hz, 2 H), 3.65 (dd, *J* = 5.8, 12.6 Hz, 1 H), 2.62 - 2.43 (m, 2 H), 2.37 - 2.27 (m, 1 H), 2.25 - 2.15 (m, 1 H), 2.11 - 1.96 (m, 2 H), 1.94 - 1.78 (m, 2 H) ppm. ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 210.1, 139.6, 136.2, 129.6, 120.6, 119.4, 110.2, 56.8, 42.2, 35.3, 27.8, 25.4 ppm. IR: $\tilde{\nu}$ = 3043 (w), 2936 (m), 2862 (w), 1707 (s), 1522 (s), 1325 (s), 1068 (s), 810 (s), 730 (s), 559 (s) cm⁻¹. MS (EI-TOF) *m/z* (%) 240.15 (18) [M⁺], 239.1 (100), 211.15 (30), 182.1 (61), 169.1 (27), 156.05 (32), 115.05 (22). HRMS (EI-TOF): [M + H]⁺ calcd. for C₁₆H₁₈NO: 240.1383; found: 240.1383.

Synthesis of 2-(3-methylbenzothiophen-5-yl)cyclohexanone 3ao



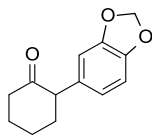
Compound **3ao** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 5-chloro-3-methylbenzothiophene (188 mg, 1.00 mmol) and isolated as a beige solid (156 mg, 0.64 mmol, 64%).

Compound **3ao** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 5-chloro-3-methylbenzothiophene (188 mg, 1.00 mmol) and isolated as a beige solid (117 mg, 0.48 mmol, 48%).

m.p.: 66 – 68 °C. ¹H NMR (300 MHz, CDCl₃) δ = 7.83 (d, *J* = 8.3 Hz, 1 H), 7.54 - 7.45 (m, 1 H), 7.19 - 7.11 (m, 1 H), 7.10 - 7.03 (m, 1 H), 3.78 (dd, *J* = 5.6, 12.2 Hz, 1 H), 2.66 - 2.47 (m, 2 H), 2.44 (s, 3 H), 2.41 - 2.30 (m, 1 H), 2.29 - 2.11 (m, 2 H), 2.11 - 2.01 (m, 1 H), 1.98 - 1.82 (m, 2 H) ppm. ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 210.5, 139.8, 138.9, 134.6, 131.9, 125.0, 122.6, 121.8, 121.4, 57.5, 42.2, 35.5, 27.8, 25.4, 13.9 ppm. IR: $\tilde{\nu}$ = 3050 (w), 2927 (m), 2854 (m), 1704 (s), 1445 (s), 1123 (m), 765 (s), 730 (s), 423 (m) cm⁻¹. MS (EI-TOF) *m/z* (%) 244.1 (100) [M⁺], 216.1 (31), 200.05 (29), 187.05 (71), 174.05 (27), 173.05 (33), 161.05 (38). HRMS (EI-TOF): [M + H]⁺ calcd. for C₁₅H₁₇OS: 245.0995; found: 245.0995.

EXPERIMENTELLER TEIL

Synthesis of 2-(1,3-benzodioxol-5-yl)cyclohexanone **3ap**



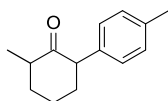
[CAS: 63765-11-7]

Compound **3ap** was prepared following the general procedure **A** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 5-chloro-1,3-benzodioxole (160 mg, 1.00 mmol) and isolated as a beige solid (91 mg, 0.42 mmol, 42%).

Compound **3ap** was prepared following the general procedure **B** for the arylation of cyclohexanone (196 mg, 2.00 mmol) with 5-chloro-1,3-benzodioxole (160 mg, 1.00 mmol) and isolated as a beige solid (61 mg, 0.28 mmol, 28%).

m.p.: 91 – 93 °C. ^1H NMR (300 MHz, CDCl_3) δ = 6.78 (d, J = 7.9 Hz, 1 H), 6.65 (d, J = 1.8 Hz, 1 H), 6.59 (dd, J = 8.1, 1.8 Hz, 1 H), 5.94 (s, 2 H), 3.54 (dd, J = 11.6, 5.2 Hz, 1 H), 2.59 - 2.37 (m, 2 H), 2.32 - 2.09 (m, 2 H), 2.06 - 1.90 (m, 2 H), 1.89 - 1.77 (m, 2 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 210.4, 147.6, 146.4, 132.6, 121.5, 109.0, 108.2, 100.9, 57.1, 42.2, 35.4, 27.8, 25.4 ppm. IR: $\tilde{\nu}$ = 3079 (w), 2945 (m), 2929 (m), 2854 (w), 1704 (s), 1496 (s), 1444 (s), 1256 (s), 1032 (s), 933 (s), 803 (s), 788 (s), 529 (s) cm^{-1} . MS (EI-TOF) m/z (%) 218.1 (100) [M^+], 174.05 (24), 161.05 (49), 148.05 (31), 135.0 (36), 131.05 (66), 103.05 (26). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{13}\text{H}_{15}\text{O}_3$: 219.1016; found: 219.1019. The analytical data (NMR) matched those reported in the literature.²⁹⁸

Synthesis of 2-methyl-6-(4-methylphenyl)cyclohexanone **3ba**



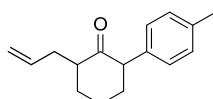
Compound **3ba** was prepared following the general procedure **A** for the arylation of 2-methylcyclohexanone (229 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as an orange brown solid (113 mg, 0.56 mmol, 56%).

Compound **3ba** was prepared following the general procedure **B** for the arylation of 2-methylcyclohexanone (229 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as an orange brown solid (58 mg, 0.29 mmol, 29%).

m.p.: 38 – 40 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.15 (d, J = 7.9 Hz, 2 H), 7.08 - 6.97 (m, 2 H), 3.69 - 3.48 (m, 1 H), 2.70 - 2.48 (m, 1 H), 2.34 (s, 3 H), 2.31 - 2.14 (m, 2 H), 2.09 - 1.82

(m, 3 H), 1.60 - 1.51 (m, 1 H), 1.07 (d, $J = 6.6$ Hz, 3 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) $\delta = 211.4, 136.3, 135.8, 128.9, 128.5, 57.3, 45.8, 37.2, 36.4, 25.8, 21.1, 14.7$ ppm. IR: $\tilde{\nu} = 3024$ (w), 2968 (m), 2928 (s), 2859 (m), 1704 (s), 1515 (m), 1445 (m), 1124 (m), 1037 (s), 807 (s), 518 (s) cm^{-1} . MS (EI-TOF) m/z (%) 202.1 (76) [M^+], 144.1 (100), 131.05 (87), 129.05 (42), 118.05 (98), 117.05 (58), 105.05 (33). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{14}\text{H}_{19}$: 203.1430; found: 203.1432.

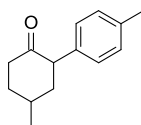
Synthesis of 2-(4-methylphenyl)-6-allyl-cyclohexanone 3ca



Compound **3ca** was prepared following the general procedure **A** for the arylation of 2-allylcyclohexanone (285 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a dark yellow oil (149 mg, 0.65 mmol, 65%).

Product + isomer: ^1H NMR (300 MHz, CDCl_3) $\delta = 7.19 - 7.12$ (m, 2 H), 7.11 - 6.99 (m, 2 H), 5.91 - 5.64 (m, 1 H), 5.11 - 4.94 (m, 2 H), 3.69 - 3.53 (m, 1 H), 2.66 - 2.45 (m, 2 H), 2.41 - 2.22 (m, 5 H), 2.20 - 1.80 (m, 4 H), 1.60 - 1.38 (m, 1 H) ppm. Main product: ^{13}C NMR (75 MHz, CDCl_3) $\delta = 210.4, 136.6, 135.6, 129.3, 128.5, 127.5, 116.2, 57.5, 50.8, 36.5, 34.6, 33.9, 25.7, 21.0$ ppm. Isomer: $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) $\delta = 212.9, 136.3, 135.8, 129.3, 128.9, 127.5, 116.5, 53.9, 48.2, 34.5, 32.4, 32.2, 25.7, 21.0$ ppm. IR: $\tilde{\nu} = 3074$ (w), 3009(w), 2975 (w), 2931 (m), 2860 (w), 1711 (s), 1516 (m), 1446 (m), 1042 (m), 910 (m), 809 (m) cm^{-1} . MS (EI-TOF) m/z (%) 228.15 (64) [M^+], 144.1 (100), 131.05 (55), 129.05 (55), 118.05 (85), 117.1 (68), 105.05 (70). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{16}\text{H}_{20}\text{O}$: 229.1587; found: 229.1588.

Synthesis of 4-methyl-2-(4-methylphenyl)cyclohexanone 3da



[CAS: 71268-38-7]

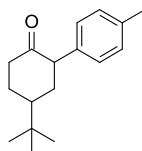
Compound **3da** was prepared following the general procedure **A** for the arylation of 4-methylcyclohexanone (229 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a dark yellow oil (138 mg, 0.68 mmol, 68%).

EXPERIMENTELLER TEIL

Compound **3da** was prepared following the general procedure **B** for the arylation of 4-methylcyclohexanone (229 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a dark yellow oil (111 mg, 0.55 mmol, 55%).

^1H NMR (300 MHz, CDCl_3) δ = 7.20 - 7.10 (m, 2 H), 7.08 - 6.96 (m, 2 H), 3.63 (dd, J = 13.4, 5.3 Hz, 1 H), 2.58 - 2.45 (m, 2 H), 2.34 (s, 3 H), 2.27 - 2.03 (m, 3 H), 1.82 - 1.65 (m, 1 H), 1.65 - 1.44 (m, 1 H), 1.06 (d, J = 6.2 Hz, 3 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 210.4, 136.4, 135.7, 129.0, 128.5, 56.3, 43.7, 41.6, 35.7, 32.4, 21.3, 21.1 ppm. IR: $\tilde{\nu}$ = 3023 (w), 2952 (m), 2923 (m), 2868 (w), 1713 (s), 1516 (m), 1456 (m), 1128 (m), 801 (s), 590 (m), 537 (s), 505 (m) cm^{-1} . MS (EI-TOF) m/z (%) 202.1 (80) [M^+], 158.1 (95), 145.1 (70), 143.05 (100), 131.05 (46), 118.05 (47), 117.05 (48). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{14}\text{H}_{19}\text{O}$: 203.1430; found: 203.1431. The analytical data (NMR) matched those reported in the literature.³⁰²

Synthesis of 4-(1,1-dimethylethyl)-2-(4-methylphenyl)cyclohexanone 3ea



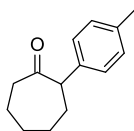
[CAS: 87240-65-1]

Compound **3ea** was prepared following the general procedure **A** for the arylation of 4-*tert*-butylcyclohexanone (312 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a colorless solid (156 mg, 0.64 mmol, 64%).

Compound **3ea** was prepared following the general procedure **B** for the arylation of 4-*tert*-butylcyclohexanone (312 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a colorless solid (128 mg, 0.52 mmol, 52%).

m.p.: 95 – 97 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.20 - 7.13 (m, 2 H), 7.08 - 7.00 (m, 2 H), 3.63 - 3.53 (m, 1 H), 2.57 - 2.44 (m, 2 H), 2.35 (s, 3 H), 2.31 - 2.15 (m, 2 H), 1.81 - 1.72 (m, 2 H), 1.69 - 1.58 (m, 1 H), 0.95 (s, 9 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 210.6, 136.5, 136.1, 129.1, 128.5, 56.6, 47.5, 41.7, 36.9, 32.5, 28.5, 27.6, 21.1 ppm. IR: $\tilde{\nu}$ = 3027 (w), 2964 (m), 2924 (m), 2866 (m), 1708 (s), 1515 (m), 1131 (m), 811 (s), 595 (m), 547 (s), 495 (s) cm^{-1} . MS (EI-TOF) m/z (%) 244.15 (62) [M^+], 187.1 (100), 169.1 (44), 144.1 (37), 143.05 (71), 105.05 (75), 57.1 (40). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{17}\text{H}_{25}\text{O}$: 245.1900; found: 245.1900. The analytical data (NMR) matched those reported in the literature.³⁰³

Synthesis of 2-(4-methylphenyl)cycloheptanone 3fa



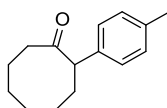
[CAS: 108011-18-3]

Compound **3fa** was prepared following the general procedure **A** for the arylation of cycloheptanone (227 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a light yellow solid (127 mg, 0.61 mmol, 61%).

Compound **3fa** was prepared following the general procedure **B** for the arylation of cycloheptanone (227 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a light yellow solid (41 mg, 0.20 mmol, 20%).

m.p.: 54 – 56 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.13 (s, 4 H), 3.69 (dd, J = 11.5, 4.1 Hz, 1 H), 2.76 - 2.63 (m, 1 H), 2.53 (td, J = 4.3, 3.0 Hz, 1 H), 2.33 (s, 3 H), 2.22 - 1.87 (m, 5 H), 1.57 (s, 1 H), 1.53 - 1.38 (m, 2 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 213.7, 137.3, 136.5, 129.2, 127.7, 58.4, 42.6, 31.9, 30.0, 28.5, 25.4, 21.0 ppm. IR: $\tilde{\nu}$ = 3043 (w), 3021 (w), 2965 (w), 2923 (m), 2845 (w), 1690 (s), 1512 (m), 1453 (w), 1321 (m), 1161 (m), 939 (m), 825 (m), 788 (s), 530 (s) cm^{-1} . MS (EI-TOF) m/z (%) 202.15 (58) [M^+], 131.1 (100), 118.1 (54), 117.1 (31), 115.05 (21), 105.1 (43), 91.1 (26). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{14}\text{H}_{19}\text{O}$: 203.1430; found: 203.1432. The analytical data (NMR) matched those reported in the literature.³⁰⁴

Synthesis of 2-(4-methylphenyl)cyclooctanone **3ga**



[CAS: 1278594-26-5]

Compound **3ga** was prepared following the general procedure **A** for the arylation of cyclooctanone (258 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a light yellow oil (172 mg, 0.80 mmol, 80%).

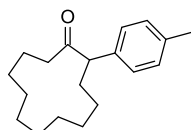
Compound **3ga** was prepared following the general procedure **B** for the arylation of cyclooctanone (258 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a light yellow oil (44 mg, 0.20 mmol, 20%).

^1H NMR (300 MHz, CDCl_3) δ = 7.26 - 7.20 (m, 2 H), 7.16 - 7.08 (m, 2 H), 3.75 (dd, J = 12.4, 3.0 Hz, 1 H), 2.68 - 2.56 (m, 1 H), 2.34 - 2.31 (m, 3 H), 2.30 - 2.19 (m, 1 H), 2.02 - 1.88 (m, 3

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H), 1.82 - 1.69 (m, 2 H), 1.69 - 1.31 (m, 5 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 216.6, 136.6, 136.3, 129.2, 127.6, 57.1, 40.0, 31.3, 27.0, 26.8, 26.7, 24.6, 21.0 ppm. IR: $\tilde{\nu}$ = 3022 (w), 2924 (m), 2855 (w), 1697 (s), 1512 (m), 1464 (m), 1326 (w), 1158 (w), 817 (s), 530 (m) cm^{-1} . MS (EI-TOF) m/z (%) 216.15 (34) [M^+], 131.05 (100), 118.05 (62), 117.05 (23), 115.0 (16), 105.05 (45), 91.05 (21). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{15}\text{H}_{21}\text{O}$: 217.1587; found: 217.1586. The analytical data (NMR) matched those reported in the literature.³⁰⁵

Synthesis of 2-(4-methylphenyl)cyclododecanone 3ha



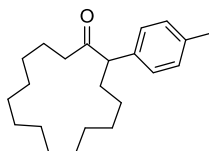
[CAS: 109318-91-4]

Compound **3ha** was prepared following the general procedure **A** for the arylation of cyclododecanone (368 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a beige solid (236 mg, 0.87 mmol, 87%).

Compound **3ha** was prepared following the general procedure **B** for the arylation of cyclododecanone (368 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a beige solid (191 mg, 0.70 mmol, 70%).

m.p.: 64 – 66 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.23 - 7.06 (m, 4 H), 4.05 - 3.94 (m, 1 H), 2.46 - 2.35 (m, 2 H), 2.32 (s, 3 H), 2.32 - 2.22 (m, 1 H), 1.98 - 1.82 (m, 1 H), 1.63 - 1.45 (m, 4 H), 1.43 - 1.28 (m, 12 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 212.1, 136.7, 136.7, 129.4, 127.9, 55.2, 39.7, 31.5, 25.6, 25.6, 24.8, 24.4, 24.2, 24.1, 22.8, 22.3, 21.0 ppm. IR: $\tilde{\nu}$ = 3025 (w), 2923 (s), 2854 (s), 1699 (s), 1512 (m), 1460 (m), 1023 (w), 813 (s) 547 (m), 507 (s) cm^{-1} . MS (EI-TOF) m/z (%) 272.2 (63) [M^+], 244.25 (22), 145.1 (25), 131.1 (71), 118.05 (80), 117.1 (25), 105.05 (100). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{19}\text{H}_{29}\text{O}$: 273.2213; found: 273.2209.

Synthesis of 2-(4-methylphenyl)cyclopentadecanone 3ia

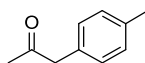


Compound **3ia** was prepared following the general procedure **A** for the arylation of cyclopentadecanone (453 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a beige solid (245 mg, 0.78 mmol, 78%, mono/diarylation = 17:1).

Compound **3ia** was prepared following the general procedure **A** for the arylation of cyclopentadecanone (453 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a beige solid (151 mg, 0.48 mmol, 48).

m.p.: 37 – 39 °C. ¹H NMR (300 MHz, CDCl₃) δ = 7.16 - 7.12 (m, 3 H), 6.90 - 6.81 (m, 1 H), 3.75 (dd, *J* = 9.4, 5.3 Hz, 1 H), 2.49 (ddd, *J* = 15.3, 7.8, 5.5 Hz, 1 H), 2.35 - 2.31 (m, 3 H), 2.30 - 2.21 (m, 2 H), 1.79 - 1.65 (m, 1 H), 1.63 - 1.52 (m, 2 H), 1.44 - 1.27 (m, 20 H) ppm. Monoarylation product: ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 211.9, 136.6, 136.4, 129.4, 128.0, 57.6, 41.3, 32.1, 27.6, 27.0, 26.8, 26.8, 26.4, 26.4, 26.2, 23.6, 21.0 ppm. Diarylation product: ¹³C NMR (75 MHz, CDCl₃) δ = 211.6, 136.2, 136.0, 128.9, 128.3, 57.8, 41.3, 32.6, 27.6, 27.0, 26.9, 26.7, 26.4, 26.4, 26.3, 23.6, 21.0 ppm. IR: $\tilde{\nu}$ = 3024 (w), 2928 (s), 2863 (m), 1696 (s), 1496 (m), 1471 (m), 1443 (m), 1249 (s), 1128 (m), 816 (s), 747 (m), 521 (s) cm⁻¹. MS (EI-TOF) *m/z* (%) 315.25 (22), 314.25 (91) [M⁺], 286.25 (26), 145.05 (28), 131.05 (65), 118.05 (73), 105.05 (100). HRMS (EI-TOF): [M + H]⁺ calcd. for C₂₂H₃₅O: 315.2682; found: 315.2681.

Synthesis of 1-(4-methylphenyl)propan-2-one 3ja



[CAS:2096-86-8]

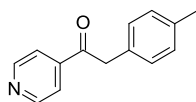
Compound **3ja** was prepared following the general procedure **D** for the arylation of acetone (581 mg, 10.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a colorless oil (68 mg, 0.46 mmol, 46%).

Compound **3ja** was prepared following the general procedure **D** for the arylation of acetone (581 mg, 10.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) at room temperature using L2 and isolated as a colorless oil (55 mg, 0.37 mmol, 37%).

¹H NMR (300 MHz, CDCl₃) δ = 7.19 - 7.06 (m, 4 H), 3.66 (s, 2 H), 2.35 (s, 3 H), 2.15 (s, 3 H) ppm. ¹³C{¹H} NMR (75 MHz, CDCl₃) δ = 206.7, 136.7, 131.2, 129.5, 129.2, 50.7, 29.1, 21.1 ppm. IR: $\tilde{\nu}$ = 3023 (w), 3004 (w), 2922 (w), 2863 (w), 1700 (s), 1512 (m), 1355 (m), 1157 (m), 785 (m), 529 (s), 489 (s) cm⁻¹. MS (EI-TOF) *m/z* (%) 148.05 (29) [M⁺], 106.05 (26), 105.05 (100), 103.0 (11), 79.0 (11), 77.0 (15). HRMS (EI-TOF): [M + H]⁺ calcd. for C₁₀H₁₃O: 149.0961; found: 149.0962. The analytical data (NMR) matched those reported in the literature.³⁰⁶

Synthesis of 2-(4-methylphenyl)-1-(4-pyridinyl)ethanone 3ka

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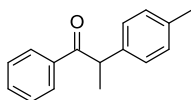


[CAS: 114443-33-3]

Compound **3ka** was prepared following the general procedure **A** for the arylation of 4-actelypyridine (250 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a light yellow solid (150 mg, 0.71 mmol, 71%).

m.p.: 119 – 121 °C. ^1H NMR (300 MHz, CDCl_3) δ = 8.85 - 8.74 (m, 2H), 7.80 - 7.72 (m, 2H), 7.15 (s, 4H), 4.24 (s, 2H), 2.33 (s, 3H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75MHz, CDCl_3) δ = 197.2, 151.0, 142.4, 137.0, 130.1, 129.6, 129.2, 121.5, 45.4, 21.0 ppm. IR: $\tilde{\nu}$ = 3027 (w), 2897 (w), 1697 (s), 1408 (s), 1336 (s), 1008 (m), 812 (s), 783 (s), 652 (s), 578 (s) cm^{-1} . MS (EI-TOF) m/z (%) 211.1 (18) [M^+], 183.1 (28), 106.05 (31), 105.05 (100), 79.05 (10), 78.05 (16), 77.05 (13). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{14}\text{H}_{14}\text{NO}$: 212.1070; found: 212.1070. The analytical data (NMR) matched those reported in the literature.³⁰⁷

Synthesis of 2-(4-methylphenyl)-1-phenyl-propan-1-one 3la

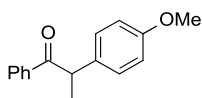


[CAS: 107271-15-8]

Compound **3la** was prepared following the general procedure **C** for the arylation of phenyl ethyl ketone (201 mg, 1.50 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a yellow oil (200 mg, 0.89 mmol, 89%).

Compound **3la** was prepared following the general procedure **B** for the arylation of phenyl ethyl ketone (201 mg, 1.50 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a yellow oil (63 mg, 0.28 mmol, 28%).

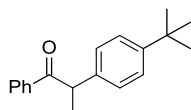
^1H NMR (300 MHz, CDCl_3) δ = 7.98 - 7.93 (m, 2 H), 7.51 - 7.44 (m, 1 H), 7.42 - 7.34 (m, 2 H), 7.21 - 7.15 (m, 2 H), 7.14 - 7.07 (m, 2 H), 4.66 (q, J = 6.8 Hz, 1 H), 2.29 (s, 3 H), 1.53 (d, J = 7.0 Hz, 3 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 200.4, 138.5, 136.5, 136.5, 132.7, 129.7, 128.8, 128.4, 127.6, 47.5, 21.0, 19.5 ppm. IR: $\tilde{\nu}$ = 3023 (w), 2974 (m), 2929 (m), 2869 (w), 1681 (s), 1512 (m), 1447 (s), 952 (s), 735 (s), 688 (s), 547 (s) cm^{-1} . MS (EI-TOF) m/z (%) 224.1 (9) [M^+], 119.1 (60), 117.1 (12), 106.05 (9), 105.05 (100), 91.05 (15), 77.05 (27). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{16}\text{H}_{17}\text{O}$: 225.1274; found: 225.1273. The analytical data (NMR) matched those reported in the literature.²⁹³

Synthesis of 2-(4-methoxyphenyl)-1-phenyl-propan-1-one 3lc

[CAS: 84839-92-9]

Compound **3lc** was prepared following the general procedure **C** for the arylation of phenyl ethyl ketone (201 mg, 1.50 mmol) with 4-chloroanisole (143 mg, 1.00 mmol) and isolated as a yellow oil (206 mg, 0.86 mmol, 86%).

^1H NMR (300 MHz, CDCl_3) δ = 8.00 - 7.92 (m, 2 H), 7.52 - 7.45 (m, 1 H), 7.43 - 7.35 (m, 2 H), 7.25 - 7.18 (m, 2 H), 6.88 - 6.80 (m, 2 H), 4.65 (q, J = 7.0 Hz, 1 H), 3.76 (s, 3 H), 1.52 (d, J = 6.8 Hz, 3 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 200.5, 158.5, 136.5, 133.5, 132.7, 128.8, 128.7, 128.4, 114.4, 55.2, 47.0, 19.5 ppm. IR: $\tilde{\nu}$ = 3028 (w), 2972 (w), 2931 (w), 2870 (w), 1679 (s), 1509 (s), 1032 (m), 932 (m), 734 (s), 689 (s) cm^{-1} . MS (EI-TOF) m/z (%) 240.1 (8) [M^+], 136.05 (13), 135.1 (100), 105.0 (26), 91.05 (9), 77.0 (18). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{16}\text{H}_{17}\text{O}_2$: 241.1223; found: 241.1223. The analytical data (NMR) matched those reported in the literature.²⁹⁵

Synthesis of 2-[4-(1,1-dimethylethyl)phenyl]-1-phenyl-propan-1-one 3ld

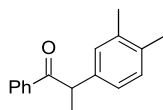
[CAS: 255836-61-4]

Compound **3ld** was prepared following the general procedure **C** for the arylation of phenyl ethyl ketone (201 mg, 1.50 mmol) with 1-*tert*-butyl-4-chlorobenzene (169 mg, 1.00 mmol) and isolated as a light yellow solid (240 mg, 0.90 mmol, 90%).

m.p.: 86 – 87 °C. ^1H NMR (300 MHz, CDCl_3) δ = 8.01 - 7.95 (m, 2 H), 7.53 - 7.46 (m, 1 H), 7.44 - 7.37 (m, 2 H), 7.34 - 7.29 (m, 2 H), 7.25 - 7.20 (m, 2 H), 4.69 (q, J = 6.8 Hz, 1 H), 1.53 (d, J = 6.8 Hz, 3 H), 1.28 (s, 9 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 200.5, 149.7, 138.2, 136.6, 132.7, 128.8, 128.4, 127.4, 125.8, 47.2, 34.4, 31.3, 19.5 ppm. IR: $\tilde{\nu}$ = 3026 (w), 2965 (m), 2931 (w), 2868 (w), 1677 (s), 1450 (m), 1004 (m), 951 (s), 755 (s), 710 (s), 573 (s) cm^{-1} . MS (EI-TOF) m/z (%) 266.1 (8) [M^+], 161.1 (91), 146.1 (16), 131.1 (18), 117.1 (5), 105.0 (100), 91.0 (8), 77.0 (25). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{19}\text{H}_{23}\text{O}$: 267.1743; found: 267.1741. The analytical data (NMR) matched those reported in the literature.³⁰⁸

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Synthesis of 2-(3,4-dimethylphenyl)-1-phenyl-propan-1-one 3lf

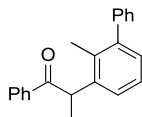


[CAS: 64394-39-4]

Compound **3lf** was prepared following the general procedure **C** for the arylation of phenyl ethyl ketone (201 mg, 1.50 mmol) with 4-chloro-1,2-dimethyl-benzene (143 mg, 1.00 mmol) and isolated as an orange brown solid (220 mg, 0.92 mmol, 92%).

m.p.: 63 – 64 °C. ^1H NMR (300 MHz, CDCl_3) δ = 8.01 - 7.93 (m, 2 H), 7.52 - 7.34 (m, 3 H), 7.09 - 6.99 (m, 3 H), 4.63 (q, J = 6.8 Hz, 1 H), 2.21 (d, J = 6.4 Hz, 6 H), 1.54 - 1.48 (m, 3 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 200.5, 138.9, 137.2, 136.6, 135.2, 132.6, 130.2, 128.8, 128.8, 128.4, 125.2, 47.5, 19.8, 19.6, 19.3 ppm. IR: $\tilde{\nu}$ = 3003 (w), 2978 (w), 2931 (w), 2867 (w), 1676 (s), 1450 (m), 957 (m), 733 (s), 693 (s), 595 (m) cm^{-1} . MS (EI-TOF) m/z (%) 238.1 (15) [M^+], 134.1 (12), 133.1 (100), 117.05 (10), 105.05 (72), 91.05 (9), 77.05 (18). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{17}\text{H}_{19}\text{O}$: 239.1430; found: 239.1431.

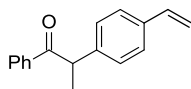
Synthesis of 2-(2-methyl-3-phenyl-phenyl)-1-phenyl-propan-1-one 3lh



Compound **3lh** was prepared following the general procedure **C** for the arylation of phenyl ethyl ketone (201 mg, 1.50 mmol) with 3-chloro-2-methylbiphenyl (211 mg, 1.00 mmol) and isolated as a dark yellow oil (285 mg, 0.95 mmol, 95%).

^1H NMR (300 MHz, CDCl_3) δ = 7.93 - 7.86 (m, 2 H), 7.53 - 7.46 (m, 1 H), 7.46 - 7.34 (m, 5 H), 7.34 - 7.29 (m, 2 H), 7.18 - 7.05 (m, 3 H), 4.88 (q, J = 6.8 Hz, 1 H), 2.39 (s, 3 H), 1.54 (d, J = 6.8 Hz, 3 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 201.1, 143.4, 142.5, 140.7, 136.6, 132.7, 132.0, 129.4, 128.7, 128.5, 128.5, 128.0, 126.8, 126.1, 126.1, 44.8, 18.2, 16.7 ppm. IR: $\tilde{\nu}$ = 3025 (w), 2975 (w), 2939 (w), 2866 (w), 1682 (s), 1447 (m), 949 (m), 721 (s), 702 (s) cm^{-1} . MS (EI-TOF) m/z (%) 300.15 (49) [M^+], 195.1 (45), 167.05 (25), 166.05 (13), 165.05 (32), 105.0 (100), 77.0 (17). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{22}\text{H}_{21}\text{O}$: 301.1587; found: 301.1584.

Synthesis of 1-phenyl-2-(4-ethenylphenyl)propan-1-one 3lm

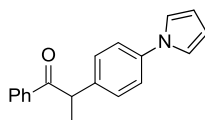


[CAS: 1315258-40-2]

Compound **3lm** was prepared following the general procedure **C** for the arylation of phenyl ethyl ketone (201 mg, 1.50 mmol) with 1-chloro-4-vinyl-benzene (143 mg, 1.00 mmol) and isolated as an orange brown solid (215 mg, 0.91 mmol, 91%).

m.p.: 64 – 66 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.99 - 7.92 (m, 2 H), 7.52 - 7.45 (m, 1 H), 7.43 - 7.32 (m, 4 H), 7.28 - 7.23 (m, 2 H), 6.66 (dd, J = 10.8, 17.6 Hz, 1 H), 5.70 (dd, J = 1.0, 17.5 Hz, 1 H), 5.21 (dd, J = 0.9, 11.0 Hz, 1 H), 4.69 (q, J = 6.8 Hz, 1 H), 1.54 (d, J = 6.8 Hz, 3 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 200.2, 141.0, 136.5, 136.3, 136.3, 132.8, 128.7, 128.5, 127.9, 126.8, 113.8, 47.6, 19.4 ppm. IR: $\tilde{\nu}$ = 3061 (w), 2977 (m), 2929 (m), 2866 (w), 1677 (s), 1446 (m), 951 (s), 904 (s), 842 (s), 729 (s), 688 (s) cm^{-1} . MS (EI-TOF) m/z (%) 236.1 (13) $[\text{M}^+]$, 131.05 (32), 115.0 (7), 106.0 (8), 105.0 (100), 91.0 (13), 77.0 (26). HRMS (EI-TOF): $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{17}\text{H}_{17}\text{O}$: 237.1274; found: 237.1274. The analytical data (NMR) matched those reported in the literature.³⁰⁹

Synthesis of 1-phenyl-2-(4-pyrrol-1-ylphenyl)propan-1-one 3ln

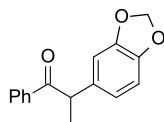


Compound **3ln** was prepared following the general procedure **C** for the arylation of phenyl ethyl ketone (201 mg, 1.50 mmol) with 1-(4-chlorophenyl)-1H-pyrrole (181 mg, 1.00 mmol) and isolated as a light yellow solid (214 mg, 0.78 mmol, 78%).

m.p.: 100 – 102 °C. ^1H NMR (300 MHz, CDCl_3) δ = 8.04 - 7.93 (m, 2 H), 7.56 - 7.47 (m, 1 H), 7.47 - 7.29 (m, 6 H), 7.05 (t, J = 2.2 Hz, 2 H), 6.33 (t, J = 2.2 Hz, 2 H), 4.74 (q, J = 6.8 Hz, 1 H), 1.59 (s, 3 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 200.1, 139.6, 138.7, 136.3, 132.9, 128.9, 128.7, 128.6, 121.0, 119.2, 110.4, 47.1, 19.4 ppm. IR: $\tilde{\nu}$ = 3041 (w), 2982 (w), 2936 (w), 1678 (s), 1523 (s), 1327 (s), 952 (m), 722 (s), 707 (s), 544 (s) cm^{-1} . MS (EI-TOF) m/z (%) 275.1 (26) $[\text{M}^+]$, 171.1 (14), 170.1 (100), 128.05 (8), 105.0 (26), 77.05 (13). HRMS (EI-TOF): $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{18}\text{NO}$: 276.1383; found: 276.1383.

Synthesis of 2-(1,3-benzodioxol-5-yl)-1-phenyl-propan-1-one 3lp

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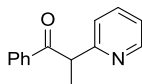


[CAS: 917906-01-5]

Compound **3lp** was prepared following the general procedure **C** for the arylation of phenyl ethyl ketone (201 mg, 1.50 mmol) with 5-chloro-1,3-benzodioxole (160 mg, 1.00 mmol) and isolated as an light yellow solid (169 mg, 0.67 mmol, 67%).

m.p.: 63 – 64 °C. ^1H NMR (300 MHz, CDCl_3) δ = 7.99 - 7.93 (m, 2 H), 7.54 - 7.46 (m, 1 H), 7.45 - 7.35 (m, 2 H), 6.82 - 6.70 (m, 3 H), 5.95 - 5.88 (m, 2 H), 4.61 (q, J = 6.8 Hz, 1 H), 1.51 (d, J = 6.8 Hz, 3 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 200.2, 148.0, 146.5, 136.4, 135.2, 132.8, 128.7, 128.5, 121.0, 108.6, 108.1, 101.0, 47.4, 19.5 ppm. IR: $\tilde{\nu}$ = 3066 (w), 2982 (m), 2932 (w), 2884 (w), 1679 (s), 1450 (s), 1035 (s), 832 (s), 745 (s), 699 (s) cm^{-1} . MS (EI-TOF) m/z (%) 254.05 (15) [M^+], 150.05 (10), 149.05 (100), 119.0 (15), 105.0 (26), 91.0 (21), 77.0 (17). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{16}\text{H}_{15}\text{O}_3$: 255.1016; found: 255.1015. The analytical data (NMR) matched those reported in the literature.³¹⁰

Synthesis of 1-phenyl-2-(2-pyridyl)propan-1-one 3lq

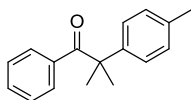


[CAS: 92199-25-2]

Compound **3lq** was prepared following the general procedure **C** for the arylation of phenyl ethyl ketone (201 mg, 1.50 mmol) with 2-chloropyridine (114 mg, 1.00 mmol) and isolated as a yellow oil (125 mg, 0.59 mmol, 59%).

^1H NMR (300 MHz, CDCl_3) δ = 8.57 - 8.49 (m, 1 H), 8.07 - 7.98 (m, 2 H), 7.59 (dt, J = 1.8, 7.7 Hz, 1 H), 7.51 - 7.44 (m, 1 H), 7.42 - 7.33 (m, 2 H), 7.25 (td, J = 1.1, 7.9 Hz, 1 H), 7.11 (ddd, J = 1.2, 4.9, 7.5 Hz, 1 H), 4.95 (q, J = 7.0 Hz, 1 H), 1.65 - 1.55 (m, 3 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 199.5, 161.0, 149.6, 136.9, 136.3, 132.8, 128.9, 128.4, 121.9, 121.8, 50.6, 17.9 ppm. IR: $\tilde{\nu}$ = 3060 (w), 2978 (w), 2933 (w), 2871 (w), 1682 (s), 1588 (s), 1432 (s), 952 (s), 747 (s), 700 (s), 570 (s) cm^{-1} . MS (EI-TOF) m/z (%) 211.1 (3) [M^+], 210.1 (4), 183.1 (31), 105.0 (100), 77.0 (43). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{14}\text{H}_{14}\text{NO}$: 212.1070; found: 212.1074. The analytical data (NMR) matched those reported in the literature.³¹¹

Synthesis of 2-methyl-1-phenyl-2-(4-methylphenyl)propan-1-one 3ma



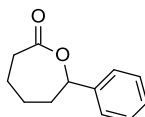
[CAS: 14271-33-1]

Compound **3ma** was prepared following the general procedure **A** for the arylation of isobutyrophenone (306 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a yellow oil (123 mg, 0.52 mmol, 52%).

Compound **3ma** was prepared following the general procedure **A** for the arylation of isobutyrophenone (306 mg, 2.00 mmol) with 4-chlorotoluene (127 mg, 1.00 mmol) and isolated as a yellow oil (120 mg, 0.50 mmol, 50%).

^1H NMR (300 MHz, CDCl_3) δ = 7.53 - 7.51 (m, 1 H), 7.50 - 7.48 (m, 1 H), 7.40 - 7.34 (m, 1 H), 7.27 - 7.15 (m, 6 H), 2.36 (s, 3 H), 1.60 (s, 6 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 203.9, 142.2, 136.4, 136.4, 131.6, 129.7, 127.9, 125.6, 51.0, 27.8, 21.0 ppm. IR: $\tilde{\nu}$ = 3056 (w), 3023 (w), 2972 (m), 2926 (w), 1674 (s), 1446 (m), 1246 (s), 972 (s), 817 (s), 708 (s) cm^{-1} . MS (EI-TOF) m/z (%) 238.8 (32) [M^+], 133.9 (11), 132.9 (100), 132.0 (20), 104.9 (53), 77.0 (8). HRMS (EI-TOF): [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{17}\text{H}_{19}\text{O}$: 239.1430; found: 239.1430. The analytical data (NMR) matched those reported in the literature.³¹²

Synthesis of 7-phenyloxepan-2-one **4**



[CAS: 50975-46-7]

Compound **4** was prepared following the literature procedure.³¹³ To a solution of 2-phenylcyclohexanone **3ab** (1.00 eq, 0.5 mmol, 89 mg) in 4 mL CH_2Cl_2 was added *m*CPBA (2.40 eq, 1.2 mmol, 269 mg), at 0 °C. After stirring at rt overnight, the reaction mixture was quenched with 10% K_2CO_3 solution and a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$. The aqueous layer was separated and extracted with CH_2Cl_2 . The combined organic layer was dried (MgSO_4), filtered and concentrated under reduced pressure. The resulting crude product was purified by silica gel column chromatography (cyclohexane/EtOAc, gradient) to afford 7-phenyloxepan-2-one as a colorless solid (87 mg, 0.46 mmol, 92%).

m.p.: 68 – 70°C. ^1H NMR (300 MHz, CDCl_3) δ = 7.43 - 7.27 (m, 5 H), 5.30 (d, J = 9.0 Hz, 1 H), 2.83 - 2.72 (m, 2 H), 2.17 - 1.96 (m, 4 H), 1.87 - 1.65 (m, 2 H) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ = 174.8, 140.8, 128.5, 128.0, 125.8, 82.0, 37.4, 34.9, 28.6, 22.8 ppm. IR: $\tilde{\nu}$ =

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3029 (w), 2980 (w), 2928 (w), 2868 (w), 1717 (s), 1446 (m), 1144 (s), 1010 (s), 752 (s), 702 (s), 588 (s) cm^{-1} . MS (EI-TOF) m/z (%) 190.0 (8) $[\text{M}^+]$, 130.0 (8), 117.05 (39), 105.0 (36), 85.0 (100), 84.0 (75), 77.0 (30), 56.0 (30), 55.0 (68). HRMS (EI-TOF): $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_2$: 191.1067; found: 191.1064. The analytical data (NMR) matched those reported in the literature.³¹⁴

7.6 Cu/Pd-Katalysierte decarboxylierende Kreuzkupplung von Pyridinsäurederivaten

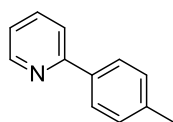
7.6.1 Studien zur decarboxylierenden Kreuzkupplung von 2-Picolin- und 2-Pyrimidincarbonsäure

7.6.1.1 Allgemeine Informationen

Alle Reaktionen dieses Teilprojekts wurden auf die gleiche Art und Weise durchgeführt wie in der „Experimental Section“ des beigefügten Manuskripts in Kapitel 5.4.2 beschrieben. Produkte der Reaktionsoptimierung welche dort nicht aufgeführt sind, werden im nachfolgenden Unterkapitel erwähnt.

7.6.1.2 Charakterisierung der Produkte

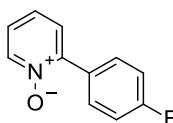
2-(4-Methylphenyl)-pyridin **3ab**



[CAS: 4467-06-5]

MS (EI, 70 eV), m/z (%): 169 (100) [M^+], 168 (68), 167 (30), 63 (10), 51 (14), 50 (12). Die massenspektrometrischen Daten entsprechen denen aus der Literatur.³¹⁵

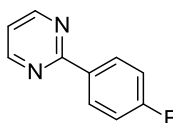
2-(4-Fluorphenyl)-pyridin-N-Oxid **3bc**



[CAS: 1262526-01-1]

^{19}F -NMR (377 MHz, DMSO-d_6): $\delta = -111.3$ ppm. Die NMR-Daten entsprechen denen aus der Literatur.³¹⁶

2-(4-Fluorphenyl)-pyrimidin **3cc**



[CAS: 68049-17-2]

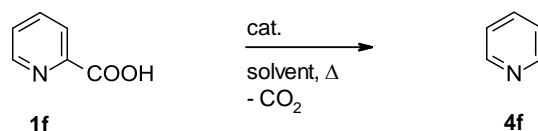
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^{19}F -NMR (377 MHz, DMSO- d_6): $\delta = -111.2$ ppm. MS (EI, 70 eV), m/z (%): 175 (13), 174 (100) [M^+], 173 (9), 147 (7), 122 (8), 121 (56), 94 (13). Die NMR-Daten entsprechen denen aus der Literatur.³¹⁷

7.6.2 Synthesis of 3-Substituted 2-Arylpyridines via Cu/Pd-Catalyzed Decarboxylative Cross-Coupling of Picolinic Acids with (Hetero)Aryl Halides

7.6.2.1 Optimization of the reaction conditions

Tabelle 29. Optimization of the reaction conditions.



Entry	[M]	N-Ligand	[Pd]	P-Ligand	solvent	Yield (%)	
						3aa	4a
1	Cu ₂ O	Phen	PdCl ₂	PPh ₃	NMP/Mes	49	n.d.
2	“	“	“	“	NMP	19	trace
3	“	“	“	“	Mes	5	n.d.
4	“	“	“	“	DMF	35	trace
5	“	“	“	“	DMAc	36	9
6	“	“	“	“	DMSO	60	7
7	“	“	Pd(COD)Cl ₂	“	“	74	8
8	“	“	PdBr ₂	“	“	51	14
9	“	“	PdI ₂	“	“	54	11
10	“	“	Pd(OAc) ₂	“	“	49	23
11	“	“	Pd(TFA) ₂	“	“	53	6
12	“	“	Pd(acac) ₂	“	“	67	9
13	“	“	Pd(F ₆ -acac) ₂	“	“	30	31
14 ^a	CuCl	“	Pd(COD)Cl ₂	“	“	66	n.d.
15 ^a	CuBr	“	“	“	“	58	n.d.

16 ^a	CuI	“	“	“	“	71	8
17	Ag ₂ CO ₃	“	“	“	“	66	10
18	Ag ₂ O	“	“	“	“	52	30
19	Cu ₂ O	Me ₂ -phen	“	“	“	62	n.d.
20	“	Me ₄ -phen	“	“	“	83	n.d.
21	“	Ph ₂ -phen	“	“	“	79	9
22	“	NO ₂ -phen	“	“	“	49	17
23	“	2,2'-bipy	“	“	“	70	7
24	“	Pyridine	“	“	“	72	6
25	“	Me ₄ -phen	“	P(<i>p</i> -Tol) ₃	“	84	trace
26	“	“	“	P(<i>o</i> -Tol) ₃	“	78	7
27	“	“	“	PCy ₃	“	28	trace
28	“	“	“	P(2-Furyl) ₃	“	74	7
29	“	“	“	BINAP	“	75	n.d.
30	“	“	“	JohnPhos	“	41	8
31	“	“	“	SPhos	“	80	6
32	“	“	“	XPhos	“	74	11
33	“	“	“	CyJohnPhos	“	82	10
34	“	“	“	DavePhos	“	92	7
35	“	-	“	“	“	93	trace
36 ^b	“	-	“	“	“	64	12
37 ^c	“	-	“	“	“	23	7
38 ^d	“	-	“	“	“	18	5
39	-	-	“	“	“	7	32
40	Cu ₂ O	-	“	-	“	12	trace
41	“	-	-	-	“	n.d.	n.d.

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Reaction conditions: 0.5 mmol **1a**, 1.0 mmol **2a**, [M] (5 mol%), N-ligand (10 mol%), [Pd] (5 mol%), *P*-ligand (15 mol%), solvent (2 mL), 130 °C, 24 h; ¹⁹F-NMR yield with 1,4-difluorobenzene as internal standard. ^a 10 mol% [M] was used; ^b 120 °C; ^c 110 °C; ^d 100 °C.

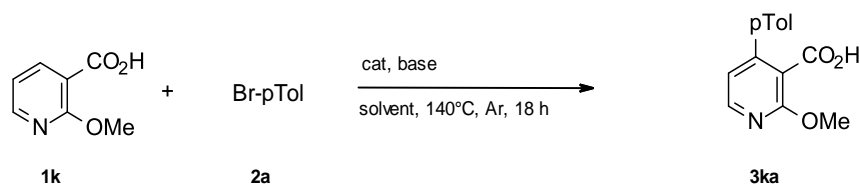
7.7 Rhodium-catalyzed *ortho*-Arylation of (Hetero)aromatic Acids

7.7.1 General procedure for the *ortho*-arylation

An oven-dried 20 mL vial was charged with $\text{Rh}_2(\text{OAc})_4$ (8.84 mg, 0.02 mmol), benzoic acid (0.5 mmol), K_2CO_3 (104 mg, 0.75 mmol), and closed with a septum cap. After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, dry DMF (2 mL) and an aryl bromide (0.75 mmol) were added via syringe. The resulting mixture was stirred at 140 °C for 18 h. After cooling down to room temperature NMP (2 mL), K_2CO_3 (1 mmol) and MeI (2.5 mmol) were added and stirred at 60 °C for 2 h. After the reaction was complete, it was diluted with EtOAc (10 mL) and washed with aqueous LiCl solution (1M), water and brine (20 mL each), then the aqueous phases were extracted with EtOAc (3×20 mL). The combined organic phases 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/cyclohexane gradient), yielding the corresponding biaryl.

7.7.2 Screening of the reaction conditions

Tabelle 30. Screening of the reaction conditions for the *ortho*-arylation of **1k** with **2a**.



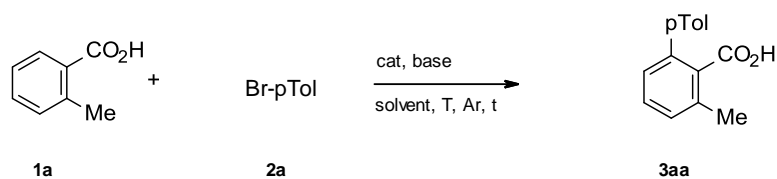
Entry	Catalyst / mol%	Solvent / mL	Base / equiv	Additive / equiv	3ka (%)
1 ^[b]	5.0 CataCXium® A Pd G3	2.0 DMF	2.2 Cs_2CO_3	Molecular sieves	16
2 ^[c]	4.0 $[\text{RuCl}_2(p\text{-cym})]_2$	2.0 NMP	1.1 K_2CO_3	0.08 $[\text{HPEt}_3]\text{BF}_4$	0
3	4.0 $\text{Rh}_2(\text{OAc})_4$	2.0 DMAc	1.0 K_2CO_3	-	79
4	“	2.0 DMI	“	-	61
5	“	2.0 propylene carbonate	“	-	1
6	“	2.0 quinoline	“	-	0
7	“	2.0 diglyme	“	-	81
8	“	2.0 Trichloroethanol	“	-	0
9	-	2.0 DMF	1.5 K_2CO_3	-	0

EXPERIMENTELLER TEIL

10 ^[d]	4.0 Rh ₂ (OAc) ₄	“	“	-	90
11 ^[e]	“	“	“	-	0
12 ^[f]	“	“	“	-	85
13 ^[g]	“	“	“	-	99
14	“	0.5 DMF	“	-	84
15	“	1.0 DMF	“	-	90
16	“	1.5 DMF	“	-	90
17	“	2.5 DMF	“	-	87
18	“	3.0 DMF	“	-	86
19	“	“	“	1.0 AcOH	86
20	“	“	“	5.0 AcOH	16
21	“	“	“	1.1 H ₂ O	87
22 ^[h]	“	“	“	-	76
23	“	“	“	0.04 IMes·HCl	88

[a] Reaction conditions: **1k** (0.5 mmol), **2a** (0.75 mmol), catalyst, base, solvent, 140 °C, 18 h, yields determined by GC analysis using *n*-Tetradecane as internal standard. [b] 4-chlorotoluene, 145 °C. [c] 100 °C. [d] 150 °C. [e] 120 °C. [f] **1k** (0.5 mmol), **2a** (0.5 mmol). [g] **1k** (0.75 mmol), **2a** (0.5 mmol) [h] reaction carried out under air.

Tabelle 31. Screening of the reaction conditions for the ortho-arylation of **1a** with **2a**.

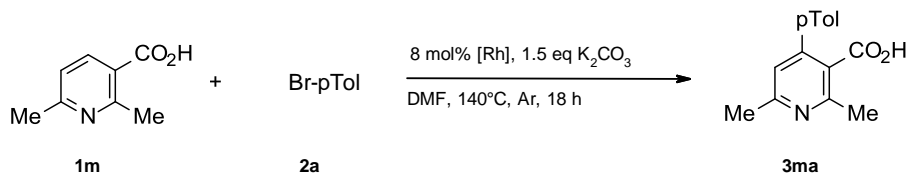


Entry	Solvent (amount)	K ₂ CO ₃ (equiv.)	Additive	Catalyst	3aa (%)
1	2.0 DMF	1.5	-	Rh ₂ (OAc) ₄	97 (93)
2	“	0	-	“	6
3	“	0.5	-	“	47

4	“	1.0	-	“	94
5	“	2.0	-	“	98
6	2.0 NMP	1.5	“	“	25
7	2.0 DMAc	“	-	“	88
8	2.0 DMI	“	-	“	12
9	2.0 propylene carbonate	“	-	“	4
10	2.0 quinoline	“	-	“	3
11	2.0 DMSO	“	-	“	25
12	2.0 diglyme	“	-	“	67
13	2.0 Trichloroethanol	“	-	“	0
14	2.0 mesitylene	“	-	“	5
15	2.0 DMF	1.5	-	-	0
16 ^[b]	“	“	-	Rh ₂ (OAc) ₄	2
17 ^[c]	“	“	-	“	0
18 ^[d]	“	“	-	“	71
19	“	“	1.1 H ₂ O	“	91

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), [Rh] (8 mol%), K₂CO₃, solvent (2.0 mL), 140 °C, 18 h, yields determined by GC analysis using *n*-Tetradecane as internal standard. [b] 130 °C. [c] 120 °C. [d] under air.

Tabelle 32. Screening of the rhodium source for the ortho-arylation of **1m** with **2a**.



Entry	Catalyst	3ma (%)
1	Rh ₂ (OAc) ₄	65
2 ^[b]	“	66

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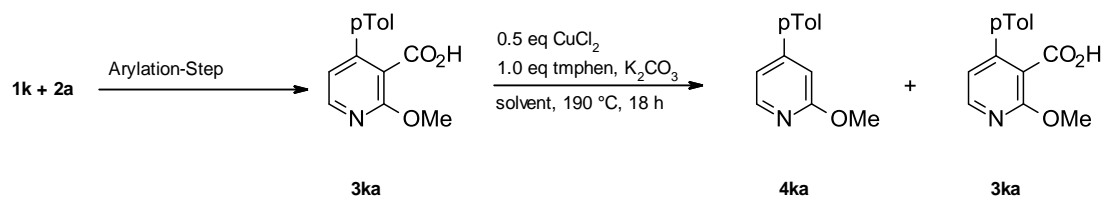
3	Rh(OAc) ₃	60
4	[Rh(OH)(cod)] ₂	65
5	[RhCp*Cl ₂] ₂	64
6	Rh ₂ (octanoate) ₄	66
7	[Rh(cod)Cl] ₂	62
8	[Rh(cod)(MeCN) ₂] ₂ BF ₄	63
9	Rh(acac) ₃	66
10	Rh ₂ (CF ₃ COO) ₄	70
11	[Rh(coe) ₂ Cl] ₂	70
12	[Rh(acac)(norbornadiene)]	65
13	[RhCl(norbornadiene)] ₂	63
14	[RhCl(hexadiene)] ₂	71
15	[Rh(CO)H(PPh ₃) ₃]	66
16	[Rh(acac)(CO) ₂]	71
17	[Rh(acac)(cod)]	62

[a] Reaction conditions: **1c** (0.5 mmol), **2a** (0.75 mmol), [Rh] (8 mol%), K₂CO₃ (0.75 mmol), DMF (2.0 mL), 140 °C, 18 h, yields determined by GC analysis using *n*-Tetradecane as internal standard. [b] 1 mol% Rh₂(OAc)₄.

7.7.3 General procedure for the one-pot *ortho*-arylation and protodecarboxylation

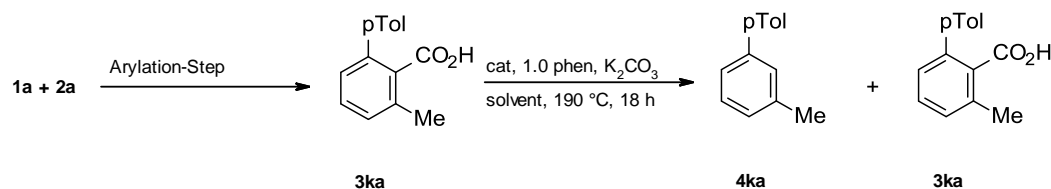
An oven-dried 20 mL vial was charged with Rh₂(OAc)₄ (0.552 mg, 0.0025 mmol), benzoic acid (0.5 mmol), K₂CO₃ (104 mg, 0.75 mmol), and closed with a septum cap. After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, dry DMF (2 mL) and an aryl bromide (0.75 mmol) were added via syringe. The resulting mixture was stirred at 140 °C for 18 h. After cooling down to room temperature, CuCl₂ (0.25 mmol) and phen (0.5 mmol) were added. After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, dry quinoline (4 mL) was added via syringe and the resulting mixture was stirred at 190 °C overnight. After cooling down to room temperature NMP (2 mL), K₂CO₃ (1 mmol) and MeI (2.5 mmol) were added and stirred at 60 °C for 2 h.

7.7.4 Protodecarboxylation Experiment

Tabelle 33. Protodecarboxylation of **4ka**.^[a]

Entry	K ₂ CO ₃ / equiv	Solvent	4ka (%)	3ka (%)
1	0.5	NMP	9	18
2	“	DMF	15	13
3	“	quin	44	-
4	1.0	“	72 (45)	-

[a] Reaction conditions: Solvent from reaction mixture of Arylation was removed, CuCl₂ (0.5 equiv), tmphen (1.0 equiv), K₂CO₃, solvent (4 ml). 190 °C, Argon atmosphere. Yields of the corresponding methyl esters determined by GC analysis after esterification with K₂CO₃ (2 eq) and MeI (5 eq) in NMP using *n*-tetradecane as the internal standard; yields of isolated product is given in parentheses.

Tabelle 34. Protodecarboxylation of **4aa**.^[a]

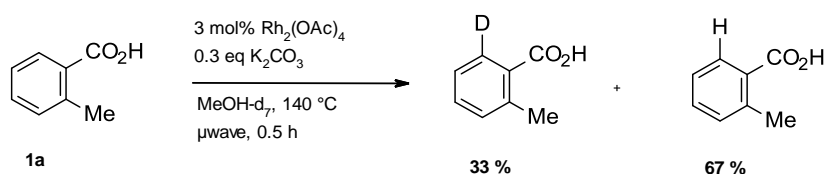
Entry	cat / equiv	K ₂ CO ₃ / equiv	Solvent / mL	4ka (%)	3ka (%)
1	0.5 CuBr	-	quinoline	82 (80)	-
2	0.3 CuCl ₂	0.1	“	98	-
3	“	“	NMP	0	79
4	“	“	DMF	44	45

[a] Reaction conditions: Solvent from reaction mixture of Arylation was removed, cat, phen (1.0 equiv), K₂CO₃, solvent (2 ml). 190 °C, Argon atmosphere. [b] Yields of the corresponding methyl esters determined by GC analysis after esterification with K₂CO₃ (2 eq) and MeI (5 eq) in NMP using *n*-tetradecane as the internal standard; yields of isolated product is given in parentheses.

7.7.5 Mechanistic investigations

7.7.5.1 *ortho*-Deuteration Experiment

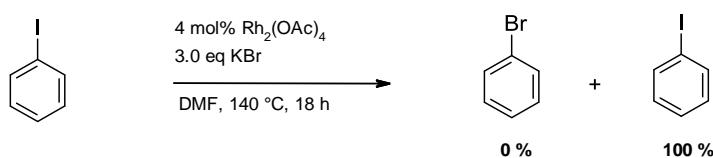
An oven-dried 5 mL μ wave-vial was charged with $\text{Rh}_2(\text{OAc})_4$ (6.63 mg, 0.015 mmol), 2-methylbenzoic acid **1a** (69.5 mg, 0.5 mmol), and K_2CO_3 (20.7 mg, 0.15 mmol), and closed with a septum cap. After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, dry MeOH-d_7 (1.5 mL) was added via syringe. The resulting mixture was stirred at 140 °C for 0.5 h inside the μ wave. After cooling down to room temperature, the yields were determined by $^1\text{H-NMR}$ analysis.



Schema 43. *ortho*-Deuteration of 2-methylbenzoic acid **1a**.

7.7.5.2 Halogenexchange Experiment

An oven-dried 20 mL vial was charged with $\text{Rh}_2(\text{OAc})_4$ (8.84 mg, 0.02 mmol) and potassium bromide (179 mg, 1.5 mmol), and closed with a septum cap. After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, dry DMF (2 mL) and iodobenzene (0.5 mmol) were added via syringe. The resulting mixture was stirred at 140 °C for 18 h. After cooling down to room temperature, the yields were determined by GC and GC-MS analysis using *n*-Tetradecane as internal standard.

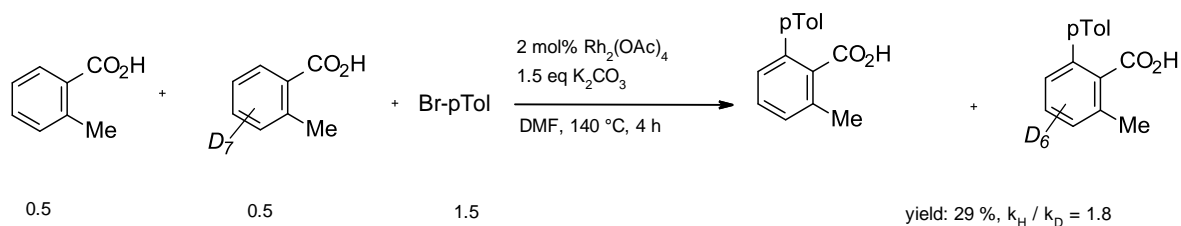


Schema 44. Halogenexchange Experiment.

7.7.5.3 Competitive kinetic isotope effect

An oven-dried 20 mL vial was charged with $\text{Rh}_2(\text{OAc})_4$ (1.77 mg, 0.004 mmol), 2-methylbenzoic acid (13.8 mg, 0.1 mmol), 2-methylbenzoic acid- d_7 (14.5 mg, 0.1 mmol), K_2CO_3 (41.5 mg, 0.3 mmol), and closed with a septum cap. After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, dry DMF (1 mL) and 4-bromotoluene (0.3 mmol) were added via syringe. The resulting mixture was stirred at 140 °C for 4 h. After cooling down to room temperature NMP (1 mL), K_2CO_3 (0.5 mmol) and MeI (1.75 mmol) were added

and stirred at 60 °C for 2 h. Yields of the corresponding methyl esters were determined by GC and GC-MS analysis using *n*-Tetradecane as internal standard.



Schema 45. Competitive kinetic isotopic effect.

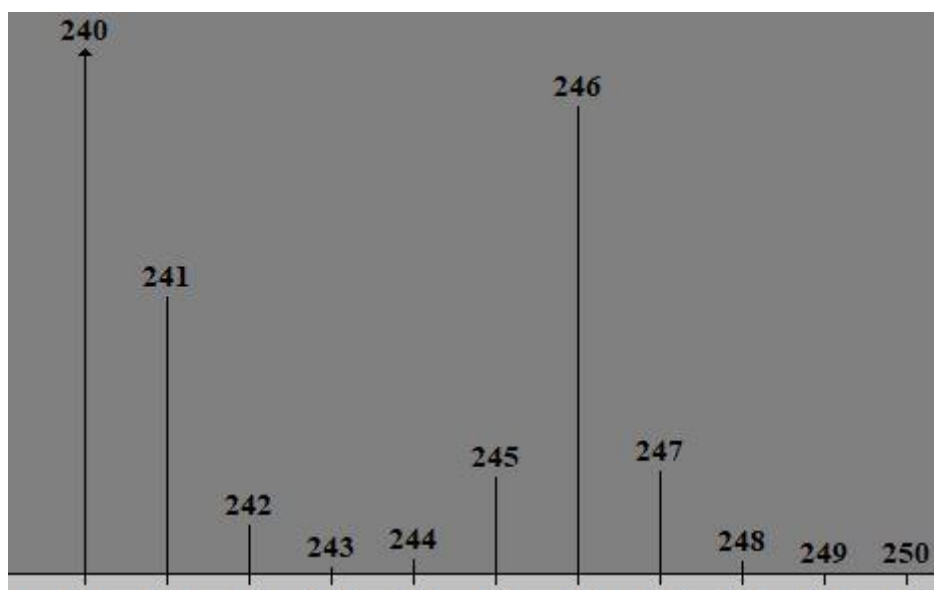


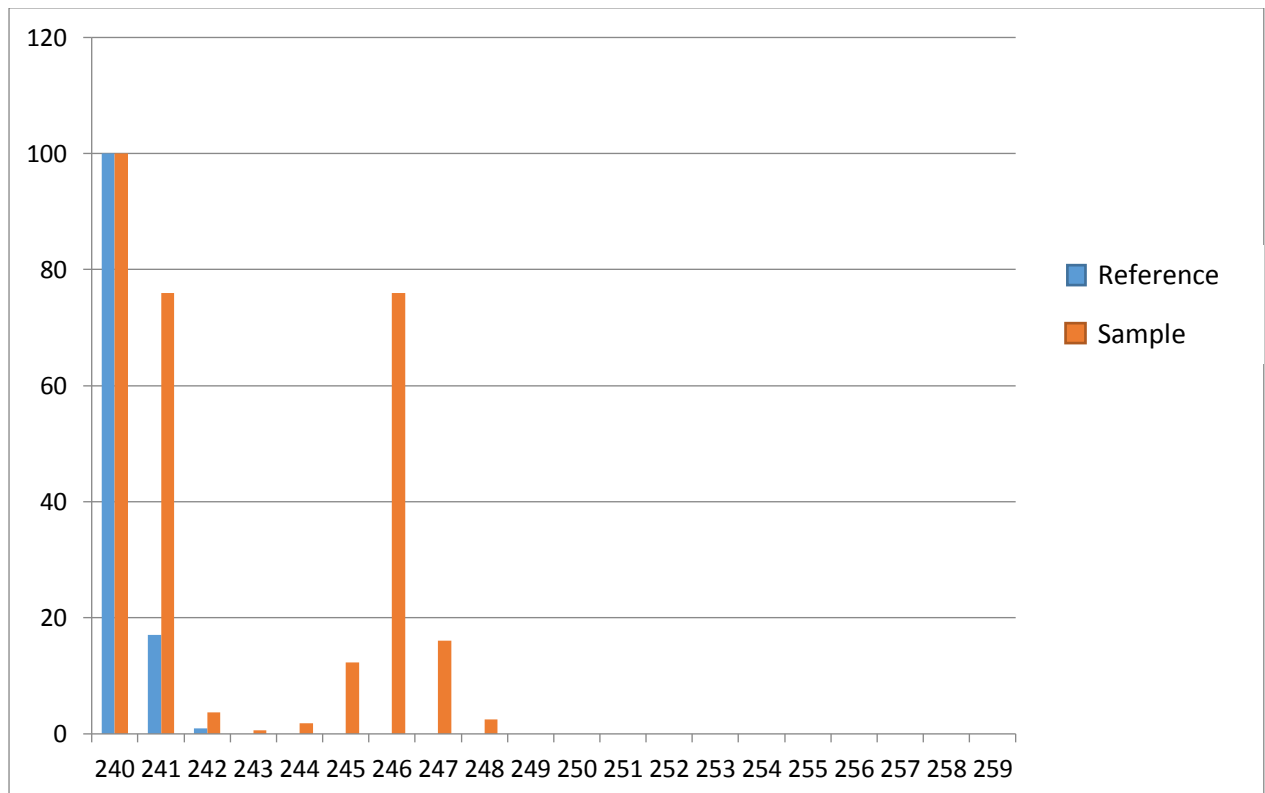
Abbildung 8. GC-MS data of the kinetic isotopic effect.

The relative intensity of each M^+ m/z fragment of the sample was utilized to quantify its isotopic deviation compared to natural abundance (reference):

peak nr.	m/z	D0	
		Reference (natural abundance)	Sample (relative intensities)
1	240	100	100
2	241	17	75,9
3	242	1	3,7
4	243	0	0,6

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5	244	0	1,9
6	245	0	12,3
7	246	0	75,9
8	247	0	16,0
9	248	0	2,5
10	249	0	0



This yields the following D0:D1:D2:D3:D4:D5:D6:D7 projected populations:

	% du total
D0	40,8
D1	24,1
D2	-3,0
D3	0,5

D4	0,7
D5	4,9
D6	30,2
D7	1,4
D8	0,5
D9	-0,1
D10	0,0
D11	0,0
D12	0,0
D13	0,0
D14	0,0
D15	0,0

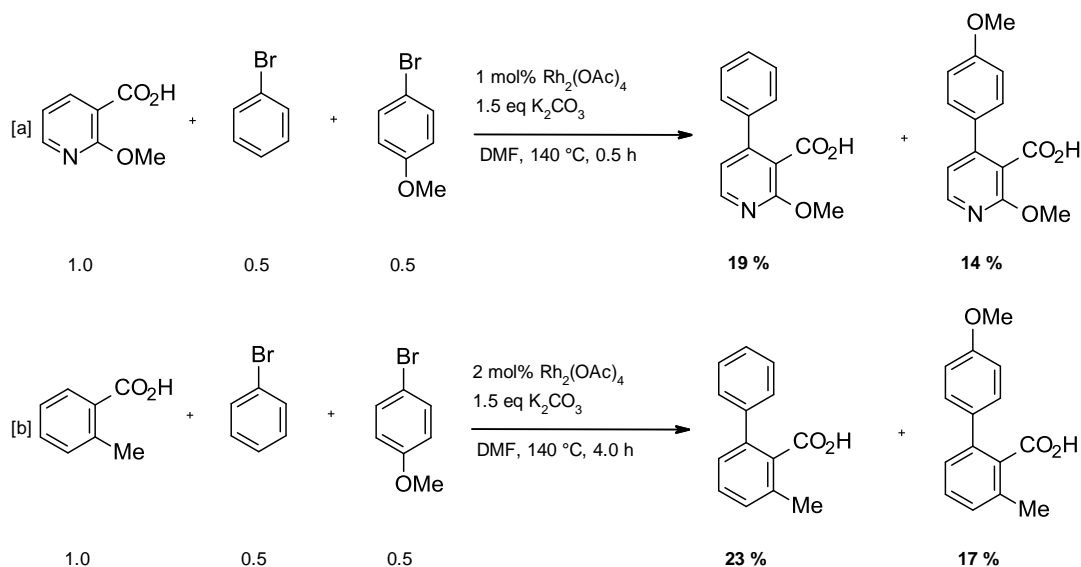
Population of D2 of -3% (in reality of course approximatively 0%) gives an idea of the precision/quality of the data). In this case, it is acceptable. (This is also why it is important to have a concentrated GCMS profile, for more precise relative m/z ratios).

D0 and D1 can be considered to belong to the same group (there can always be a bit of background scrambling, as long as it does not override the overall kinetic picture). Likewise, D5, D6 and D7 can be considered to belong to the labelled population. The initial KIE is therefore $(D0+D1)/(D5+D6+D7) = 1.8$.

7.7.5.4 One-pot competition experiment with two different aryl bromides

An oven-dried 20 mL vial was charged with $Rh_2(OAc)_4$ (2.21 mg, 0.001 mmol), 2-methoxynicotinic acid (78.9 mg, 0.5 mmol), K_2CO_3 (104 mg, 0.5 mmol), and closed with a septum cap. After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, dry DMF (2 mL), bromobenzene (0.25 mmol) and 4-bromoanisole (0.25 mmol) were added via syringe. The resulting mixture was stirred at 140 °C for 0.5 h. After cooling down to room temperature NMP (2 mL), K_2CO_3 (1., mmol) and MeI (2.50 mmol) were added and stirred at 60 °C for 2 h. Yields of the corresponding methyl esters determined by GC analysis using *n*-Tetradecane as internal standard.

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Schema 46. Competition experiment between electron-rich and electron-neutral bromobenzene.

Competition experiment shows that no product formation is privileged.

7.7.5.5 ESI investigations

Electrospray ionization mass spectrometry (ESI-MS) was performed with an ion trap instrument (Bruker amazon ETD). The investigated cations were produced in the positive electrospray ionization mode. The scan speed was 4650 m/z s in maximum-resolution scan mode (0.18 fwhm/m/z). The scan range was at least 70 to 3000 m/z. Sample solutions of reaction mixture in water at concentrations of approximately 10^{-5} M were continuously infused into the ESI chamber at a flow rate of $120 \mu\text{L min}^{-1}$ by using a syringe pump. N_2 gas was used as the drying gas at a flow rate of 3.0 to 4.0 L min^{-1} heated to $220 ^\circ\text{C}$. The solutions were sprayed at a nebulizer gas pressure of 3 to 4 psi with the electrospray needle held at 4.5 kV. Helium was used as a buffer gas with a partial pressure of ca. 3×10^{-3} mbar inside the ion trap. Bruker trapControl 7.2 software controlled the instrument and data analysis was performed with Data Analysis 4.2 software. The calculated MS spectra were created with the Isotope Distribution Calculator and Mass Spec Plotter from Scientiific Instrument Services.

An oven-dried 20 mL vial was charged with the corresponding amount of Rh_2OAc_4 (0.02 mmol, 4 mol%-dimer), 2-methyl-benzoic acid (68.1 mg, 0.5 mmol), K_2CO_3 (104 mg, 0.75 mmol), and closed with a septum cap. After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, dry DMF (2 mL), *p*-bromotoluene (0.75 mmol) was added via syringe. The resulting mixture was stirred at $140 ^\circ\text{C}$ for 16 h.

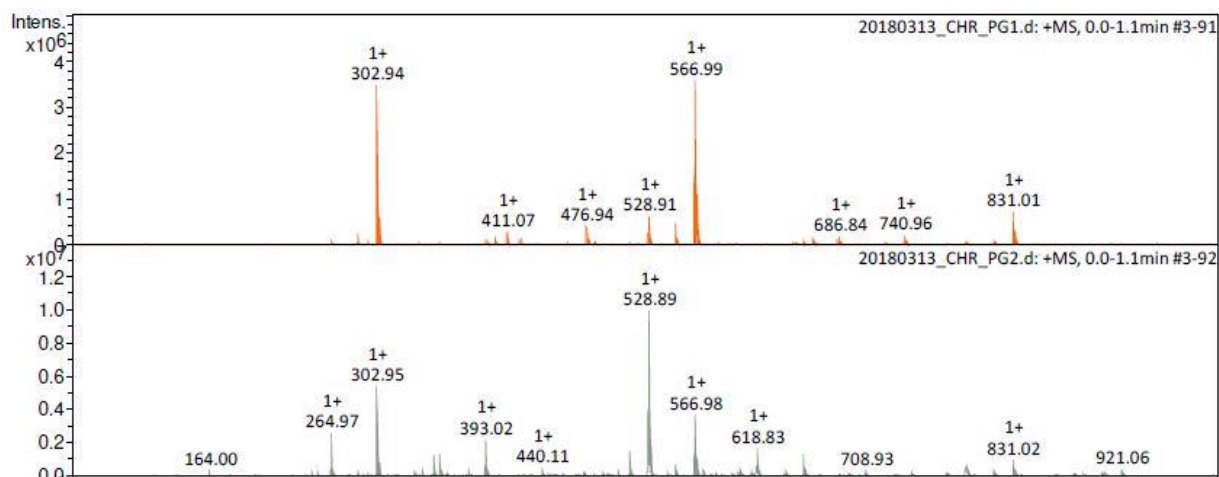


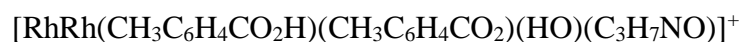
Abbildung 9. Experimental ESI-MS spectra from the reaction of 1a with 2a in DMF.

Experimental ESI-MS Spectrum of 2-methyl-benzoic acid and $\text{Rh}_2(\text{OAc})_4$ reaction mixture (upper, orange spectra) and with 2,5-Norbornadiene-rhodium(I) chloride dimer $\text{Rh}_2(\text{C}_7\text{H}_8)_2\text{Cl}_2$ (below, grey spectra) under described conditions. Measured in water. Positive mass spectra are shown.

For a better understanding of the ESI-MS results, different Rh-catalysts were investigated under otherwise identical conditions. The common mass fragments observed in each of the spectra were picked out and analyzed in detail.

For example 528.89/528.91 or 566.98/566.99
Possible interpretation of main fragments:

Peak: 566.99



2x Rh

2x 2-methyl-benzoic acid

1x OH

1x DMF

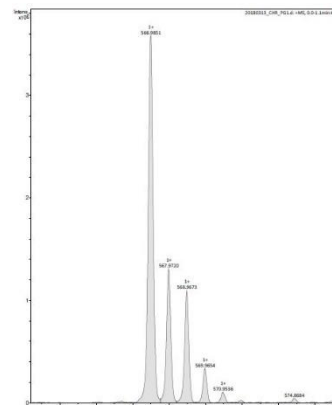


Abbildung 10. Experimental ESI-MS Spectrum Zoom of Abbildung 9.

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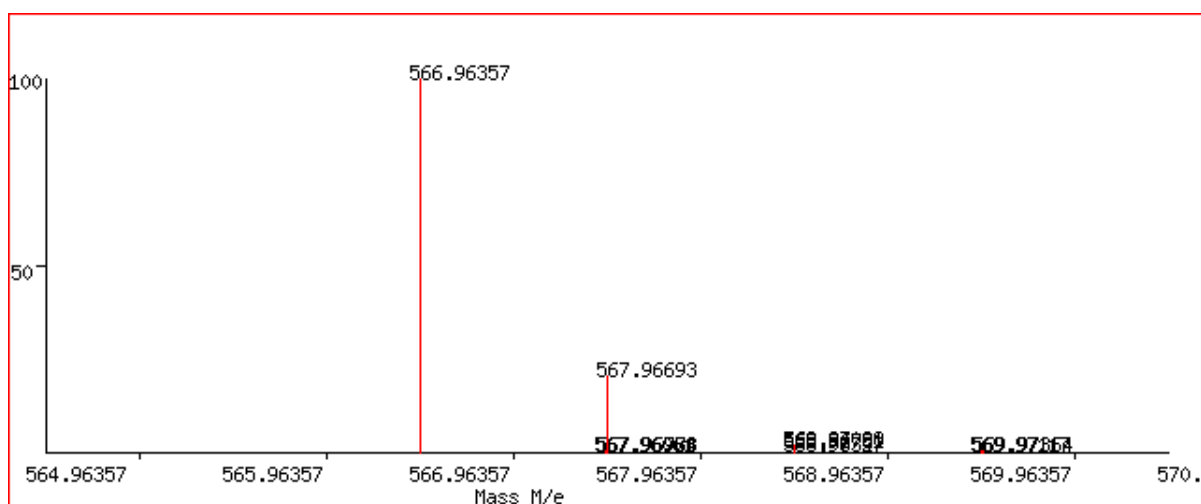


Abbildung 11. Calculated MS Spectra of Abbildung 10.

566.96357	100
567.96061	0.4
567.96693	20.5
567.96778	0.2
567.96984	0.4
568.96397	0.1
568.96781	1.2
568.97028	2
568.9732	0.1
569.97117	0.2
569.97364	0.1

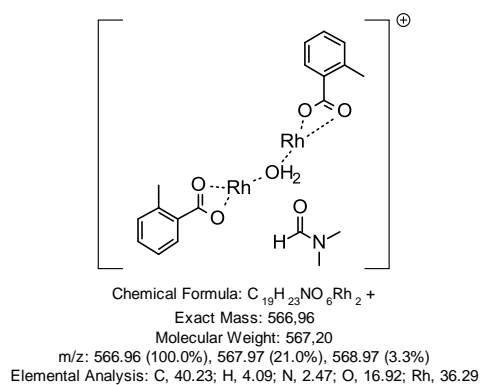


Abbildung 12. Conceivable fragment, spectral pattern is in agreement with ortho-metalated Rh(II) species.

other possibility: $[\text{RhRh}(\text{C}_{15}\text{H}_{13}\text{O}_2)(\text{C}_8\text{H}_8\text{O}_2)]^+$

2x Rh

1x 2-methyl-benzoic acid

1x Product 3aa -H

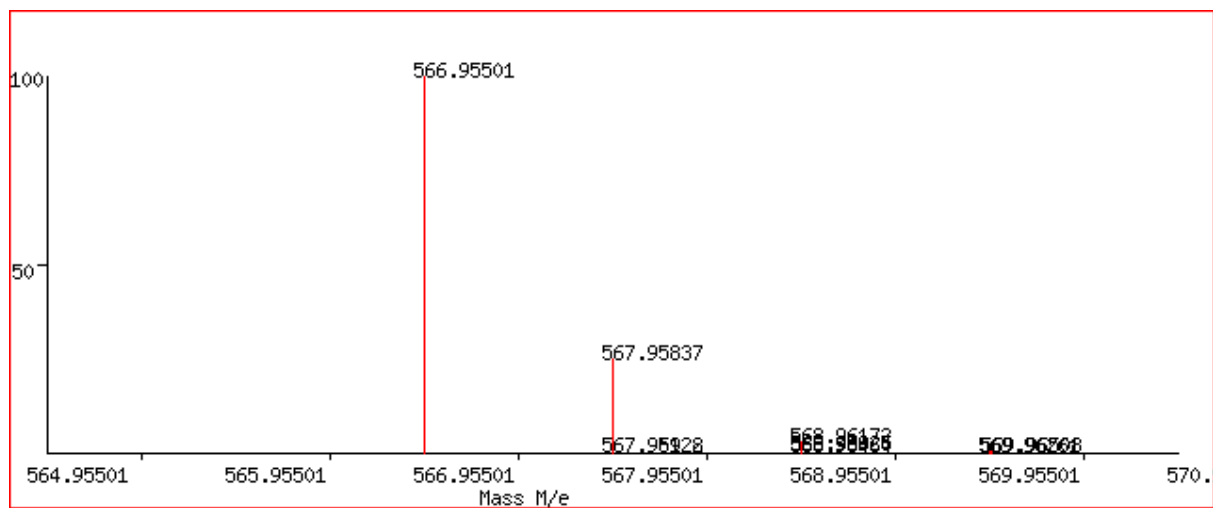


Abbildung 13. Calculated MS SPectra of $[\text{RhRh}(\text{C}_{15}\text{H}_{13}\text{O}_2)(\text{C}_8\text{H}_8\text{O}_2)]^+$.

566.95501 100

567.95837 24.9

567.95922 0.2

567.96128 0.3

568.95925 0.8

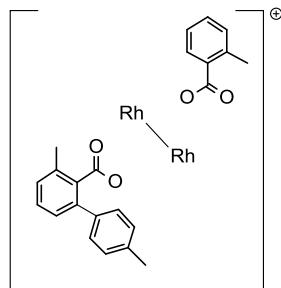
568.96172 3

568.96464 0.1

569.96261 0.2

569.96508 0.2

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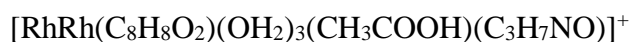


Chemical Formula: $C_{23}H_{21}O_4Rh_2$ +
 Exact Mass: 566,95
 Molecular Weight: 567,22
 m/z: 566.95 (100.0%), 567.96 (25.3%), 568.96 (3.9%)
 Elemental Analysis: C, 48.70; H, 3.73; O, 11.28; Rh, 36.28

Abbildung 14. Conceivable fragment, spectral pattern is in agreement with ortho-metalated Rh(II) species.

Possible interpretation of main fragments:

Peak: 528.88



2x Rh

1x 2-methyl-benzoic acid

3x H₂O

1x Acetic Acid

1x DMF

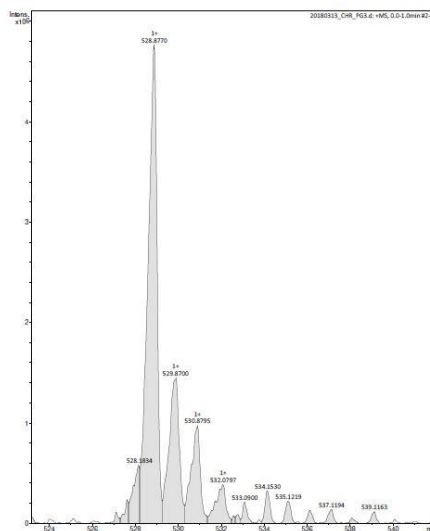


Abbildung 15. Experimental ESI-MS Spectrum Zoom of Abbildung 9.

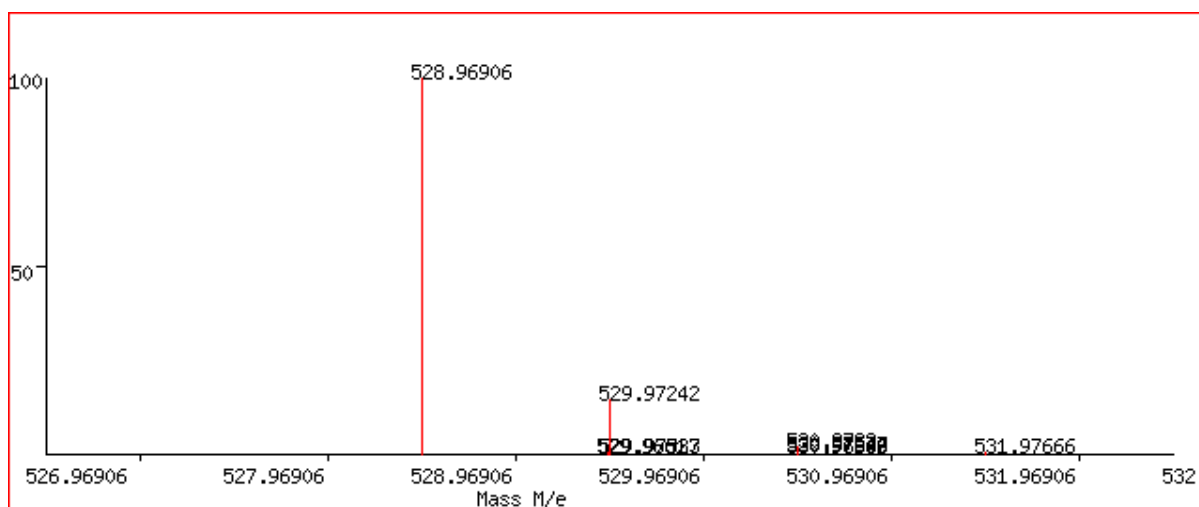
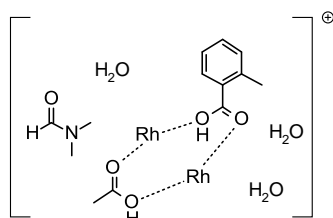


Abbildung 16. Calculated MS Spectra of Abbildung 15.

528.96906 100

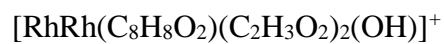
529.9661 0.4
 529.97242 14.1
 529.97327 0.3
 529.97533 0.4
 530.96946 0.1
 530.9733 1.6
 530.97577 0.9
 530.97869 0.1
 531.97666 0.2



Chemical Formula: $C_{13}H_{25}NO_8Rh_2^+$
 Exact Mass: 528,97
 Molecular Weight: 529,15
 m/z: 528.97 (100.0%), 529.97 (14.7%), 530.97 (1.7%)
 Elemental Analysis: C, 29.51; H, 4.76; N, 2.65; O, 24.19; Rh, 38.89

Abbildung 17. Conceivable fragment, spectral pattern is in agreement with ortho-metalated Rh(II) species.

Peak: 476.94



2x Rh

1x 2-methyl-benzoic acid

1x Acetic acid

1x "OH"

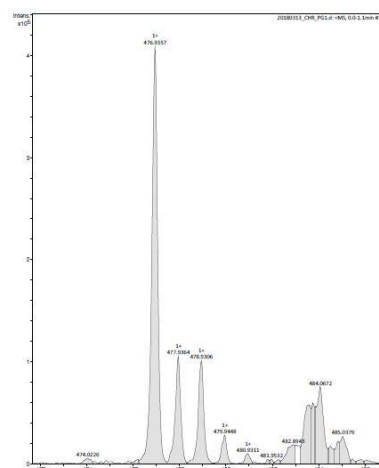


Abbildung 18. Experimental ESI-MS Spectrum Zoom of Abbildung 9.

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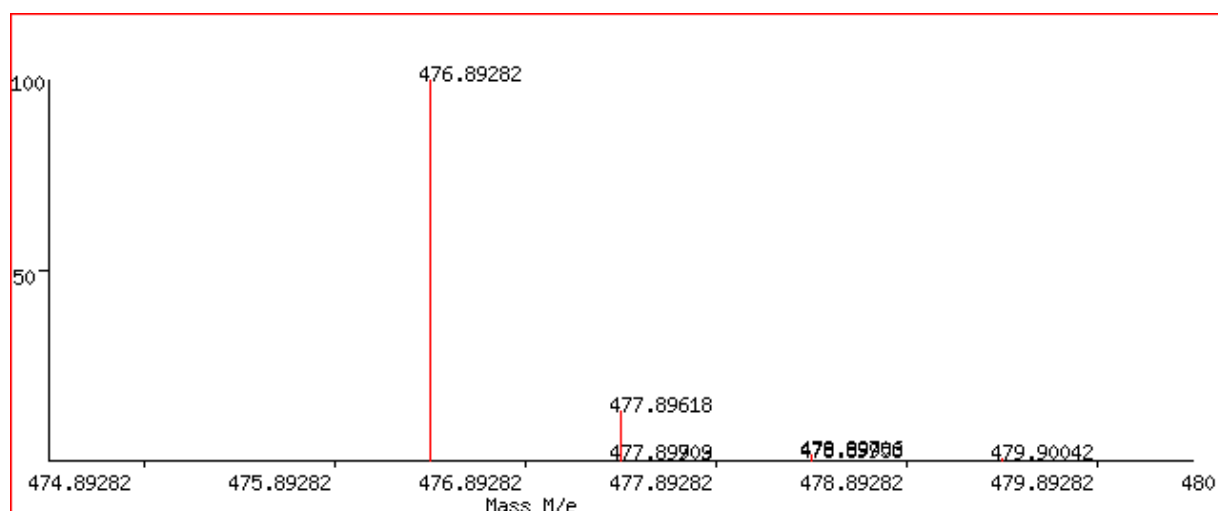


Abbildung 19. Calculated MS Spectra of Abbildung 18.

476.89282 100

477.89618 13

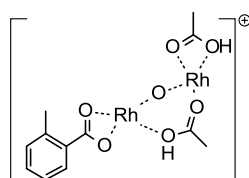
477.89703 0.3

477.89909 0.2

478.89706 1.4

478.89953 0.8

479.90042 0.2



Chemical Formula: $C_{12}H_{15}O_7Rh_2^+$
Exact Mass: 476,89
Molecular Weight: 477,05
m/z: 476.89 (100.0%), 477.90 (13.4%), 478.90 (2.3%)
Elemental Analysis: C, 30.21; H, 3.17; O, 23.48; Rh, 43.14

Abbildung 20. Conceivable fragment, spectral pattern is in agreement with ortho-metalated Rh(II) species.

An oven-dried 20 mL vial was charged with the corresponding amount of Rh_2OAc_4 (0.02 mmol, 4 mol%-dimer), 2-methyl-benzoic acid (68.1 mg, 0.5 mmol), K_2CO_3 (104 mg, 0.5 mmol), and closed with a septum cap. After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, dry NMP (2 mL) was added via syringe. The resulting mixture was stirred at 140 °C for 16 h.

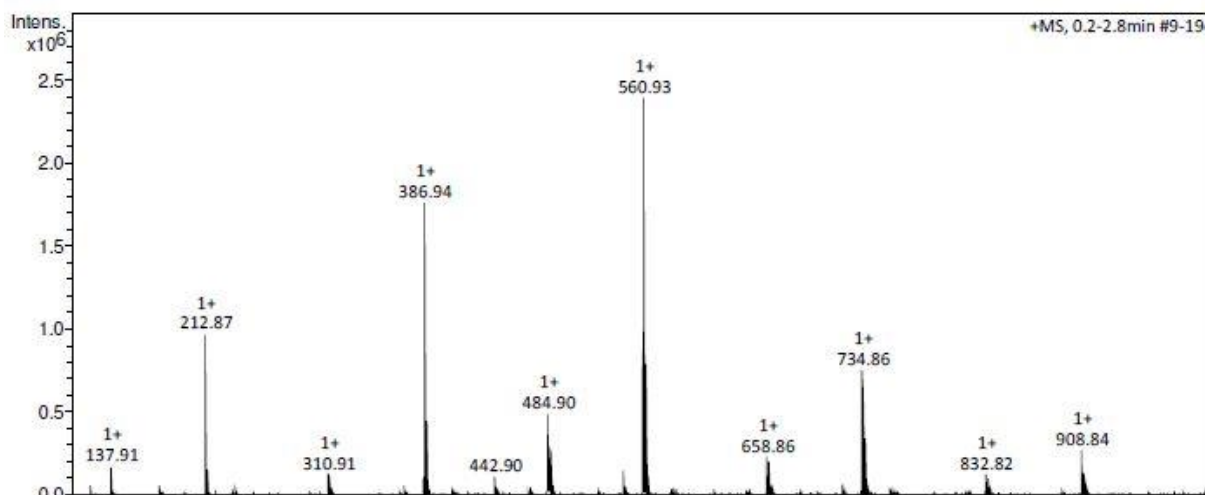


Abbildung 21. Experimental ESI-MS Spectrum without 4-Bromotoluene in NMP.

Experimental ESI-MS Spectrum of 2-methyl-benzoic acid/ $\text{Rh}_2(\text{OAc})_4$ reaction mixture without p-Bromotoluene under described conditions. Measured in water. Positive mass spectra are shown.

Possible interpretation of main fragments:

Peak: 560.93



2x Rh

1x 2-methyl benzoic acid

1x NMP

2x Acetic Acid

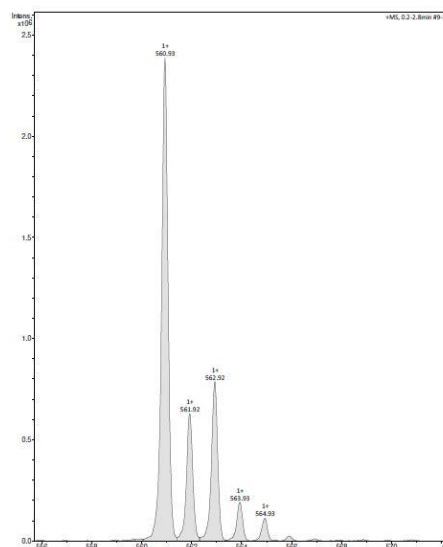


Abbildung 22. Experimental ESI-MS Spectrum Zoom of Abbildung 21.

EXPERIMENTELLER TEIL

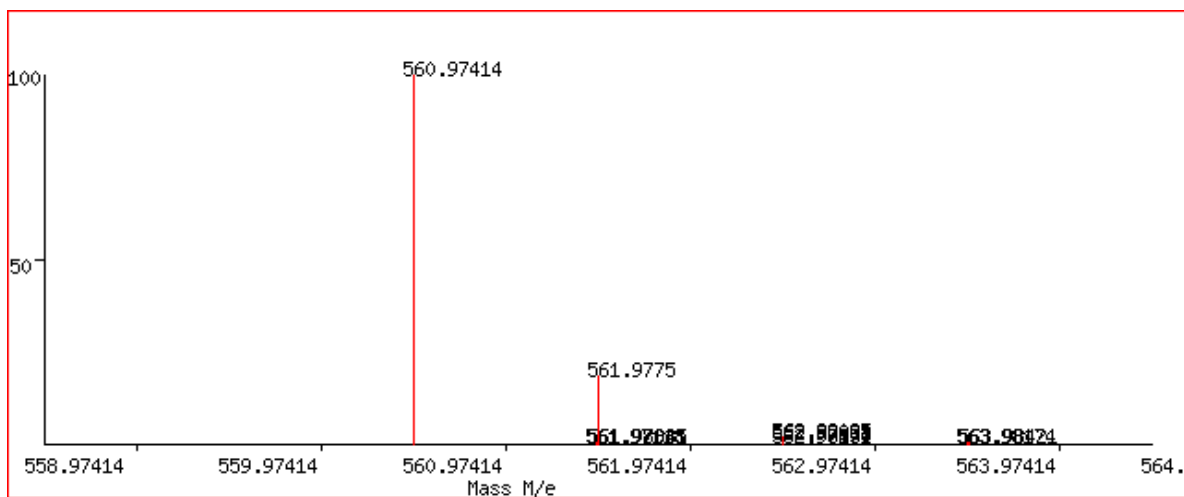


Abbildung 23. Calculated MS Spectra of Abbildung 22.

560.97414 100

561.97118 0.4

561.9775 18.4

561.97835 0.3

561.98041 0.4

562.97454 0.1

562.97838 1.4

562.98085 1.6

562.98171 0.1

562.98377 0.1

563.98174 0.3

563.98421 0.1

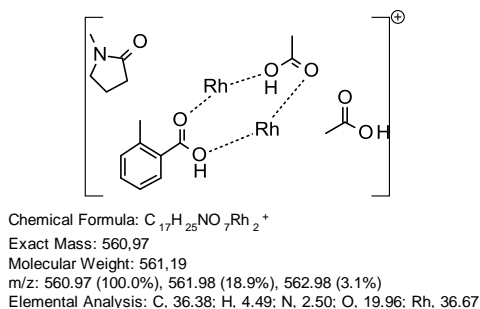


Abbildung 24. Conceivable fragment, spectral pattern is in agreement with ortho-metalated Rh(II) species.

An oven-dried 20 mL vial was charged with the corresponding amount of Rh_2OAc_4 (0.02 mmol, 4 mol%-dimer), 2-methyl-benzoic acid (68.1 mg, 0.5 mmol), K_2CO_3 (104 mg, 0.5 mmol), and closed with a septum cap. After the vessel was flushed with 3 alternating vacuum and nitrogen purge cycles, dry NMP (2 mL), *p*-bromotoluene (0.75 mmol) was added via syringe. The resulting mixture was stirred at 140 °C for 16 h.

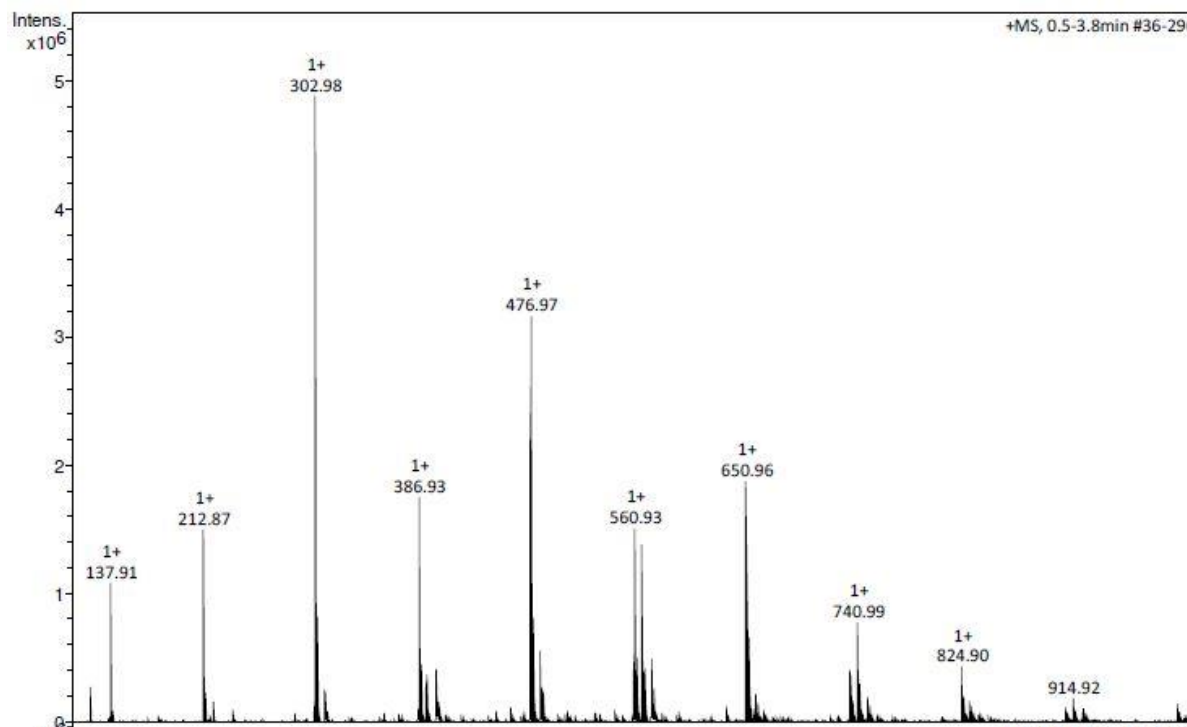


Abbildung 25. Experimental ESI-MS spectra from the reaction of **1a** with **2a** in NMP.

ESI-MS Spectrum of 2-methyl-benzoic acid/ $\text{Rh}_2(\text{OAc})_4$ reaction mixture under described conditions. Measured in water. Positive mass spectra are shown.

Possible interpretation of main fragments:

476: see above

560: see above

Peak: 650



2x Rh

1x product **3aa**

1x Acetic acid

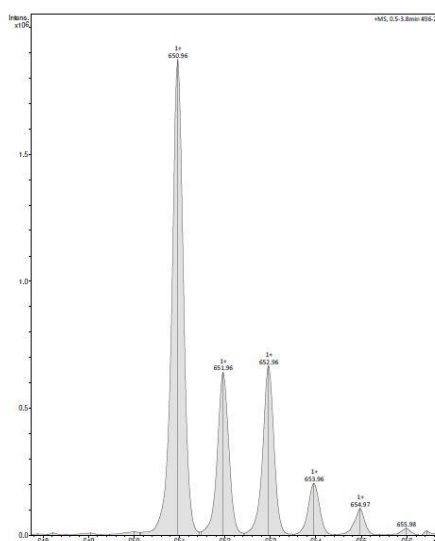


Abbildung 26. Experimental ESI-MS Spectrum Zoom of **Abbildung 25**.

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1x NMP

1x Na

2x H₂O

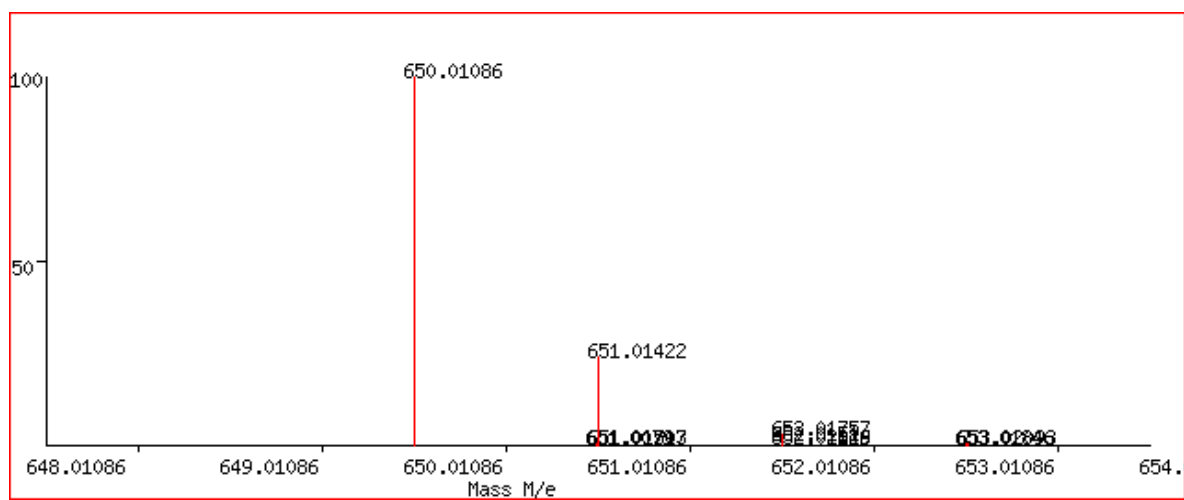


Abbildung 27. Calculated MS Spectra of Abbildung 26.

650.01086 100

651.0079 0.4

651.01422 23.8

651.01507 0.3

651.01713 0.5

652.01126 0.1

652.0151 1.4

652.01757 2.7

652.01843 0.1

652.02049 0.1

653.01846 0.3

653.02093 0.2

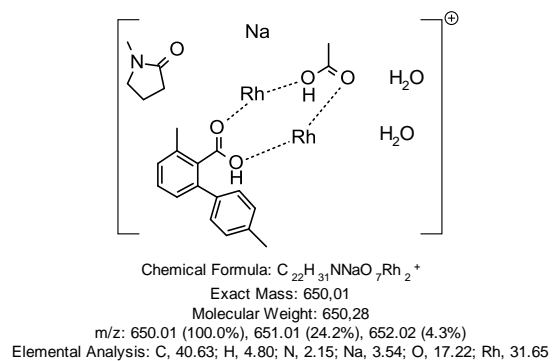
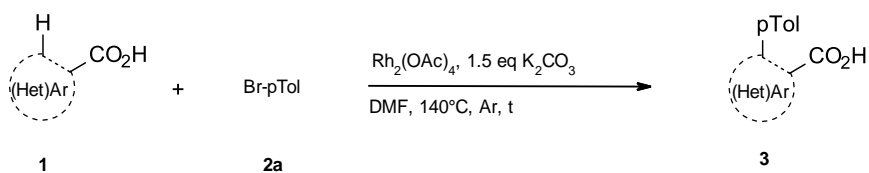


Abbildung 28. Conceivable fragment, spectral pattern is in agreement with ortho-metalated Rh(II) species.

7.7.5.6 Initial rate studies^[a]

Tabelle 35. ortho-Toluic acid **1a**. Amount of $Rh_2(OAc)_4$.



Entry	amount $Rh_2(OAc)_4$ (mol%)	reaction time (h)	3aa (%)
1	2.0	2.0	0
2		4.0	84
3		6.0	95
4 ^[b]		0.5	6
5 ^[b]		1.0	46
6 ^[b]		2.0	94
7	0.5	2.0	0
8		4.0	6
9		6.0	15
10		8.0	99

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[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), Rh₂(OAc)₄, K₂CO₃ (0.75 mmol), DMF (2.0 mL), 140 °C, t, yields determined by GC analysis using *n*-Tetradecane as internal standard. [b] Additional 10 mol% of pyridine.

Tabelle 36. 2-Methoxynicotinic acid **1k**. Amount of Rh₂(OAc)₄.

Entry	amount Rh ₂ (OAc) ₄ (mol%)	reaction time (h)	3ka (%)
1	2.0	0.5	73
2	“	1.0	90
3	0.5	0.5	7
4	“	1.0	15
5	“	2.0	70
6	“	4.0	99
7	0.25	0.5	0
8	“	1.0	9
9	“	2.0	73
10	“	4.0	99
11	0.125	1.0	0
12	“	“	0
13	0.25	“	0
14	0.25	“	0
15	0.5	“	13
16	0.5	“	22
17	1.0	“	21
18	1.0	“	52
19	2.0	“	91
20	2.0	“	91

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), Rh₂(OAc)₄, K₂CO₃ (0.75 mmol), DMF (2.0 mL), 140 °C, t, yields determined by GC analysis using *n*-Tetradecane as internal standard.

The data of Tabelle 35 and Tabelle 36 (with 2 mol% $\text{Rh}_2(\text{OAc})_4$) was visualized in Abbildung 29, presenting two different kinds of reactivity. The 2-Methoxynicotinic acid (blue curve) shows a high initial rate, suggesting a rapid formation of the active species between substrate and catalyst and a complete formation of the product after already 4 h.

Whereas the o-Toluic acid (black curve) compared to the substrate of 2-Methoxynicotinic acid, the o-Toluic acid shows a long incubation time of almost 4 hours whereas after this time the 2-Methoxynicotinic acid had already full conversion. After this very slow incubation time, the conversion of product highly increases after 6 h and has its maximum achieved after 8 h. Interestingly, this substrate needs much longer to form an active species to push the reaction into the direction of the product. Intrigued by those findings, we added 10 mol% of pyridine and repeated the reactions with o-Toluic acid (red curve). In this case, the curve resembles more the one of 2-Methoxynicotinic acid, showing a rapid product formation without a long incubation time. This shows that dirhodium tetracarboxylates are not easily cleaved and will re-form whenever possible. The addition of strongly coordinating pyridine helps to break up the structure.

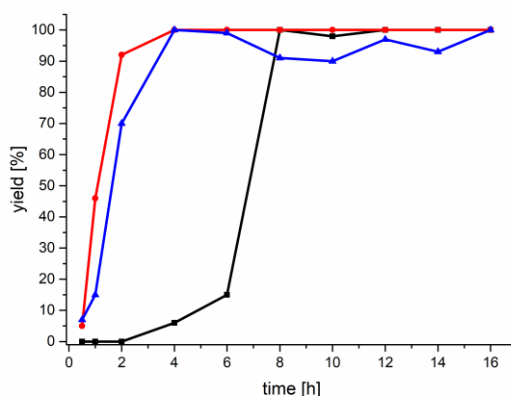


Abbildung 29. GC yields, conversion to product **3ka** (blue curve) and **3aa** (red and black curve) over time.

In the following, 2-Methoxynicotinic acid was used as the model substrate because the o-Toluic acid showed a long incubation time, which made the kinetic studies not reproducible and difficult to evaluate.

The catalytic loading of $\text{Rh}_2(\text{OAc})_4$ was changed from 0.50 mol% up to 2.00 mol% as presented in Tabelle 36 and interpreted in the following Abbildung 30. Values between 0.125 mol% and 0.25 mol% were not included in kinetic calculations because of no conversion.

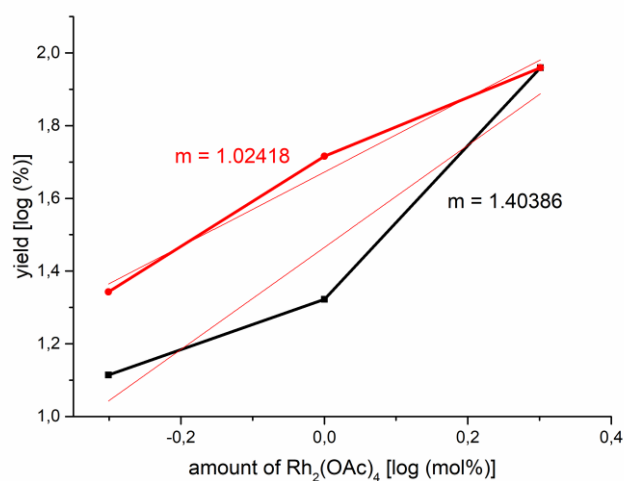
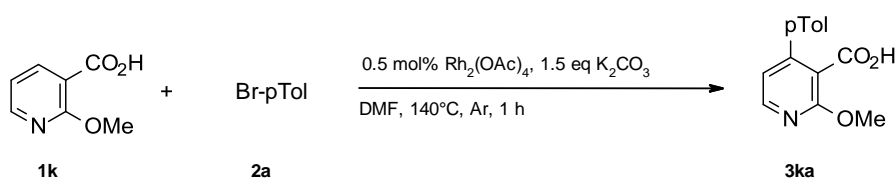


Abbildung 30. Kinetic order of $\text{Rh}_2(\text{OAc})_4$.

The measured results (experiments done twice) can be found in Abbildung 30 and are comparable to each other. These results show an approximately first order in Rhodium catalyst (1.2 +/-0.2).

Tabelle 37. Amount of 4-bromotoluene **2a**.^[a]



Entry	amount 4-bromotoluene (equiv)	3ka (%)
1	0.375	14
2	“	38
3	0.75	57
4	“	57
5	1.5	66
6	“	70
7	3.0	75
8	“	76
9	6.0 [“]	77

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), Rh₂(OAc)₄ (0.5 mol%), K₂CO₃ (0.75 mmol), DMF (2.0 mL), 140 °C, 1 h, yields determined by GC analysis using *n*-Tetradecane as internal standard.

The first point was left out of calculations because of too strong deviations.

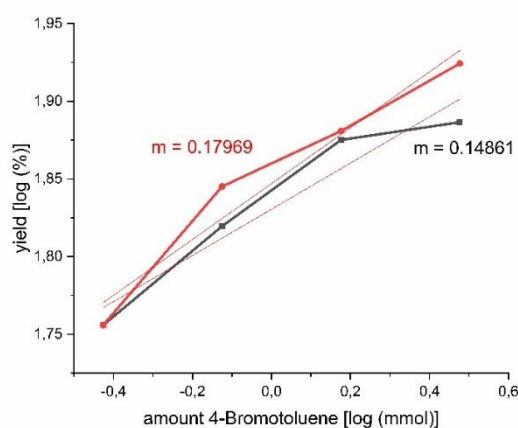


Abbildung 31. Kinetic order of *p*-Bromotoluene.

These results show an almost zero initial kinetic order (+0.2 for the 4-Bromotoluene substrate). Meaning that the C-Br activation is clearly not rate determining and the reaction is independent towards the 4-Bromotoluene, playing no role in the rate determining step.

Finally, the kinetic order for 2-Methoxynicotinic acid was determined. The results present two different sectors. The first one is between 0.375 eq. and 1.50 eq. present a steadily increase. Nevertheless, these points run at almost full conversion and therefore they are no longer in the linear approximation area. This part of the data is therefore not meaningful. Only points starting at 1.50 equivalents are incorporated in to further studies.

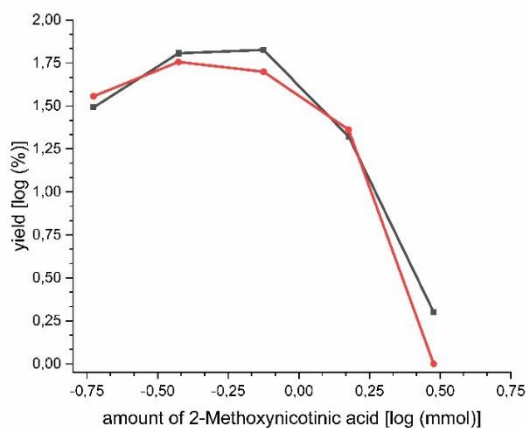


Abbildung 32. Kinetic order of 2-Methoxynicotinic acid.

EXPERIMENTELLER TEIL

As mentioned above the last three points are used for mechanistic kinetic data. Therefore, the results were presented in Abbildung 33.

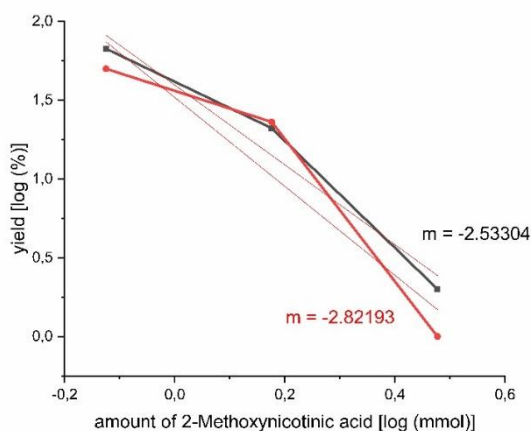


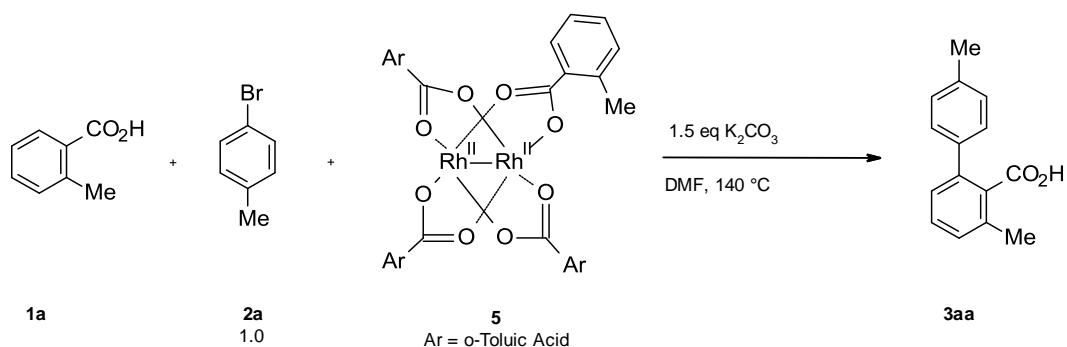
Abbildung 33. Kinetic order for 2-methoxynicotinic acid between 1.5 and 6 eq.

The last points, implying the negative slope present a highly negative kinetic order of approximately -2.6. A clear poisoning effect of that component, presumably through the pyridyl-Rhodium interaction.

7.7.5.7 Synthesis and test reactions of $Rh_2(o\text{-Toluic acid})_4$

$RhCl_3 \cdot 3H_2O$ (280 mg, 1.23 mmol) and Potassium *o*-Toluic acid Carboxylate (1.29 g, 7.38 mmol) in ethanol (20 mL) were refluxed under argon for an hour. The initial orange solution rapidly became green. After cooling to room temperature, the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2 , ethyl acetate/cyclohexane gradient). The resulting blue crystals were washed with warm methanol and collected by filtration. Additionally, the filtrate was allowed to cool down to $-20\text{ }^\circ\text{C}$ overnight, resulting in additional product. $Rh_2(o\text{-Toluic acid})_4$ (**5**) was obtained as blue crystals (213 mg, 0.285 mmol, 23%) that decompose after one day under air.

HRMS-ESI (m/z): [M^+] calcd. for $C_{32}H_{28}O_8Rh_2$: 745.9894; Found: 745.9889.

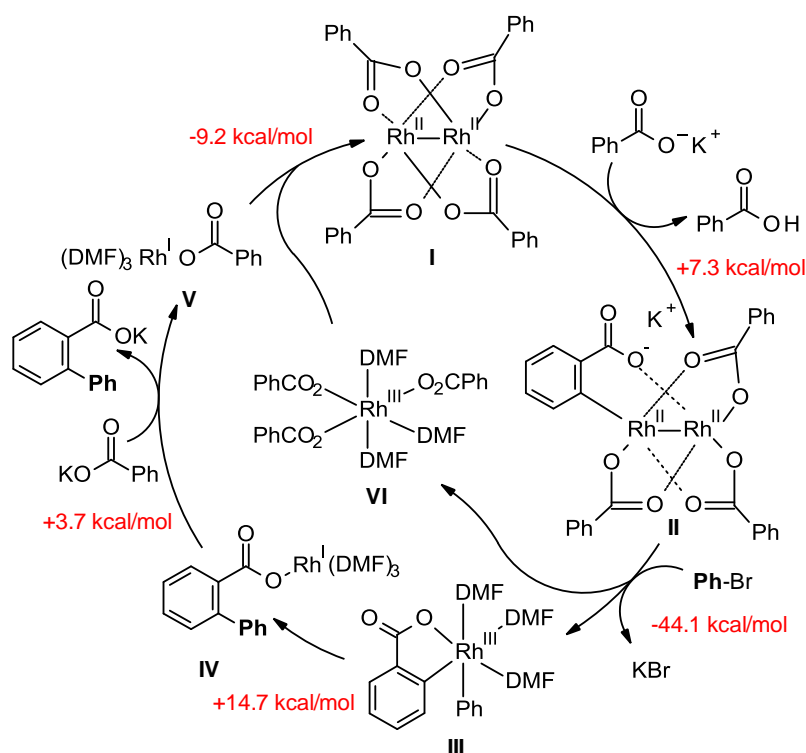
Tabelle 38. Test reactions of $\text{Rh}_2(\text{o-Toluic acid})_4$.^[a]

Entry	2a (equiv)	$\text{Rh}_2(\text{o-Toluic acid})_4$ (equiv)	Reaction time (h)	3aa (%)
1	1	0.02	0.5	0
2	“	0.02	2.0	0
3	“	0.02	18.0	91
4 ^[b]	-	0.5	1.0	100

[a] Reaction conditions: $\text{Rh}_2(\text{o-Toluic acid})_4$, **2a** (0.5 mmol), K_2CO_3 (1.5 equiv), DMF (2.0 mL), 140 °C, yields determined by GC analysis using *n*-Tetradecane as internal standard. [b] **2a** (0.1 mmol), DMF (1.0 mL).

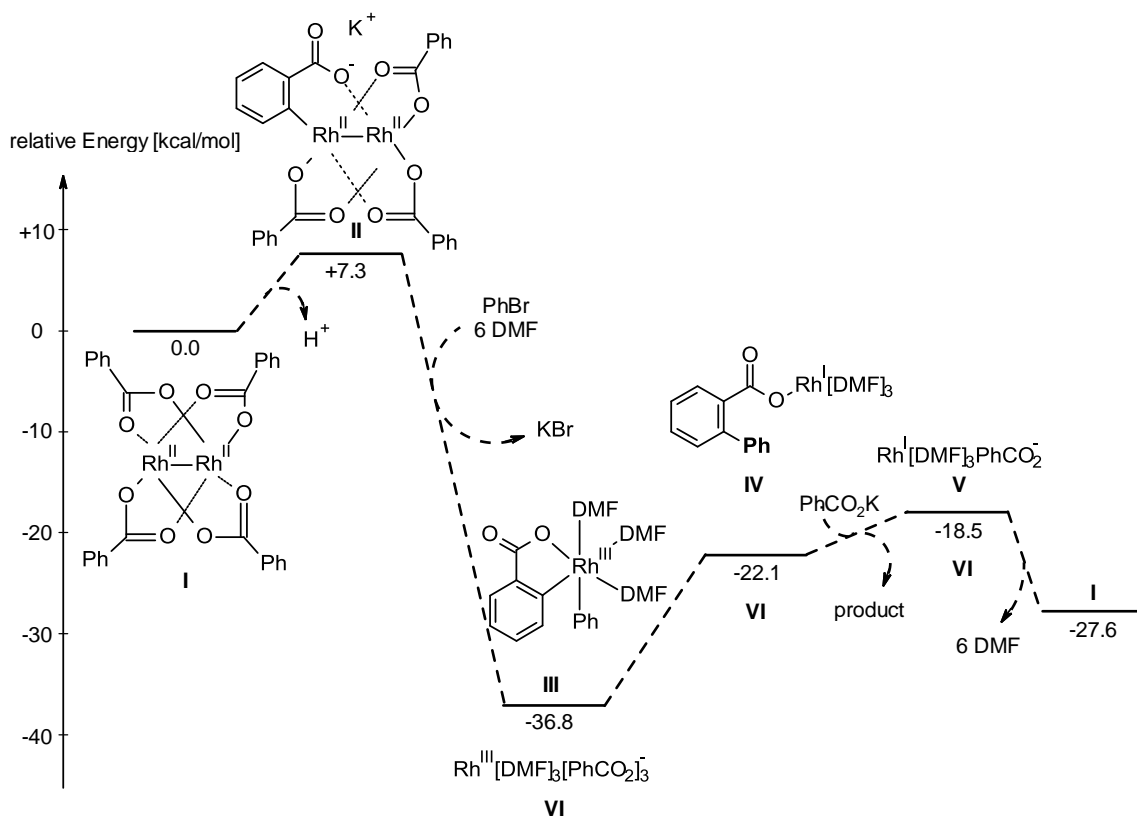
In catalytic amounts, $\text{Rh}_2(\text{o-Toluic acid})_4$ shows a similar incubation period like $\text{Rh}_2(\text{OAc})_4$. Therefore, we reasoned that an acetate benzoate transfer in the $\text{Rh}_2(\text{OAc})_4$ catalyzed coupling of **1a** with **2a** is not responsible for the long incubation period. When $\text{Rh}_2(\text{o-Toluic acid})_4$ is used as the coupling partner for **2a** instead of **1a**, the product **3aa** can quickly be obtained in quantitative yield.

7.7.5.8 DFT Calculations: Overview of the calculated structures, including counter ions and solvent molecules



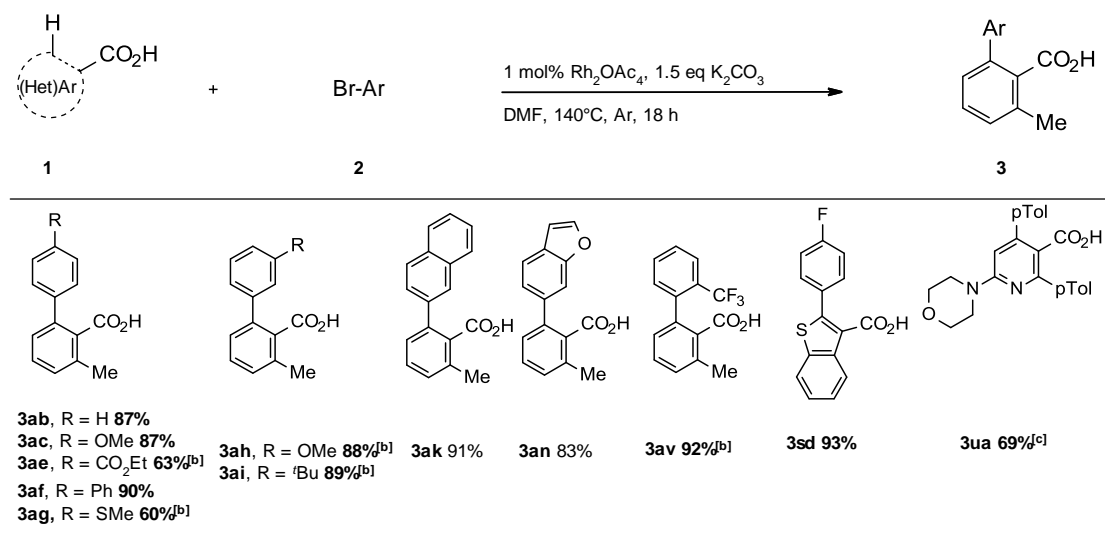
Schema 47. Proposed mechanistic cycle with calculated reaction energies (ΔE) for each step.

Calculations of the relative energies were performed with TURBOMOLE 7.3,³¹⁸ using the B3LYP hybrid functional^{319,320} including Grimme's dispersion correction D3³²¹ and def2-TZVP³²² basis sets, which includes a small core Stuttgart-Dresden effective core potential for Rhodium (MEFIT, WB). The resolution of identity (RI) approximation was used with the corresponding def2 basis sets to fit the charge density and the m5 grid for the integration of XC interactions was employed. Solvent effects were simulated as a dielectric continuum using the COSMO³²³ model ($\epsilon = 38.3$, default atomic radii). Structures were fully optimized until a true minimum was located (no imaginary frequencies).



Scheme 48. Energy profile of the proposed catalytic cycle.

7.7.6 Additional Experiments demonstrating the Scope

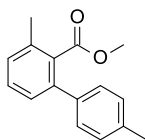


Scheme 49. Additional Experiments demonstrating the scope.^[a]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), Rh₂(OAc)₄ (1 mol%), K₂CO₃ (0.75 mmol), DMF (2.0 mL), 140 °C, 18 h. Yields of the corresponding methyl esters after esterification with K₂CO₃ (2 equiv) and MeI (5 equiv) in NMP. [b] 4 mol% Rh₂(OAc)₄. [c] **2a** (1.25 mmol), 4 mol% Rh₂(OAc)₄.

7.7.7 Synthesis and characterization of products

*Synthesis of 3,4'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester **3aa***

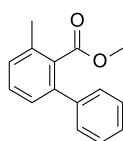


[CAS: 1097018-21-7]

Compound **3aa** was prepared following the general procedure for the *ortho*-Arylation, starting from *ortho*-toluic acid (**1a**) 68.1 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (94.2 μ L, 131 mg, 0.75 mmol). After purification, **3aa** was obtained as colorless solid (109 mg, 0.454 mmol, 91%).

m.p.: 62-63 °C. ^1H NMR (300 MHz, CDCl_3): δ = 7.37 (t, J = 1.0 Hz, 1 H), 7.27 - 7.32 (m, 2 H), 7.18 - 7.26 (m, 4 H), 3.64 (s, 3 H), 2.42 (s, 3 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 170.4 (s), 140.0 (s), 137.9 (s), 137.0 (s), 135.3 (s), 133.1 (s), 129.3 (s), 129.0 (s, 2 C), 128.8 (s), 128.0 (s, 2 C), 127.2 (s), 51.8 (s), 21.1 (s), 19.6 (s) ppm. MS (EI, 70 eV) m/z (%): 241.0 (28), 240.2 (100), 210.2 (9), 209.2 (66), 208.2 (38), 166.3 (12), 165.3 (25). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_2\text{H}^+$: 241.1229; Found: 241.1222. IR: $\tilde{\nu}$ = 3027 (w), 2950 (w), 1726 (s), 1259 (s), 1119 (m), 1066 (s), 788 (s) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²³⁹

*Synthesis of 3-methyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester **3ab***



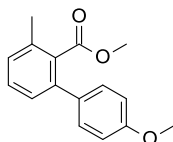
[CAS: 941320-77-0]

Compound **3ab** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% $\text{Rh}_2(\text{OAc})_4$ (2.21 mg, 0.005 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and bromobenzene (**2b**) (79.4 μ L, 118 mg, 0.75 mmol). After purification, **3ab** was obtained as colorless oil (98.2 mg, 0.434 mmol, 87%).

^1H NMR (400 MHz, CDCl_3): δ = 7.17 - 7.33 (m, 6 H), 7.11 (dt, J = 7.8, 1.3 Hz, 2 H), 3.47 (s, 3 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 170.2 (s), 140.9 (s), 140.1 (s), 135.4 (s), 133.1 (s), 129.4 (s), 129.0 (s), 128.2 (s, 2 C), 128.2 (s, 2 C), 127.3 (s), 127.2 (s), 51.7 (s), 19.6 (s) ppm. MS (EI, 70 eV) m/z (%): 226.9 (15), 226.0 (70), 196.1 (13), 195.2 (100), 194.4

(47), 167.2 (12), 165.2 (20). HRMS-ESI (m/z): $[M+H^+]$ calcd. for $C_{15}H_{14}O_2H^+$: 227.1072; Found: 227.1062. IR: $\tilde{\nu}$ = 3059 (w), 2996 (w), 2948 (w), 1725 (s), 1435 (m), 1265 (s), 1121 (m), 1091 (m), 1066 (m), 745 (s) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.³²⁴

Synthesis of 4'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester 3ac

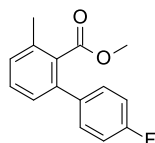


[CAS: 1097018-19-3]

Compound **3ac** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% $Rh_2(OAc)_4$ (2.21 mg, 0.005 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 4-bromoanisole (**2c**) (95.1 μ L, 142 mg, 0.75 mmol). After purification, **3ac** was obtained as colorless oil (111 mg, 0.433 mmol, 87%).

1H NMR (300 MHz, $CDCl_3$): δ = 7.18 - 7.31 (m, 3 H), 7.07 - 7.17 (m, 2 H), 6.80 - 6.92 (m, 2 H), 3.77 (s, 3 H), 3.57 (s, 3 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.5 (s), 159.0 (s), 139.6 (s), 135.3 (s), 133.3 (s), 133.2 (s), 129.3 (s), 129.3 (s), 128.7 (s), 127.2 (s), 113.7 (s), 55.2 (s), 51.8 (s), 19.6 (s) ppm. MS (EI, 70 eV) m/z (%): 257.0 (16), 256.0 (100), 226.3 (14), 225.4 (68), 224.6 (48), 209.3 (12), 181.2 (10). HRMS-ESI (m/z): $[M+H^+]$ calcd. for $C_{16}H_{16}O_3H^+$: 257.1178; Found: 257.1193. IR: $\tilde{\nu}$ = 3440 (w), 3064 (w), 2999 (w), 2949 (w), 2837 (w), 1723 (s), 1610 (m), 1514 (m), 1460 (m), 1247 (s), 1179 (m), 1221 (m), 1089 (m), 1066 (m), 1031 (m), 836 (m), 789 (s), 572 (m) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²³⁹

Synthesis of 4'-fluoro-3-methyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester 3ad



[CAS: 1809272-60-3]

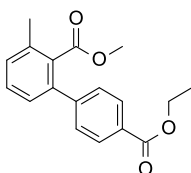
Compound **3ad** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% $Rh_2(OAc)_4$ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene (**2d**) (83.4 μ L, 133 mg, 0.75 mmol). After purification, **3ad** was obtained as colorless solid (116 mg, 0.475 mmol, 95%).

EXPERIMENTELLER TEIL

m.p.: 63-64 °C.

^1H NMR (400 MHz, CDCl_3): δ = 7.29 - 7.41 (m, 3 H), 7.21 (dd, J = 16.3, 7.7 Hz, 2 H), 7.03 - 7.13 (m, 2 H), 3.63 (s, 3 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 170.1 (s), 162.3 (d), 139.0 (s), 136.9 (d), 135.5 (s), 133.2 (s), 129.8 (d), 129.3 (d), 127.1 (s), 115.3 (s), 115.0 (s), 51.8 (s), 19.6 (s) ppm. ^{19}F NMR (41 MHz, CDCl_3): δ = -117.33 ppm. MS (EI, 70 eV) m/z (%): 244.9 (16), 244.0 (68), 214.3 (12), 213.2 (100), 212.3 (26), 183.3 (13), 165.2 (11). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{15}\text{H}_{13}\text{FO}_2\text{H}^+$: 245.0978; Found: 245.0966. IR $\tilde{\nu}$ = 3044 (w), 2995 (w), 2949 (w), 1737 (s), 1509 (m), 1263 (s), 1223 (s), 1120 (m), 1089 (m), 1065 (m), 843 (m), 793 (s), 773 (m), 741 (m), 582 (m) cm^{-1} .

Synthesis of 3-methyl-[1,1'-biphenyl]-2,4'-dicarboxylic acid 4'-ethyl 2-methyl ester 3ae

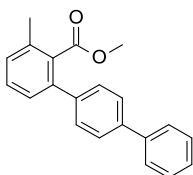


[CAS: 2040483-22-3]

Compound **3ae** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% $\text{Rh}_2(\text{OAc})_4$ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and ethyl-4-bromobenzoate (**2e**) (121 μL , 174 mg, 0.75 mmol). After purification, **3ae** was obtained as colorless solid (95 mg, 0.317 mmol, 63%).

m.p.: 76-77 °C. ^1H NMR (300 MHz, CDCl_3): δ = 8.02 - 8.12 (m, 2 H), 7.40 - 7.49 (m, 2 H), 7.38 (d, J = 7.7 Hz, 1 H), 7.19 - 7.30 (m, 2 H), 4.41 (q, J = 7.2 Hz, 2 H), 3.59 (s, 3 H), 2.42 (s, 3 H), 1.42 (t, J = 7.1 Hz, 3 H) ppm. ^{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, 4 C), 129.4 (s), 128.2 (s), 127.1 (s), 61.0 (s), 51.9 (s), 19.7 (s), 14.3 (s) ppm. MS (EI, 70 eV) m/z (%): 299.0 (21), 298.0 (100), 267.2 (30), 253.2 (73), 195.2 (55), 194.3 (27), 165.2 (23). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{18}\text{H}_{18}\text{O}_4\text{H}^+$: 299.1283; Found: 299.1277. IR $\tilde{\nu}$ = 3030 (w), 2984 (w), 2955 (w), 1713 (s), 1271 (s), 1118 (m), 1101 (s), 1065 (m), 772 (s), 708 (s) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁶⁸

Synthesis of 3-methyl-[1,1':4',1'-terphenyl]-2-carboxylic acid methyl ester 3af

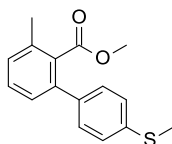


[CAS: 1809272-56-7]

Compound **3af** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% Rh₂(OAc)₄ (2.21 mg, 0.005 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 4-bromobiphenyl (**2f**) (194 mg, 0.75 mmol). After purification, **3af** was obtained as colorless solid (135 mg, 0.448 mmol, 90%).

m.p.: 78-79 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.61 - 7.68 (m, 4 H), 7.42 - 7.50 (m, 4 H), 7.34 - 7.42 (m, 2 H), 7.21 - 7.30 (m, 2 H), 3.64 (s, 3 H), 2.43 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 170.4 (s), 140.6 (s), 140.1 (s), 139.9 (s), 139.7 (s), 135.5 (s), 133.1 (s), 129.5 (s), 129.2 (s), 128.8 (s, 2 C), 128.6 (s, 2 C), 127.4 (s, 2 C), 127.2 (s, 2 C), 127.0 (s), 127.0 (s), 51.9 (s), 19.7 (s) ppm. MS (EI, 70 eV) *m/z* (%): 303.1 (22), 302.1 (100), 272.2 (12), 271.4 (67), 270.5 (22), 269.5 (19), 77.1 (8). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₂₁H₁₈O₂H⁺: 303.1385; Found: 303.1386. IR: $\tilde{\nu}$ = 3056 (w), 3028 (w), 2950 (w), 1728 (s), 1258 (s), 1116 (m), 1091 (m), 1065 (m), 764 (s), 695 (m) cm⁻¹.

Synthesis of 4'-methylthio-3-methyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester 3ag



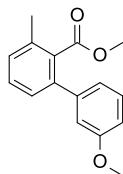
Compound **3ag** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% Rh₂(OAc)₄ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 4-bromothioanisole (**2g**) (155 mg, 0.75 mmol). After purification, **3ag** was obtained as colorless solid (81 mg, 0.297 mmol, 60%).

m.p.: 95-97 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.36 (t, *J* = 7.7 Hz, 1 H), 7.24 - 7.33 (m, 4 H), 7.18 - 7.24 (m, 2 H), 3.63 (s, 3 H), 2.52 (s, 3 H), 2.40 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 170.3 (s), 139.4 (s), 137.8 (s), 137.6 (s), 135.5 (s), 133.1 (s), 129.4 (s), 129.1 (s), 128.6 (s, 2 C), 127.1 (s), 126.3 (s, 2 C), 51.9 (s), 19.7 (s), 15.7 (s) ppm. MS (EI, 70 eV) *m/z* (%): 273.0 (17), 272.1 (100), 241.3 (30), 225.2 (18), 194.3 (19), 193.3 (12), 165.2 (10). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₆H₁₆O₂SH⁺: 273.0949; Found: 273.0939. IR: $\tilde{\nu}$ = 3048 (w),

EXPERIMENTELLER TEIL

3029 (w), 2998 (w), 2950 (w), 1725 (s), 1262 (s), 1119 (m), 1098 (m), 1063 (m), 831 (m), 799 (s), 407 (m) cm^{-1} .

*Synthesis of 3'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester **3ah***

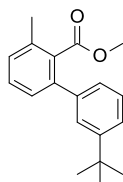


[CAS: 2040483-23-4]

Compound **3ah** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% $\text{Rh}_2(\text{OAc})_4$ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 3-bromoanisole (**2h**) (94.8 μL , 140 mg, 0.75 mmol). After purification, **3ah** was obtained as colorless oil (113 mg, 0.441 mmol, 88%).

^1H NMR (300 MHz, CDCl_3): δ = 7.23 - 7.36 (m, 2 H), 7.15 - 7.23 (m, 2 H), 6.80 - 6.98 (m, 3 H), 3.79 (s, 3 H), 3.59 (s, 3 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 170.2 (s), 159.4 (s), 142.2 (s), 139.9 (s), 135.4 (s), 133.1 (s), 129.4 (s), 129.3 (s), 129.1 (s), 127.1 (s), 120.6 (s), 113.5 (s), 113.2 (s), 55.2 (s), 51.8 (s), 19.6 (s) ppm. MS (EI, 70 eV) m/z (%): 257.0 (12), 256.0 (85), 226.2 (16), 225.3 (78), 224.5 (100), 182.2 (11), 181.3 (12). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_3\text{H}^+$: 257.1178; Found: 257.1168. IR: $\tilde{\nu}$ = 3442 (w), 3062 (w), 2948 (w), 2835 (w), 1725 (s), 1576 (m), 1466 (m), 1265 (s), 1228 (m), 1120 (m), 1066 (m), 1040 (m), 776 (m), 699 (m) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁶⁸

*Synthesis of 3'-(1,1-dimethylethyl)-3-methyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester **3ai***

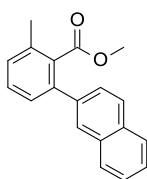


[CAS: 2051922-36-0]

Compound **3ai** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% $\text{Rh}_2(\text{OAc})_4$ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 1-bromo-3-tert-butylbenzene (**2i**) (129 μL , 161 mg, 0.75 mmol). After purification, **3ai** was obtained as colorless oil (125 mg, 0.443 mmol, 89%).

^1H NMR (400 MHz, CDCl_3): δ = 7.41 - 7.53 (m, 4 H), 7.29 - 7.37 (m, 3 H), 3.70 (s, 3 H), 2.52 (s, 3 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 170.3 (s), 151.0 (s), 140.6 (s), 140.5 (s), 135.3 (s), 133.2 (s), 129.3 (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, 3 C), 19.6 (s) ppm. MS (EI, 70 eV) m/z (%): 282.1 (39), 267.1 (34), 236.2 (20), 235.2 (100), 207.3 (32), 195.2 (21), 193.3 (59). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{19}\text{H}_{22}\text{O}_2\text{H}^+$: 283.1698; Found: 283.1697. IR: $\tilde{\nu}$ = 3061 (w), 3025 (w), 2953 (m), 1726 (s), 1435 (m), 1267 (s), 1117 (m), 1100 (m), 1067 (s), 785 (s), 707 (s) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁶⁸

Synthesis of 2-methyl-6-(2-naphthalenyl)-benzoic acid methyl ester 3ak

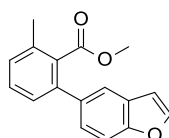


[CAS: 54811-42-6]

Compound **3ak** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% $\text{Rh}_2(\text{OAc})_4$ (2.21 mg, 0.005 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 2-bromonaphthalene (**2k**) (157 mg, 0.75 mmol). After purification, **3ak** was obtained as yellow oil (126 mg, 0.455 mmol, 91%).

^1H NMR (300 MHz, CDCl_3): δ = 7.73 - 7.85 (m, 4 H), 7.38 - 7.50 (m, 3 H), 7.22 - 7.37 (m, 2 H), 7.13 - 7.22 (m, 1 H), 3.48 (s, 3 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 170.3 (s), 140.0 (s), 138.3 (s), 135.5 (s), 133.3 (s), 133.2 (s), 132.4 (s), 129.4 (s), 129.2 (s), 128.1 (s), 127.9 (s), 127.6 (s), 127.5 (s), 127.0 (s), 126.5 (s), 126.2 (s), 126.0 (s), 51.8 (s), 19.7 (s) ppm. MS (EI, 70 eV) m/z (%): 277.1 (18), 276.2 (100), 246.3 (13), 245.4 (43), 244.6 (31), 215.4 (9), 202.3 (9). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{19}\text{H}_{16}\text{O}_2\text{H}^+$: 277.1229; Found: 277.1217. IR: $\tilde{\nu}$ = 3439 (w), 3054 (w), 3020 (w), 2947 (w), 1723 (s), 1588 (w), 1433 (m), 1265 (s), 1116 (m), 1065 (m), 789 (s), 732 (s), 478 (s) cm^{-1} .

Synthesis of 2-methyl-6-(5-benzofuranyl)-benzoic acid methyl ester 3an



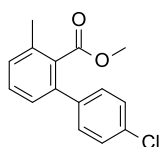
Compound **3an** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% $\text{Rh}_2(\text{OAc})_4$ (2.21 mg, 0.005 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg,

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0.50 mmol) and 5-bromo-1-benzofurane (**2n**) (97 μ L, 152 mg, 0.75 mmol). After purification, **3an** was obtained as yellow oil (110 mg, 0.413 mmol, 83%).

^1H NMR (300 MHz, CDCl_3): δ = 7.50 - 7.63 (m, 2 H), 7.40 - 7.50 (m, 1 H), 7.22 - 7.34 (m, 2 H), 7.11 - 7.22 (m, 2 H), 6.72 (dd, J =2.2, 0.9 Hz, 1 H), 3.50 (s, 3 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 170.4 (s), 154.3 (s), 145.5 (s), 140.2 (s), 135.8 (s), 135.3 (s), 133.5 (s), 129.3 (s), 128.8 (s), 127.5 (s), 127.5 (s), 124.8 (s), 120.8 (s), 111.0 (s), 106.7 (s), 51.8 (s), 19.7 (s) ppm. MS (EI, 70 eV) m/z (%): 266.1 (86), 235.1 (79), 234.1 (100). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{17}\text{H}_{14}\text{O}_3\text{H}^+$: 267.1021; Found: 267.1004. IR: $\tilde{\nu}$ = 3022 (w), 2948 (w), 1723 (s), 1454 (m), 1263 (s), 1110 (m), 1079 (m), 1029 (m), 768 (s), 734 (s) cm^{-1} .

Synthesis of 4'-chloro-3-methyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester 3ap

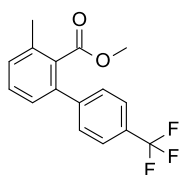


[CAS: 1809272-61-4]

Compound **3ap** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% $\text{Rh}_2(\text{OAc})_4$ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 1-bromo-4-chlorobenzene (**2p**) (87 μ L, 144 mg, 0.75 mmol). After purification, **3ap** was obtained as colorless oil (112 mg, 0.430 mmol, 86%).

^1H NMR (400 MHz, CDCl_3): δ = 7.34 - 7.41 (m, 3 H), 7.29 - 7.33 (m, 2 H), 7.24 (d, J = 7.6 Hz, 1 H), 7.19 (d, J = 7.6 Hz, 1 H), 3.63 (s, 3 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 170.0 (s), 139.3 (s), 138.8 (s), 135.6 (s), 133.5 (s), 133.0 (s), 129.5 (s, 2 C), 129.4 (s, 2 C), 129.4 (s), 128.4 (s), 127.0 (s), 51.8 (s), 19.6 (s) ppm. MS (EI, 70 eV) m/z (%): 261.9 (19), 260.0 (58), 231.3 (34), 230.3 (20), 229.3 (100), 193.3 (21), 165.2 (19). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{15}\text{H}_{13}\text{ClO}_2\text{H}^+$: 261.0682; Found: 261.0671. IR: $\tilde{\nu}$ = 3441 (w), 3063 (w), 2995 (w), 1724 (s), 1459 (m), 1265 (s), 1121 (m), 1084 (s), 1014 (m), 835 (m), 787 (s), 520 (m) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁶⁸

Synthesis of 3-methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid methyl ester 3aq

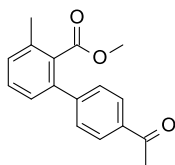


[CAS: 486437-71-2]

Compound **3aq** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% Rh₂(OAc)₄ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 4-bromo- α,α,α -trifluorotoluene (**2q**) (108 μ L, 172 mg, 0.75 mmol). After purification, **3aq** was obtained as colorless oil (131 mg, 0.445 mmol, 89%).

¹H NMR (400 MHz, CDCl₃): δ = 7.61 (d, *J* = 8.3 Hz, 2 H), 7.43 (d, *J* = 8.3 Hz, 2 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 7.3 Hz, 1 H), 7.15 (d, *J* = 7.6 Hz, 1 H), 3.55 (s, 3 H), 2.37 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 169.8 (s), 144.6 (s), 138.7 (s), 135.9 (s), 133.1 (s), 129.9 (s), 129.6 (s), 128.6 (s), 127.1 (s), 125.5 (s), 125.2 (q), 122.8 (s), 51.9 (s), 19.7 (s) ppm. ¹⁹F NMR (41 MHz, CDCl₃): δ = -64.67 ppm. MS (EI, 70 eV) *m/z* (%): 294.9 (9), 294.0 (42), 275.3 (8), 264.3 (14), 263.3 (100), 262.5 (30), 165.2 (12). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₆H₁₃F₃O₂H⁺: 295.0946; Found: 295.0935. IR: $\tilde{\nu}$ = 3067 (w), 2999 (w), 2952 (w), 1762 (s), 1323 (2), 1264 (m), 1109 (s), 1062 (s), 1018 (m), 847 (w), 790 (w), 609 (w) cm⁻¹.

Synthesis of 4'-acetyl-3-methyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester 3ar



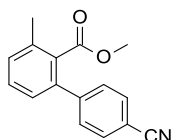
[CAS: 1809272-58-9]

Compound **3ar** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% Rh₂(OAc)₄ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 4'-bromoacetophenone (**2r**) (151 mg, 0.75 mmol). After purification, **3ar** was obtained as colorless solid (116 mg, 0.432 mmol, 87%).

m.p.: 127-128 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.00 (dt, *J* = 8.4, 1.8 Hz, 2 H), 7.47 (dt, *J* = 8.6, 1.8 Hz, 2 H), 7.40 (t, *J* = 7.9 Hz, 1 H), 7.19 - 7.31 (m, 2 H), 3.61 (s, 3 H), 2.64 (s, 3 H), 2.42 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 197.7 (s), 169.9 (s), 145.8 (s), 139.0 (s), 136.0 (s), 135.9 (s), 133.0 (s), 129.9 (s), 129.6 (s), 128.5 (s, 2 C), 128.4 (s, 2 C), 127.0 (s), 51.9 (s), 26.6 (s), 19.7 (s) ppm. MS (EI, 70 eV) *m/z* (%): 268.0 (22), 254.2 (17), 253.2 (100), 195.3 (10), 43.0 (8). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₇H₁₆O₃H⁺: 269.1178; Found: 269.1172. IR: $\tilde{\nu}$ = 3064 (w), 3001 (w), 2950 (w), 1719 (s), 1680 (s), 1270 (s), 846 (m), 796 (m), 602 (m) cm⁻¹.

Synthesis of 4'-cyano-3-methyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester 3as

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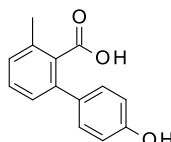


[CAS: 2055238-78-1]

Compound **3as** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% Rh₂(OAc)₄ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 4-bromobenzonitrile (**2s**) (138 mg, 0.75 mmol). After purification, **3as** was obtained as colorless solid (25 mg, 0.099 mmol, 20%).

m.p.: 73-74 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.69 (dt, *J* = 8.6, 1.7 Hz, 2 H), 7.47 (dt, *J* = 8.6, 1.7 Hz, 2 H), 7.37 - 7.44 (m, 1 H), 7.27 - 7.32 (m, 1 H), 7.16 - 7.21 (m, 1 H), 3.61 (s, 3 H), 2.42 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 169.6 (s), 145.7 (s), 138.3 (s), 136.1 (s), 132.9 (s), 132.1 (s, 2 C), 130.3 (s), 129.7 (s), 129.0 (s), 126.9 (s, 2 C), 118.7 (s), 111.3 (s), 52.0 (s), 19.7 (s) ppm. MS (EI, 70 eV) *m/z* (%): 251.0 (39), 221.1 (15), 220.1 (100), 219.1 (33), 191.2 (10), 190.2 (15), 165.2 (11). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₆H₁₃NO₂H⁺: 252.1025; Found: 252.1018. IR: 252.1018. $\tilde{\nu}$ = 3026 (w), 2953 (w), 2228 (m), 1723 (s), 1270 (s), 1121 (m), 1088 (m), 1064 (m), 843 (s), 795 (s), 581 (m) cm⁻¹.

Synthesis of 4'-hydroxy-3-methyl-[1,1'-biphenyl]-2-carboxylic acid 3at



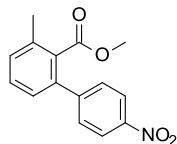
[CAS: 1261914-93-5]

Compound **3at** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% Rh₂(OAc)₄ (2.21 mg, 0.005 mmol) without further methylation, starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 4-bromophenol (**2t**) (131 mg, 0.75 mmol). After purification, **3at** was obtained as colorless solid (102 mg, 0.446 mmol, 89%).

m.p.: 203-204 °C. ¹H NMR (300 MHz, DMSO-*d*₆): δ = 12.91 (br. s., 1 H), 9.51 (s, 1 H), 7.27 - 7.41 (m, 1 H), 7.17 - 7.24 (m, 3 H), 7.14 (d, *J* = 7.5 Hz, 1 H), 6.69 - 6.83 (m, 2 H), 2.31 (s, 3 H) ppm. ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 170.8 (s), 156.9 (s), 138.3 (s), 134.6 (s), 133.6 (s), 131.1 (s), 129.3 (s, 2 C), 128.7 (s), 128.2 (s), 126.9 (s), 115.1 (s, 2 C), 19.3 (s) ppm. HRMS-ESI (*m/z*): [M+Na⁺] calcd. for C₁₄H₁₂O₃Na⁺: 251.0684; Found: 251.0677. IR: $\tilde{\nu}$ = 3488 (m),

3060 (w), 3021 (w), 2957 (w), 1665 (s), 1515 (m), 1265 (s), 1211 (s), 1170 (m), 831 (s), 775 (s), 531 (s) cm^{-1} . The analytical data (NMR) matched those reported in the literature.³²⁵

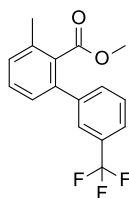
*Synthesis of 4'-nitro-3-methyl-[1,1'-Biphenyl]-2-carboxylic acid methyl ester **3au***



Compound **3au** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% $\text{Rh}_2(\text{OAc})_4$ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 1-bromo-4-nitrobenzene (**2u**) (153 mg, 0.75 mmol). After purification, **3au** was obtained as yellow solid (78 mg, 0.288 mmol, 58%).

m.p.: 99-100 °C. ^1H NMR (300 MHz, CDCl_3): δ = 8.19 - 8.33 (m, 2 H), 7.47 - 7.58 (m, 2 H), 7.37 - 7.46 (m, 1 H), 7.28 - 7.36 (m, 1 H), 7.16 - 7.25 (m, 1 H), 3.62 (s, 3 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 169.6 (s), 147.7 (s), 147.2 (s), 138.0 (s), 136.2 (s), 132.9 (s), 130.5 (s), 129.8 (s), 129.1 (s), 127.0 (s), 123.6 (s), 52.1 (s), 19.8 (s) ppm. MS (EI, 70 eV) m/z (%): 270.8 (56), 254.0 (59), 240.1 (97), 239.0 (43), 194.1 (100), 193.1 (33), 165.0 (61). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{15}\text{H}_{13}\text{NO}_4\text{H}^+$: 272.0923; Found: 272.0916. IR: $\tilde{\nu}$ = 3076 (w), 2950 (w), 1723 (s), 1589 (m), 1516 (s), 1344 (s), 1263 (s), 1067 (w), 847 (s), 753 (s) cm^{-1} .

*Synthesis of 3-methyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid methyl ester **3av***



[CAS: 2022197-28-8]

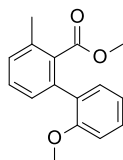
Compound **3av** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% $\text{Rh}_2(\text{OAc})_4$ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 3-bromobenzotrifluoride (**2v**) (106 μL , 170 mg, 0.75 mmol). After purification, **3av** was obtained as colorless oil (136 mg, 0.462 mmol, 92%).

^1H NMR (400 MHz, CDCl_3): δ = 7.50 (s, 1 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.31 - 7.43 (m, 2 H), 7.23 (t, J = 7.6 Hz, 1 H), 7.11 (d, J = 8.1 Hz, 1 H), 7.06 (d, J = 7.6 Hz, 1 H), 3.45 (s, 3 H), 2.26 (s, 3 H) ppm. ^{13}C NMR: (101 MHz, CDCl_3): δ = 169.8 (s), 141.7 (s), 138.6 (s), 135.8 (s), 133.2 (s), 131.6 (s), 131.6 (s), 130.5 (s), 129.8 (s), 129.6 (s), 128.8 (s), 127.1 (s), 125.0 (q), 124.1 (q),

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51.8 (s), 19.6 (s), ppm. ^{19}F NMR (41 MHz, CDCl_3): $\delta = -64.79$ ppm. MS (EI, 70 eV) m/z (%): 294.0 (41), 275.1 (8), 264.2 (16), 263.1 (100), 262.2 (34), 215.2 (10), 165.2 (16). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{O}_2\text{H}^+$: 295.0946; Found: 295.0942. IR: $\tilde{\nu} = 3067$ (w), 2998 (w), 2953 (w), 1727 (s), 1433 (m), 1335 (s), 1264 (s), 1120 (s), 1067 (s), 782 (m), 703 (s) cm^{-1} .

Synthesis of 2'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester 3aw

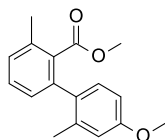


[CAS: 1809272-65-8]

Compound **3aw** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% $\text{Rh}_2(\text{OAc})_4$ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 2-bromoanisole (**2w**) (95.4 μL , 143 mg, 0.75 mmol). After purification, **3aw** was obtained as yellow oil (105 mg, 0.410 mmol, 82%).

^1H NMR (400 MHz, CDCl_3): $\delta = 7.29 - 7.42$ (m, 2 H), 7.19 - 7.27 (m, 3 H), 7.02 (td, $J = 7.5$, 1.0 Hz, 1 H), 6.92 - 6.98 (m, 1 H), 3.77 (s, 3 H), 3.57 (s, 3 H), 2.47 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): $\delta = 169.5$ (s), 156.2 (s), 137.3 (s), 135.7 (s), 133.3 (s), 130.5 (s), 130.0 (s), 129.3 (s), 129.3 (s), 128.8 (s), 128.3 (s), 120.4 (s), 110.5 (s), 55.3 (s), 51.3 (s), 20.2 (s) ppm. MS (EI, 70 eV) m/z (%): 256.0 (64), 226.2 (16), 225.3 (100), 224.6 (20), 210.3 (17), 209.3 (31), 181.2 (19). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_3\text{H}^+$: 257.1176; Found: 257.1168. IR: $\tilde{\nu} = 3060$ (w), 2993 (w), 2948 (w), 2835 (w), 1724 (s), 1433 (m), 1262 (s), 1165 (m), 1066 (m), 745 (s) cm^{-1} .

Synthesis of 4'-methoxy-2',3-dimethyl-[1,1'-biphenyl]-2-carboxylic acid methyl ester 3ax

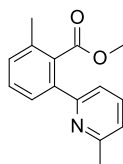


[CAS: 2051922-34-8]

Compound **3ax** was prepared following the general procedure for the *ortho*-Arylation, starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 2-bromo-5-methoxytoluene (**2x**) (171 μL , 155 mg, 0.75 mmol). After purification, **3ax** was obtained as colorless oil (102 mg, 0.376 mmol, 75%).

^1H NMR (300 MHz, CDCl_3): δ = 7.25 - 7.36 (m, 1 H), 7.15 - 7.24 (m, 1 H), 6.99 - 7.09 (m, 2 H), 6.79 (d, J = 2.8 Hz, 1 H), 6.67 - 6.75 (m, 1 H), 3.83 (s, 3 H), 3.52 (s, 3 H), 2.40 (s, 3 H), 2.12 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 169.9 (s), 158.8 (s), 139.5 (s), 137.5 (s), 135.0 (s), 134.2 (s), 132.6 (s), 130.2 (s), 128.8 (s), 128.7 (s), 127.6 (s), 115.2 (s), 110.3 (s), 55.1 (s), 51.6 (s), 20.4 (s), 19.7 (s) ppm. MS (EI, 70 eV) m/z (%): 271.0 (17), 270.1 (100), 240.3 (12), 239.4 (48), 238.6 (52), 196.2 (13), 195.3 (28). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{17}\text{H}_{18}\text{O}_3\text{H}^+$: 271.1334; Found: 271.1327. IR: $\tilde{\nu}$ = 3444 (w), 3061 (w), 2998 (w), 2835 (w), 1727 (s), 1608 (m), 1504 (m), 1461 (m), 1266 (s), 1236 (s), 111 (m), 1082 (m), 1065 (m), 1041 (m), 793 (m), 601 (w), 472 (w) cm^{-1} . The analytical Data (NMR) matched those reported in the literature.²⁶⁸

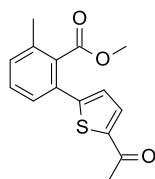
Synthesis of 3-methyl-4-(5-methyl-2-pyridinyl)-2-carboxylic acid methyl ester 3ay



Compound **3ay** was prepared following the general procedure for the *ortho*-Arylation, starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 2-bromo-6-methylpyridine (**2y**) (86.3 μL , 130 mg, 0.75 mmol). After purification, **3ay** was obtained as colorless oil (36 mg, 0.150 mmol, 30%).

^1H NMR (400 MHz, CDCl_3): δ = 7.63 (t, J = 7.6 Hz, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.32 - 7.42 (m, 2 H), 7.25 (d, J = 7.3 Hz, 1 H), 7.08 (d, J = 7.6 Hz, 1 H), 3.75 (s, 3 H), 2.57 (s, 3 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 170.5 (s), 157.5 (s), 156.9 (s), 138.6 (s), 136.8 (s), 136.1 (s), 133.0 (s), 130.3 (s), 129.3 (s), 126.1 (s), 121.5 (s), 118.9 (s), 51.5 (s), 24.4 (s), 19.6 (s) ppm. MS (EI, 70 eV) m/z (%): 240.9 (13), 226.0 (15), 211.1 (16), 210.1 (100), 209.0 (36), 183.1 (11), 180.1 (13). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{15}\text{H}_{15}\text{NO}_2\text{H}^+$: 242.1181; Found: 242.1175. IR: $\tilde{\nu}$ = 3064 (w), 2989 (w), 2947 (w), 1726 (s), 1574 (m), 1450 (m), 1264 (s), 1110 (m), 1071 (m), 777 (s) cm^{-1} .

Synthesis of 2-methyl-6-(5-acetyl-2-thienyl)-benzoic acid methyl ester 3az

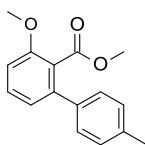


EXPERIMENTELLER TEIL

Compound **3az** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% Rh₂(OAc)₄ (8.84 mg, 0.02 mmol), starting from *ortho*-toluic acid (**1a**) (68.1 mg, 0.50 mmol) and 2-acetyl-5-bromothiophene (**2z**) (155 mg, 0.75 mmol). After purification, **3az** was obtained as yellow oil (19 mg, 0.068 mmol, 14%).

¹H NMR (400 MHz, CDCl₃): δ = 7.59 (d, *J* = 3.8 Hz, 1 H), 7.27 - 7.35 (m, 2 H), 7.20 - 7.26 (m, 1 H), 7.04 (d, *J* = 3.8 Hz, 1 H), 3.73 (s, 3 H), 2.53 (s, 3 H), 2.35 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 190.6 (s), 169.7 (s), 150.6 (s), 144.4 (s), 135.8 (s), 133.2 (s), 132.7 (s), 131.2 (s), 130.7 (s), 129.6 (s), 127.4 (s), 126.9 (s), 52.3 (s), 26.6 (s), 19.6 (s) ppm. MS (EI, 70 eV) *m/z* (%): 274.05 (78), 259.05 (100). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₅H₁₄O₃SH⁺: 275.0742; Found: 275.0741. IR: $\tilde{\nu}$ = 3071 (w), 2949 (w), 1725 (s), 1657 (s), 1437 (m), 1266 (s), 1118 (m), 1070 (m), 786 (m), 596 (m) cm⁻¹.

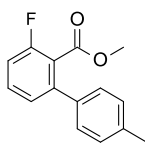
Synthesis of 3-methoxy-4'-methyl-[1,1'-Biphenyl]-2-carboxylic acid methyl ester 3ba



Compound **3ba** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxy-benzoic acid (**1b**) (76.8 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3ba** was obtained as colorless solid (114 mg, 0.446 mmol, 89%).

m.p.: 70-71 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.40 (t, *J* = 8.1 Hz, 1 H), 7.25 - 7.34 (m, 2 H), 7.20 (d, *J* = 7.9 Hz, 2 H), 6.96 (ddd, *J* = 18.2, 8.1, 1.0 Hz, 2 H), 3.89 (s, 3 H), 3.67 (s, 3 H), 2.39 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 168.6 (s), 156.4 (s), 141.2 (s), 137.3 (s), 137.1 (s), 130.4 (s), 129.1 (s, 2 C), 128.1 (s, 2 C), 123.0 (s), 122.0 (s), 109.6 (s), 56.0 (s), 52.1 (s), 21.2 (s) ppm. MS (EI, 70 eV) *m/z* (%): 257.0 (11), 256.0 (41), 226.2 (17), 225.2 (100), 210.3 (9), 182.2 (9), 152.2 (8). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₆H₁₆O₃H⁺: 257.1178; Found: 257.1172. IR: $\tilde{\nu}$ = 3001 (w), 2950 (w), 1729 (s), 1464 (m), 1256 (s), 1101 (s), 1068 (m), 789 (s) cm⁻¹.

Synthesis of 3-fluoro-4'-methyl-[1,1'-Biphenyl]-2-carboxylic acid methyl ester 3ca

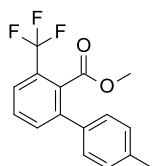


[CAS: 216442-76-1]

Compound **3ca** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% Rh₂(OAc)₄ (2.21 mg, 0.005 mmol), starting from 2- fluorobenzoic acid (**1c**) (70.8 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3ca** was obtained as colorless oil (103 mg, 0.422 mmol, 84%).

¹H NMR (400 MHz, CDCl₃): δ = 7.39 (td, *J* = 8.0, 5.7 Hz, 1 H), 7.12 - 7.27 (m, 5 H), 7.07 (t, *J* = 8.8 Hz, 1 H), 3.68 (s, 3 H), 2.36 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 163.6 (d), 158.4 (s), 142.4 (d), 137.7 (s), 136.3 (d), 131.1 (d), 129.2 (s, 2 C), 128.0 (s, 2 C), 125.4 (s), 121.4 (d), 114.2 (d), 52.3 (s), 21.1 (s) ppm. ¹⁹F NMR (41 MHz, CDCl₃): δ = -113.45 ppm. MS (EI, 70 eV) *m/z* (%): 244.9 (16), 244.1 (58), 214.2 (15), 213.1 (100), 183.2 (14), 170.2 (10), 165.2 (18). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₅H₁₃FO₂H⁺: 245.0978; Found: 245.0971. IR: $\tilde{\nu}$ = 3028 (w), 2951 (w), 1732 (s), 1459 (m), 1261 (s), 1111 (s), 1089 (m), 792 (s) cm⁻¹.

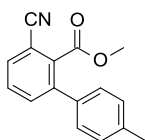
Synthesis of 3-(trifluoromethyl)-4'-methyl-[1,1'-Biphenyl]-2-carboxylic acid methyl ester 3da



Compound **3da** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% Rh₂(OAc)₄ (8.84 mg, 0.02 mmol), starting from 2-(trifluoromethyl)benzoic acid (**1d**) (97.0 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3da** was obtained as yellow oil (136 mg, 0.462 mmol, 92%).

¹H NMR (300 MHz, CDCl₃): δ = 7.63 - 7.72 (m, 1 H), 7.51 - 7.61 (m, 2 H), 7.17 - 7.32 (m, 4 H), 3.66 (s, 3 H), 2.39 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 167.9 (s), 141.3 (s), 137.9 (s), 136.2 (s), 133.5 (d), 131.3 (d), 129.5 (s), 129.2 (s, 2 C), 128.2 (s, 2 C), 127.5 (t), 124.8 (q), 123.5 (d), 52.5 (s), 21.1 (s) ppm. ¹⁹F NMR (41 MHz, CDCl₃): δ = -57.82 ppm. MS (EI, 70 eV) *m/z* (%): 295.1 (15), 294.1 (89), 264.2 (15), 263.2 (100), 243.3 (70), 215.3 (16), 165.2 (19). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₆H₁₃F₃O₂H⁺: 295.0946; Found: 295.0943. IR: $\tilde{\nu}$ = 3027 (w), 2953 (w), 1737 (s), 1326 (s), 1275 (m), 1129 (s), 1066 (s), 805 (m) cm⁻¹.

Synthesis of 3-cyano-4'-methyl-[1,1'-Biphenyl]-2-carboxylic acid methyl ester 3ea

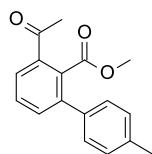


EXPERIMENTELLER TEIL

Compound **3ea** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% Rh₂(OAc)₄ (8.84 mg, 0.02 mmol), starting from 2-cyanobenzoic acid (**1e**) (73.6 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3ea** was obtained as colorless solid (63 mg, 0.251 mmol, 50%).

m.p.: 124-125 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.71 (dd, *J* = 1.0 Hz, 1 H), 7.55 - 7.67 (m, 2 H), 7.24 (s, 4 H), 3.77 (s, 3 H), 2.41 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 167.0 (s), 142.0 (s), 138.3 (s), 135.8 (s), 135.7 (s), 134.4 (s), 131.6 (s), 130.4 (s), 129.4 (s, 2 C), 128.0 (s, 2 C), 117.0 (s), 111.6 (s), 52.8 (s), 21.2 (s) ppm. MS (EI, 70 eV) *m/z* (%): 252.1 (16), 251.1 (46), 250.3 (9), 221.2 (16), 220.2 (100), 190.3 (12), 165.2 (13). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₆H₁₃NO₂H⁺: 252.1025; Found: 252.1020. IR: $\tilde{\nu}$ = 3027 (w), 2951 (w), 2230 (m), 1722 (s), 1284 (s), 1127 (m), 1081 (m), 807 (s) cm⁻¹.

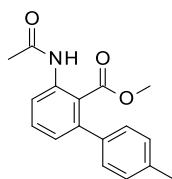
Synthesis of 3-acetyl-4'-methyl-[1,1'-Biphenyl]-2-carboxylic acid methyl ester **3fa**



Compound **3fa** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-acetylbenzoic acid (**1f**) (82.9 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3fa** was obtained as colorless solid (74 mg, 0.276 mmol, 55%).

m.p.: 97-98 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.81 (dd, *J* = 5.4, 3.6 Hz, 1 H), 7.49 - 7.60 (m, 2 H), 7.16 - 7.32 (m, 4 H), 3.69 (s, 3 H), 2.64 (s, 3 H), 2.40 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 198.3 (s), 169.8 (s), 141.0 (s), 137.6 (s), 136.2 (s), 135.9 (s), 134.2 (s), 132.8 (s), 129.1 (s), 129.0 (s, 2 C), 128.3 (s, 2 C), 127.7 (s), 52.2 (s), 27.6 (s), 21.2 (s) ppm. MS (EI, 70 eV) *m/z* (%): 267.9 (19), 254.2 (17), 253.2 (100), 237.3 (33), 221.3 (26), 165.2 (20), 43.0 (11). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₇H₁₆O₃H⁺: 269.1178; Found: 269.1174. IR: $\tilde{\nu}$ = 3055 (w), 3029 (w), 2947 (w), 1731 (s), 1684 (s), 1446 (m), 1255 (s), 1117 (m), 1068 (m), 801 (m) cm⁻¹.

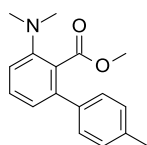
Synthesis of 3-(acetylamino)-4'-methyl-[1,1'-Biphenyl]-2-carboxylic acid methyl ester **3ga**



Compound **3ga** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% Rh₂(OAc)₄ (2.21 mg, 0.005 mmol), starting from *N*-acetylanthranilic acid (**1g**) (90.5 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3ga** was obtained as colorless solid (89 mg, 0.315 mmol, 63%).

m.p.: 137-138 °C. ¹H NMR (400 MHz, CDCl₃): δ = 9.25 (br. s., 1 H), 8.36 (d, *J* = 8.1 Hz, 1 H), 7.48 (t, *J* = 8.1 Hz, 1 H), 7.09 - 7.23 (m, 5 H), 3.47 (s, 3 H), 2.40 (s, 3 H), 2.21 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 170.1 (s), 168.5 (s), 142.9 (s), 138.9 (s), 137.7 (s), 137.0 (s), 131.6 (s), 128.9 (s, 2 C), 127.8 (s, 2 C), 125.7 (s), 120.3 (s), 119.8 (s), 52.0 (s), 25.1 (s), 21.1 (s) ppm. MS (EI, 70 eV) *m/z* (%): 283.1 (46), 252.1 (13), 251.05 (44), 241.1 (44), 236.0 (23), 224.1 (12), 210.05 (22). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₇H₁₇NO₃H⁺: 284.1287; Found: 284.1277. IR: $\tilde{\nu}$ = 3355 (w), 3021 (w), 2950 (w), 1697 (s), 1543 (m), 1462 (m), 1272 (s), 1121 (m), 801 (s) cm⁻¹.

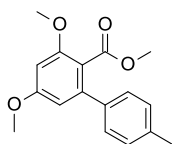
Synthesis of 3-(dimethylamino)-4'-methyl-[1,1'-Biphenyl]-2-carboxylic acid 3ha



Compound **3ha** was prepared following the general procedure for the *ortho*-Arylation, starting from anthranilic acid (**1h**) (68.8 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3ha** was obtained as yellow oil (85 mg, 0.317 mmol, 63%).

¹H NMR (400 MHz, CDCl₃): δ = 7.37 (t, *J* = 7.8 Hz, 1 H), 7.24 - 7.31 (m, 2 H), 7.20 (d, *J* = 8.1 Hz, 2 H), 7.11 (dd, *J* = 8.2, 0.9 Hz, 1 H), 7.00 (dd, *J* = 7.7, 0.9 Hz, 1 H), 3.61 (s, 3 H), 2.82 (s, 6 H), 2.40 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.2 (s), 151.4 (s), 141.1 (s), 137.9 (s), 136.9 (s), 129.9 (s), 128.9 (s), 128.8 (s), 128.1 (s), 123.7 (s), 117.7 (s), 51.9 (s), 44.8 (s), 21.1 (s) ppm. MS (EI, 70 eV) *m/z* (%): 270.0 (10), 269.1 (41), 239.2 (16), 238.3 (100), 237.5 (8), 236.3 (13), 222.3 (15). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₇H₁₉NO₂H⁺: 270.1494; Found: 270.1490. IR: $\tilde{\nu}$ = 3054 (w), 3023 (w), 2945 (w), 2783 (w), 1727 (s), 1580 (m), 1455 (m), 1256 (s), 1115 (s), 1065 (s), 956 (m), 801 (s) cm⁻¹.

Synthesis of 3,5-dimethoxy-4'-methyl-[1,1'-Biphenyl]-2-carboxylic acid methyl ester 3ia

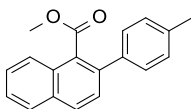


EXPERIMENTELLER TEIL

Compound **3ia** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% Rh₂(OAc)₄ (8.84 mg, 0.02 mmol), starting from 2,4-dimethoxybenzoic acid (**1i**) (92.9 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3ia** was obtained as colorless oil (142 mg, 0.433 mmol, 87%).

¹H NMR (400 MHz, CDCl₃): δ = 7.30 (d, *J* = 7.6 Hz, 2 H), 7.20 (d, *J* = 7.8 Hz, 2 H), 6.49 (q, *J* = 2.1 Hz, 2 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.62 (s, 3 H), 2.39 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 168.5 (s), 161.2 (s), 158.0 (s), 142.6 (s), 137.5 (s), 137.3 (s), 129.0 (s, 2 C), 127.8 (s, 2 C), 116.0 (s), 106.1 (s), 97.3 (s), 55.9 (s), 55.4 (s), 51.9 (s), 21.1 (s) ppm. MS (EI, 70 eV) *m/z* (%): 286.0 (29), 256.0 (18), 255.1 (100), 240.2 (9). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₇H₁₈O₄H⁺: 287.1283; Found: 287.1284. IR: $\tilde{\nu}$ = 3089 (w), 2946 (w), 1725 (s), 1599 (s), 1338 (m), 1259 (s), 1204 (s), 1143 (s), 1097 (s), 1032 (s), 822 (s), 730 (m) cm⁻¹.

Synthesis of 2-(4-methylphenyl)-1-Naphthalenecarboxylic acid methyl ester 3ja

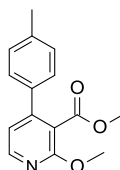


[CAS: 1415046-14-8]

Compound **3ja** was prepared following the general procedure for the *ortho*-Arylation, starting from 1-naphthoic acid (**1j**) (89.7 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3ja** was obtained as colorless oil (133 mg, 0.480 mmol, 96%).

¹H NMR (300 MHz, CDCl₃): δ = 7.92 - 8.00 (m, 2 H), 7.86 - 7.92 (m, 1 H), 7.47 - 7.63 (m, 3 H), 7.35 - 7.44 (m, 2 H), 7.21 - 7.31 (m, 2 H), 3.75 (s, 3 H), 2.43 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.2 (s), 138.0 (s), 137.9 (s), 137.4 (s), 132.2 (s), 130.0 (s), 129.9 (s), 129.8 (s), 129.2 (s), 128.4 (s), 128.1 (s), 127.5 (s), 127.4 (s), 126.2 (s), 125.0 (s), 52.2 (s), 21.2 (s) ppm. MS (EI, 70 eV) *m/z* (%): 277.1 (19), 276.2 (100), 246.5 (20), 245.5 (70), 202.3 (11). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₉H₁₆O₂H⁺: 277.1229; Found: 277.1225. IR: $\tilde{\nu}$ = 3054 (w), 3024 (w), 2947 (w), 1720 (s), 1433 (m), 1230 (s), 1135 (m), 1031 (m), 811 (s), 747 (m), 548 (m) cm⁻¹.

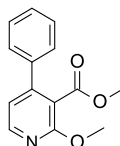
Synthesis of 2-methoxy-4-(4-methylphenyl)-3-pyridinecarboxylic acid methyl ester 3ka



Compound **3ka** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (94.2 μ L, 131 mg, 0.75 mmol). After purification, **3ka** was obtained as colorless solid (111 mg, 0.430 mmol, 86%).

m.p.: 96 - 97 °C. ^1H NMR (400 MHz, CDCl_3): δ = 8.34 (d, J = 5.3 Hz, 1 H), 7.45 (d, J = 8.3 Hz, 2 H), 7.36 (d, J = 8.1 Hz, 2 H), 7.06 (d, J = 5.3 Hz, 1 H), 4.15 (s, 3 H), 3.83 (s, 3 H), 2.52 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 167.4 (s), 160.6 (s), 149.7 (s), 147.4 (s), 138.6 (s), 134.7 (s), 129.2 (s, 2 C), 127.5 (s, 2 C), 117.4 (s), 116.1 (s), 53.9 (s), 52.1 (s), 21.0 (s) ppm. MS (EI, 70 eV) m/z (%): 257.1 (87) [M^+], 226.1 (100), 212.1 (48), 197.1 (72), 169.1 (36), 168.1, 154.0 (35). HRMS-ESI (m/z): [$\text{M}+\text{H}^+$] calcd. for $\text{C}_{15}\text{H}_{15}\text{NO}_3\text{H}^+$: 258.1130; Found: 258.1125. IR: $\tilde{\nu}$ = 3030 (w), 2996 (w), 2948 (w), 1727 (s), 1548 (m), 1271 (s), 1120 (s), 1068 (s), 813 (s) cm^{-1} .

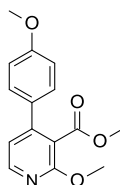
Synthesis of 2-methoxy-4-phenyl-3-pyridinecarboxylic acid methyl ester 3kb



Compound **3kb** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and bromobenzene (**2b**) (119 mg, 0.75 mmol). After purification, **3kb** was obtained as colorless solid (104 mg, 0.427 mmol, 85%),

m.p.: 75-76 °C. ^1H NMR (400 MHz, CDCl_3): δ = 8.22 (d, J = 5.3 Hz, 1 H), 7.35 - 7.46 (m, 5 H), 6.93 (d, J = 5.3 Hz, 1 H), 4.01 (s, 3 H), 3.66 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 167.3 (s), 160.7 (s), 149.9 (s), 147.6 (s, 2 C), 137.7 (s), 128.7 (s), 128.6 (s), 127.7 (s, 2 C), 117.4 (s), 116.3 (s), 54.0 (s), 52.2 (s) ppm. MS (EI, 70 eV) m/z (%): 243.1 (76) [M^+], 212.1 (100), 198.0 (47), 183.0 (70), 169.0 (28), 154.1 (56), 114.0 (27). HRMS-ESI (m/z): [$\text{M}+\text{H}^+$] calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_3\text{H}^+$: 244.0974; Found: 244.0967. IR: $\tilde{\nu}$ = 3070 (w), 2953 (w), 1732 (s), 1588 (m), 1554 (m), 1388 (s), 1276 (s), 1119 (m), 1068 (m), 763 (m) cm^{-1} .

Synthesis of 2-methoxy-4-(4-methoxyphenyl)-3-pyridinecarboxylic acid methyl ester 3kc

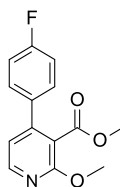


EXPERIMENTELLER TEIL

Compound **3kc** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 4-bromoanisoole (**2c**) (142 mg, 0.75 mmol). After purification, **3kc** was obtained as colorless oil (121 mg, 0.443 mmol, 89%).

^1H NMR (400 MHz, CDCl_3): δ = 8.18 (d, J = 5.3 Hz, 1 H), 7.34 (d, J = 8.6 Hz, 2 H), 6.84 - 6.97 (m, 3 H), 3.99 (s, 3 H), 3.81 (s, 3 H), 3.69 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 167.6 (s), 160.7 (s), 160.0 (s), 149.4 (s), 147.4 (s), 130.0 (s), 129.0 (s), 117.4 (s), 116.0 (s), 114.1 (s, 3 C), 55.1 (s), 54.0 (s), 52.3 (s) ppm. MS (EI, 70 eV) m/z (%): 273.1 (100) [M^+], 242.1 (68), 213.1 (48). HRMS-ESI (m/z): [$\text{M}+\text{H}^+$] calcd. for $\text{C}_{15}\text{H}_{15}\text{NO}_4\text{H}^+$: 274.1079; Found: 274.1071. IR: $\tilde{\nu}$ = 3062 (w), 2950 (w), 1729 (s), 1552 (m), 1383 (s), 1249 (s), 1113 (s), 1067 (s), 821 (s) cm^{-1} .

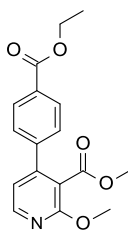
Synthesis of 2-methoxy-4-(4-fluorophenyl)-3-pyridinecarboxylic acid methyl ester 3kd



Compound **3kd** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% $\text{Rh}_2(\text{OAc})_4$ (2.21 mg, 0.005 mmol), starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene (**2d**) (133 mg, 0.75 mmol). After purification, **3kd** was obtained as yellow oil (92 mg, 0.352 mmol, 71%).

^1H NMR (400 MHz, CDCl_3): δ = 8.23 (d, J = 5.3 Hz, 1 H), 7.39 (dd, J = 8.9, 5.2 Hz, 2 H), 7.12 (t, J = 8.7 Hz, 2 H), 6.91 (d, J = 5.3 Hz, 1 H), 4.02 (s, 3 H), 3.70 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 167.3 (s), 163.1 (d), 160.8 (s), 148.9 (s), 147.8 (s), 133.8 (d), 129.7 (d, 2 C), 117.4 (s), 116.4 (s), 115.7 (d, 2 C), 54.2 (s), 52.4 (s) ppm. ^{19}F NMR (41 MHz, CDCl_3): δ = -110.52 ppm. MS (EI, 70 eV) m/z (%): 260.9 (33) [M^+], 230.0 (100), 228.9 (42), 216.0 (52), 200.9 (62), 172.0 (48), 132.0 (29). HRMS-ESI (m/z): [$\text{M}+\text{H}^+$] calcd. for $\text{C}_{14}\text{H}_{12}\text{FNO}_3\text{H}^+$: 262.0880; Found: 262.0873. IR: $\tilde{\nu}$ = 3065 (w), 2951 (w), 1730 (s), 1589 (m), 1559 (m), 1512 (s), 1383 (s), 1271 (s), 1114 (s), 1011 (s), 822 (s), 538 (m) cm^{-1} .

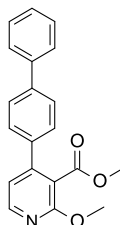
Synthesis of 2-methoxy-4-[4-(ethoxycarbonyl)phenyl]-3-pyridinecarboxylic acid methyl ester 3ke



Compound **3ke** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% Rh₂(OAc)₄ (2.21 mg, 0.005 mmol), starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and ethyl-4-bromobenzoate (**2e**) (121 μL, 174 mg, 0.75 mmol). After purification, **3ke** was obtained as colorless solid (99 mg, 0.315 mmol, 63%).

m.p.: 65-66 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.23 (d, *J* = 5.3 Hz, 1 H), 8.08 (d, *J* = 8.6, 2 H), 7.44 (d, *J* = 8.3 Hz, 2 H), 6.91 (d, *J* = 5.1 Hz, 1 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 4.00 (s, 3 H), 3.65 (s, 3 H), 1.39 (t, *J* = 7.1 Hz, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 166.9 (s), 166.0 (s), 160.8 (s), 148.9 (s), 147.9 (s), 142.1 (s), 129.8 (s, 2 C), 127.8 (s, 2 C), 117.1 (s), 116.2 (s), 61.1 (s), 54.1 (s), 52.4 (s), 14.2 (s) ppm. MS (EI, 70 eV) *m/z* (%): 315.1 (88) [M⁺], 284.1 (33), 270.1 (100), 255.1 (87), 227.1 (29), 212.1 (32), 154.1 (33). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₇H₁₇NO₅H⁺: 316.1185; Found: 316.1175. IR: $\tilde{\nu}$ = 3035 (w), 2952 (w), 1716 (s), 1587 (m), 1549 (m), 1386 (m), 1269 (s), 1103 (s), 1009 (m), 833 (m), 771 (m) cm⁻¹.

Synthesis of 2-methoxy-4-[1,1'-biphenyl]-4-yl-3-pyridinecarboxylic acid methyl ester 3kf



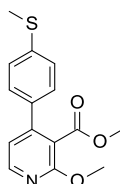
Compound **3kf** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 2-bromobiphenyl (**2f**) (194 mg, 0.75 mmol). After purification, **3kf** was obtained as colorless solid (138 mg, 0.432 mmol, 87%),

m.p.: 122 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.26 (d, *J* = 5.3 Hz, 1 H), 7.61 - 7.71 (m, 4 H), 7.44 - 7.54 (m, 4 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 6.99 (d, *J* = 5.3 Hz, 1 H), 4.05 (s, 3 H), 3.73 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 167.4 (s), 160.8 (s), 149.4 (s), 147.7 (s, 2 C), 141.5 (s), 140.1 (s), 136.6 (s), 128.8 (s), 128.2 (s, 2 C), 127.6 (s), 127.3 (s, 2 C), 127.0 (s, 2 C), 117.4 (s), 116.2 (s), 54.1 (s), 52.4 (s) ppm. MS (EI, 70 eV) *m/z* (%): 319.0 (100) [M⁺], 288.1 (55), 286.1 (16), 274.1 (35), 259.2 (59), 230.2 (30), 189.2 (15). HRMS-ESI (*m/z*): [M+H⁺] calcd. for

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$C_{20}H_{17}NO_3H^+$: 320.1286; Found: 320.1277. IR: $\tilde{\nu} = 3070$ (w), 2952 (w), 2362 (w), 1981 (w), 1736 (s), 1589 (m), 1368 (m), 1286 (m), 117 (m), 1069 (m), 768 (w) cm^{-1} .

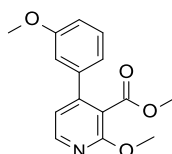
*Synthesis of 2-methoxy-4-[4-(methylthio)phenyl]-3-pyridinecarboxylic acid methyl ester **3kg***



Compound **3kg** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% $Rh_2(OAc)_4$ (2.21 mg, 0.005 mmol), starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 4-bromothioanisole (**2g**) (155 mg, 0.75 mmol). After purification, **3kg** was obtained as yellow oil (73 mg, 0.253 mmol, 51%).

1H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (d, $J = 5.3$ Hz, 1 H), 7.28 (dd, $J = 12.1, 8.6$ Hz, 4 H), 6.89 (d, $J = 5.3$ Hz, 1 H), 3.99 (s, 3 H), 3.69 (s, 3 H), 2.49 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 167.4$ (s) 160.8 (s) 149.2 (s) 147.6 (s) 139.9 (s) 134.2 (s) 128.1 (s, 2 C) 126.1 (s, 2 C) 117.3 (s) 116.1 (s) 54.1 (s) 52.4 (s) 15.2 (s) ppm. MS (EI, 70 eV) m/z (%): 289.0 (100) $[M^+]$, 258.0 (33), 256.0 (10), 244.1 (19), 229.1 (19), 200.1 (8), 154.1 (16). HRMS-ESI (m/z): $[M+H^+]$ calcd. for $C_{25}H_{15}NO_3SH^+$: 290.0851; Found: 290.0845. IR: $\tilde{\nu} = 3059$ (w), 2948 (w), 1730 (s), 1588 (m), 1567 (m), 1382 (s), 1274 (s), 1090 (s), 1008 (m), 812 (s) cm^{-1} .

*Synthesis of 2-methoxy-4-(3-methoxyphenyl)-3-pyridinecarboxylic acid methyl ester **3kh***

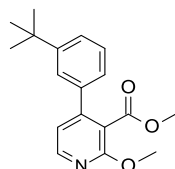


Compound **3kh** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 3-bromoanisole (**2h**) (94.8 μ L, 140 mg, 0.75 mmol). After purification, **3kh** was obtained as colorless solid (111 mg, 0.403 mmol, 81%).

m.p.: 77-78 $^{\circ}C$. 1H NMR (400 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J = 5.3$ Hz, 1 H), 7.28 - 7.36 (m, 1 H), 6.88 - 7.00 (m, 4 H), 4.01 (s, 3 H), 3.81 (s, 3 H), 3.69 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 167.3$ (s), 160.7 (s), 159.6 (s), 149.7 (s), 147.6 (s), 139.1 (s), 129.7 (s), 120.1 (s), 117.4 (s), 116.3 (s), 114.5 (s), 113.2 (s), 55.2 (s), 54.0 (s), 52.3 (s) ppm. MS (EI, 70 eV) m/z (%): 273.1 (100) $[M^+]$, 242.1 (81), 228.1 (36), 212.1 (63), 184.1 (38). HRMS-ESI (m/z):

[M+H⁺] calcd. for C₁₇H₁₇NO₅H⁺: 274.1079; Found: 274.1072. IR: $\tilde{\nu}$ = 3058 (w), 2952 (w), 1732 (s), 1588 (s), 1388 (s), 1278 (s), 1130 (m), 1069 (m), 839 (m) cm⁻¹.

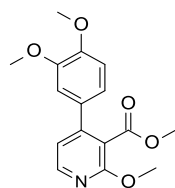
Synthesis of 2-methoxy-4-(3-(1,1-dimethylethyl)-phenyl)-3-pyridinecarboxylic acid methyl ester 3ki



Compound **3ki** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 1-bromo-3-*tert*-butylbenzene (**2i**) (129 μ L, 161 mg, 0.75 mmol). After purification, **3ki** was obtained as colorless oil (133 mg, 0.444 mmol, 89%).

¹H NMR (300 MHz, CDCl₃): δ = 8.23 (d, *J* = 5.3 Hz, 1 H), 7.40 - 7.47 (m, 2 H), 7.36 (t, *J* = 1.0 Hz, 1 H), 7.23 (dt, *J* = 7.6, 1.5 Hz, 1 H), 6.96 (d, *J* = 5.3 Hz, 1 H), 4.02 (s, 3 H), 3.68 (s, 3 H), 1.32 (s, 9 H) ppm. ¹³C NMR (75 MHz CDCl₃): δ = 167.5 (s), 160.8 (s), 151.6 (s), 150.5 (s), 147.5 (s), 137.5 (s), 128.4 (s), 125.7 (s), 125.0 (s), 124.9 (s), 117.6 (s), 116.4 (s), 54.0 (s), 52.3 (s), 34.8 (s), 31.3 (s) ppm. MS (EI, 70 eV) *m/z* (%): 299.1 (50) [M⁺], 284.1 (36), 252.1 (100), 210.1 (35). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₈H₂₁NO₃H⁺: 300.1600; Found: 300.1590. IR: $\tilde{\nu}$ = 3062 (w), 2952 (m), 1733 (s), 1590 (s), 1556 (s), 1382 (s), 1274 (s), 1117 (s), 1068 (s), 796 (m) cm⁻¹.

Synthesis of 2-methoxy-4-(3,4-dimethoxyphenyl)-3-pyridinecarboxylic acid methyl ester 3kj



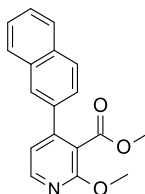
Compound **3kj** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 4-bromoveratrole (**2j**) (166 mg, 0.75 mmol). After purification, **3kj** was obtained as colorless solid (130 mg, 0.430 mmol, 86%).

m.p.: 107-108 °C. ¹H NMR: (300 MHz, CDCl₃): δ = 8.19 (d, *J* = 5.3 Hz, 1 H), 6.83 - 7.05 (m, 4 H), 4.00 (s, 3 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.71 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 167.7 (s), 160.7 (s), 149.5 (s), 148.9 (s), 147.5 (s), 130.3 (s), 120.4 (s), 117.3 (s), 116.1 (s),

EXPERIMENTELLER TEIL

111.1 (s, 2 C), 110.9 (s), 55.8 (s, 2 C), 54.0 (s), 52.4 (s). MS (EI, 70 eV) m/z (%): 302.9 (100) [M^+], 272.0 (35), 258.0 (13), 242.0 (17), 228.0 (23), 214.1 (17), 196.9 (16). HRMS-ESI (m/z): [$M+H^+$] calcd. for $C_{16}H_{17}NO_5H^+$: 304.1185; Found: 304.1176. IR: $\tilde{\nu}$ = 3065 (w), 2951 (w), 1733 (s), 1589 (m), 1518 (s), 1251 (s), 1111 (s), 1018 (s), 822 (m), 765 (m) cm^{-1} .

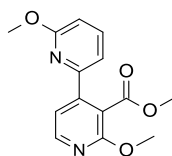
Synthesis of 2-methoxy-4-(2-naphthalenyl)-3-pyridinecarboxylic acid methyl ester **3kk**



Compound **3kk** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 2-bromonaphthalene (**2k**) (160 mg, 0.75 mmol). After purification, **3kk** was obtained as colorless solid (131 mg, 0.445 mmol, 89%).

m.p.: 103-104 °C. 1H NMR (300 MHz, $CDCl_3$): δ = 8.22 - 8.28 (d, J = 5.3 Hz, 1 H), 7.84 - 7.94 (m, 4 H), 7.49 - 7.57 (m, 3 H), 7.05 (d, J = 5.1 Hz, 1 H), 4.06 (s, 3 H), 3.65 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4 (s), 160.9 (s), 150.0 (s), 147.7 (s), 135.2 (s), 133.1 (s), 133.1 (s), 128.4 (s), 128.3 (s), 127.7 (s), 127.3 (s), 126.8 (s), 126.6 (s), 125.4 (s), 117.8 (s), 116.5 (s), 54.2 (s), 52.4 (s) ppm. MS (EI, 70 eV) m/z (%): 293.0 (100) [M^+], 262.2 (45), 260.2 (14), 248.2 (20), 233.2 (31), 232.3 (11), 204.3 (19). HRMS-ESI (m/z): [$M+H^+$] calcd. for $C_{18}H_{15}NO_3H^+$: 294.1130; Found: 294.1121. IR: $\tilde{\nu}$ = 3070 (w), 2953 (w), 1732 (s), 1588 (m), 1553 (m), 1384 (s), 1287 (s), 1127 (s), 1069 (s), 823 (s) cm^{-1} .

Synthesis of 2-methoxy-4-(5-methoxy-2-pyridinyl)-3-pyridinecarboxylic acid methyl ester **3kl**

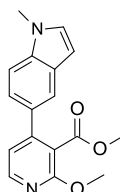


Compound **3kl** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 2-bromo-6-methoxypyridine (**2l**) (145 mg, 0.75 mmol). After purification, **3kl** was obtained as colorless oil (111 mg, 0.403 mmol, 81%).

1H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, J = 5.3 Hz, 1 H), 7.63 (dd, J = 8.4, 7.3 Hz, 1 H), 7.11 - 7.21 (m, 2 H), 6.75 (dd, J = 8.3, 0.8 Hz, 1 H), 4.00 (s, 3 H), 3.93 (s, 3 H), 3.74 (s, 3 H) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ = 167.3 (s), 163.6 (s), 161.3 (s), 152.2 (s), 147.8 (s), 147.8 (s), 139.2 (s), 116.0 (s), 115.7 (s), 115.1 (s), 111.3 (s), 54.1 (s), 53.6 (s), 52.2 (s) ppm. MS (EI, 70 eV) m/z (%): 274.1 (52) [M^+], 243.0 (100), 229.0 (25), 213.0 (27), 199.0 (20), 185.0 (13), 171.0 (15). HRMS-ESI (m/z): [$\text{M}+\text{H}^+$] calcd. for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4\text{H}^+$: 275.1032; Found: 275.1029. IR: $\tilde{\nu}$ = 3071 (w), 2951 (w), 1733 (s), 1558 (s), 1380 (s), 1257 (s), 1120 (s), 1069 (s), 801 (s) cm^{-1} .

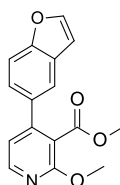
Synthesis of 2-methoxy-4-(1-methyl-1H-indol-5-yl)-3-pyridinecarboxylic acid methyl ester
3km



Compound **3km** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 5-bromo-1-methylindole (**2m**) (162 mg, 0.75 mmol). After purification, **3km** was obtained as colorless solid (122 mg, 0.411 mmol, 82%).

m.p.: 135 °C. ^1H NMR (300 MHz, CDCl_3): δ = 8.22 (d, J = 5.3 Hz, 1 H), 7.72 (dd, J = 1.8, 0.7 Hz, 1 H), 7.33 - 7.39 (m, 1 H), 7.27 - 7.32 (m, 1 H), 7.09 (d, J = 3.1 Hz, 1 H), 7.03 (d, J = 5.3 Hz, 1 H), 6.54 (dd, J = 3.1, 0.9 Hz, 1 H), 4.04 (s, 3 H), 3.79 (s, 3 H), 3.68 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 167.9 (s), 160.7 (s), 151.2 (s), 147.2 (s), 136.6 (s), 129.8 (s), 128.8 (s), 128.5 (s), 121.3 (s), 120.4 (s), 118.1 (s), 116.3 (s), 109.4 (s), 101.5 (s), 53.9 (s), 52.3 (s), 32.8 (s) ppm. MS (EI, 70 eV) m/z (%): 296.1 (100) [M^+], 265.1 (44), 249.1 (15), 236.1 (10), 207.1 (23), 167.0 (7). HRMS-ESI (m/z): [$\text{M}+\text{H}^+$] calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3\text{H}^+$: 297.1239; Found: 297.1235. IR: $\tilde{\nu}$ = 3093 (w), 2949 (w), 1739 (s), 1593 (m), 1388 (s), 1280 (s), 1115 (m), 735 (s) cm^{-1} .

Synthesis of 2-methoxy-4-(5-benzofuranyl)-3-pyridinecarboxylic acid methyl ester **3kn**



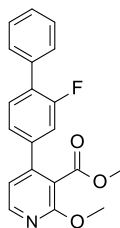
Compound **3kn** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 5-bromo-1-benzofurane (**2n**)

EXPERIMENTELLER TEIL

(152 mg, 0.75 mmol). After purification, **3kn** was obtained as colorless oil (97 mg, 0.343 mmol, 69%).

^1H NMR (300 MHz, CDCl_3): δ = 8.22 (d, J = 5.3 Hz, 1 H), 7.66 (d, J = 2.2 Hz, 1 H), 7.64 (d, J = 1.8 Hz, 1 H), 7.54 (d, J = 8.6 Hz, 1 H), 7.33 (dd, J = 8.5, 1.9 Hz, 1 H), 6.96 (d, J = 5.3 Hz, 1 H), 6.79 (dd, J = 2.3, 1.0 Hz, 1 H), 4.02 (s, 3 H), 3.65 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 167.5 (s), 160.7 (s), 154.9 (s), 150.1 (s), 147.5 (s), 145.9 (s), 132.6 (s), 127.8 (s), 124.2 (s), 120.6 (s), 117.9 (s), 116.5 (s), 111.5 (s), 106.7 (s), 54.0 (s), 52.3 (s) ppm. MS (EI, 70 eV) m/z (%): 283.1 (100) [M^+], 252.1 (77), 250.0 (23), 238.0 (38), 223.1 (61), 194.1 (48), 126.0 (18). HRMS-ESI (m/z): [$\text{M}+\text{H}^+$] calcd. for $\text{C}_{16}\text{H}_{13}\text{NO}_4\text{H}^+$: 284.0923; Found: 284.0916. IR: $\tilde{\nu}$ = 3064 (w), 2952 (m), 2363 (w), 1734 (s), 1590 (m), 1385 (m), 1283 (m), 1069 (m), 775 (w) cm^{-1} .

*Synthesis of 2-methoxy-4-(3'-fluoro[1,1'-biphenyl]-4-yl)-3-pyridinecarboxylic acid methyl ester **3ko***

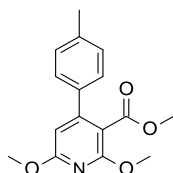


Compound **3ko** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-methoxynicotinic acid (**1k**) (78.9 mg, 0.50 mmol) and 4-bromo-2-fluorobiphenyl (**2o**) (192 mg, 0.75 mmol). After purification, **3ko** was obtained as colorless solid (124 mg, 0.367 mmol, 74%).

m.p.: 77-78 °C. ^1H NMR (300 MHz, CDCl_3): δ = 8.28 (d, J = 5.1 Hz, 1 H), 7.57 - 7.64 (m, 2 H), 7.38 - 7.56 (m, 4 H), 7.22 - 7.32 (m, 2 H), 6.98 (d, J = 5.3 Hz, 1 H), 4.05 (s, 3 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (300 MHz, CDCl_3): δ = 167.2 (s), 160.9 (s), 159.6 (d), 148.1 (d), 147.9 (s), 138.6 (d), 134.9 (d), 131.0 (d), 129.4 (d), 128.9 (d), 128.5 (s), 128.0 (s), 123.9 (d), 117.2 (s), 116.3 (s), 115.7 (d), 54.2 (s), 52.5 (s) ppm. ^{19}F NMR (41 MHz, CDCl_3): δ = -114.93 ppm.

MS (EI, 70 eV) m/z (%): 337.0 (100) [M^+], 306.2 (57), 304.0 (16), 292.2 (41), 277.1 (59), 248.2 (31), 207.1 (16). HRMS-ESI (m/z): [M^+H^+] calcd. for $\text{C}_{20}\text{H}_{16}\text{FNO}_3\text{H}^+$: 338.1192; Found: 338.1184. IR: $\tilde{\nu}$ = 3023 (w), 2951 (w), 1726 (s), 1541 (m), 1381 (s), 1280 (s), 1068 (m), 1115 (m), 769 (s), 696 (m) cm^{-1} .

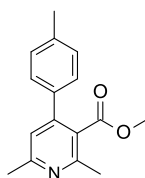
*Synthesis of 2,6-dimethoxy-4-(4-methylphenyl)-3-Pyridinecarboxylic acid methyl ester **3la***



Compound **3la** was prepared following the general procedure for the *ortho*-Arylation, starting from 2,6-dimethoxypyridine-3-carboxylic acid (**1l**) (94.4 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3la** was obtained as colorless solid (120 mg, 0.417 mmol, 84%).

m.p.: 86-87 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.13 - 7.32 (m, 4 H), 6.33 (s, 1 H), 4.01 (s, 3 H), 3.97 (s, 3 H), 3.63 (s, 3 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 167.9 (s), 163.3 (s), 160.5 (s), 153.6 (s), 138.4 (s), 135.7 (s), 129.2 (s, 2 C), 127.5 (s, 2 C), 107.9 (s), 101.8 (s), 54.0 (s), 53.7 (s), 52.1 (s), 21.2 (s) ppm. MS (EI, 70 eV) m/z (%): 287.15 (58) [M^+], 256.15 (100). HRMS-ESI (m/z): [$\text{M}+\text{H}^+$] calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_4\text{H}^+$: 288.1236; Found: 288.1231. IR: $\tilde{\nu}$ = 3010 (w), 2988 (w), 2948 (w), 1729 (s), 1594 (m), 1359 (s), 1254 (s), 1101 (m), 1049 (m), 820 (s) cm^{-1} .

Synthesis of 2,6-dimethyl-4-(4-methylphenyl)-3-Pyridinecarboxylic acid methyl ester 3ma



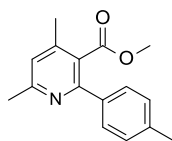
[CAS: 2082708-38-9]

Compound **3ma** was prepared following the general procedure for the *ortho*-Arylation, starting from 2,6-dimethylpyridine-3-carboxylic acid (**1m**) (77.9 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3ma** was obtained as orange solid (65 mg, 0.253 mmol, 51%).

m.p.: 70 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.25 (m, J = 1.0, 1.0 Hz, 4 H), 7.02 (s, 1 H), 3.66 (s, 3 H), 2.60 (s, 3 H), 2.58 (s, 3 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 169.8 (s), 158.7 (s), 155.0 (s), 148.2 (s), 138.4 (s), 135.7 (s), 129.3 (s, 2 C), 127.6 (s, 2 C), 125.4 (s), 121.0 (s), 52.1 (s), 24.5 (s), 22.9 (s), 21.2 (s) ppm. MS (EI, 70 eV) m/z (%): 256.0 (15), 254.8 (50) [M^+], 225.2 (17), 224.2 (100), 223.3 (21), 196.3 (10), 181.2 (8). HRMS-ESI (m/z): [$\text{M}+\text{H}^+$] calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{H}^+$: 256.1338; Found: 256.1333. IR: $\tilde{\nu}$ = 3028 (w), 2993 (w), 2949 (w), 1725 (s), 1587 (m), 1264 (s), 1204 (m), 1081 (s), 823 (m) cm^{-1} .

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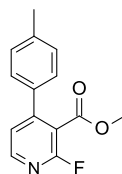
Synthesis of 4,6-dimethyl-4-(4-methylphenyl)-3-Pyridinecarboxylic acid methyl ester 3na



Compound **3na** was prepared following the general procedure for the *ortho*-Arylation, starting from 4,6-dimethylpyridine-3-carboxylic acid (**1n**) (79.6 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3na** was obtained as colorless solid (102 mg, 0.401 mmol, 80%).

m.p.: 76-78 °C. ^1H NMR (300 MHz, CDCl_3): δ = 7.47 (d, J = 8.3 Hz, 2 H), 7.22 (d, J = 8.4 Hz, 2 H), 6.99 (s, 1 H), 3.66 (s, 3 H), 2.58 (s, 3 H), 2.38 (s, 3 H), 2.37 (d, J = 0.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 169.8 (s), 158.8 (s), 156.2 (s), 145.6 (s), 138.3 (s), 137.3 (s), 129.1 (s, 2 C), 128.0 (s, 2 C), 126.1 (s), 122.8 (s), 52.1 (s), 24.5 (s), 21.3 (s), 19.3 (s) ppm. MS (EI, 70 eV) m/z (%): 256.2 (19), 241.3 (16), 240.2 (100), 224.3 (25). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{H}^+$: 256.1338; Found: 256.1333. IR: $\tilde{\nu}$ = 3015 (w), 2955 (w), 1719 (s), 1589 (m), 1273 (s), 1186 (m), 1081 (s), 835 (m) cm^{-1} .

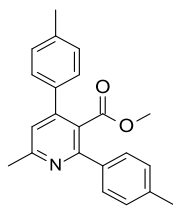
Synthesis of 2-fluoro-4-(4-methylphenyl)-3-Pyridinecarboxylic acid methyl ester 3oa



Compound **3oa** was prepared following the general procedure for the *ortho*-Arylation, starting from 2-fluoro-3-pyridinecarboxylic acid (**1o**) (72.0 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (218 mg, 1.25 mmol). After purification, **3oa** was obtained as colorless oil (77 mg, 0.315 mmol, 63%).

^1H NMR (400 MHz, CDCl_3): δ = 8.18 (d, J = 5.1 Hz, 1 H), 7.12 - 7.24 (m, 5 H), 3.66 (s, 3 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 165.0 (d), 160.3 (d), 153.2 (d), 148.3 (d), 139.5 (s), 133.7 (d), 129.6 (s), 127.7 (s), 122.2 (d), 115.2 (d), 52.7 (s), 21.2 (s) ppm. ^{19}F NMR (41 MHz, CDCl_3): δ = -67.13 ppm. MS (EI, 70 eV) m/z (%): 245.05 (69) $[\text{M}^+]$, 214.05 (100), 194.0 (43). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{14}\text{H}_{12}\text{FNO}_2\text{H}^+$: 246.0925; Found: 246.0924. IR: $\tilde{\nu}$ = 3030 (w), 2953 (w), 1733 (s), 1600 (s), 1400 (m), 1288 (s), 1163 (m), 1102 (m), 1070 (s), 910 (m), 815 (s), 599 (m) cm^{-1} .

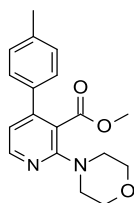
Synthesis of 6-methyl-2,4-bis(4-methylphenyl)-3-Pyridinecarboxylic acid methyl ester 3pa



Compound **3pa** was prepared following the general procedure for the *ortho*-Arylation, starting from 6-methyl-3-pyridinecarboxylic acid (**1p**) (70 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (218 mg, 1.25 mmol). After purification, **3pa** was obtained as colorless solid (108 mg, 0.326 mmol, 65%).

m.p.: 111-112 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.45 - 7.57 (m, 2 H), 7.28 - 7.34 (m, 2 H), 7.18 - 7.27 (m, 4 H), 7.13 (s, 1 H), 2.41 (s, 3 H), 2.40 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 169.6 (s), 158.9 (s), 156.4 (s), 148.8 (s), 138.4 (s), 138.4 (s), 137.1 (s), 135.5 (s), 129.3 (s), 129.1 (s), 128.2 (s), 127.8 (s), 125.4 (s), 122.0 (s), 52.1 (s), 24.6 (s), 21.3 (s), 21.2 (s) ppm. MS (EI, 70 eV) *m/z* (%): 333.2 (7), 332.2 (33), 317.5 (22), 316.6 (100), 300.6 (11). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₂₂H₂₁NO₂H⁺: 332.1651; Found: 332.1642. IR: $\tilde{\nu}$ = 3029 (w), 2949 (w), 1735 (s), 1588 (m), 1263 (m), 1203 (m), 1109 (s), 830 (s) cm⁻¹.

Synthesis of 2-(4-morpholinyl)-4-(4-methylphenyl)-3-Pyridinecarboxylic acid methyl ester
3qa



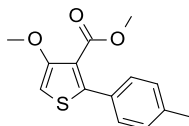
Compound **3qa** was prepared following the general procedure for the *ortho*-Arylation, starting from 6-(4-morpholinyl)-3-pyridinecarboxylic acid (**1q**) (70 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (218 mg, 0.75 mmol). After purification, **3qa** was obtained as yellow solid (136 mg, 0.435 mmol, 87%).

m.p.: 130 °C. ¹H NMR (250 MHz, CDCl₃): δ = 8.31 (d, *J* = 5.1 Hz, 1 H), 7.18 - 7.26 (m, 4 H), 6.86 (d, *J* = 5.1 Hz, 1 H), 3.74 - 3.85 (m, 4 H), 3.61 (s, 3 H), 3.28 - 3.42 (m, 4 H), 2.40 (s, 3 H) ppm. ¹³C NMR (63 MHz, CDCl₃): δ = 169.1 (s), 158.8 (s), 150.2 (s), 148.4 (s), 138.3 (s), 135.7 (s), 129.2 (s), 127.6 (s), 119.5 (s), 117.9 (s), 67.0 (s), 52.2 (s), 50.2 (s), 21.2 (s) ppm. MS (EI, 70 eV) *m/z* (%): 312.15 (68), 311.15 (62), 281.1 (83), 254.1 (79), 253.15 (100), 223.1 (90), 169.1 (58). HRMS-ESI (*m/z*): [M+H⁺] calcd. for C₁₈H₂₀N₂O₃H⁺: 313.1552; Found: 313.1608.

EXPERIMENTELLER TEIL

IR: $\tilde{\nu}$ = 3010 (w), 2987 (w), 2845 (w), 1716 (s), 1545 (m), 1433 (m), 1263 (s), 1110 (s), 963 (m), 827 (s) cm^{-1} .

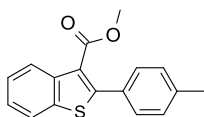
Synthesis of 3-(4-methylphenyl)-4-methoxy-2-Thiophenecarboxylic acid methyl ester 3ra



Compound **3ra** was prepared following the general procedure for the *ortho*-Arylation, starting from 4-methoxythiophene-3-carboxylic acid (**1r**) (83.3 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3ra** was obtained as yellow oil (118 mg, 0.450 mmol, 90%).

^1H NMR (400 MHz, CDCl_3): δ = 7.32 (d, J = 8.1 Hz, 2 H), 7.20 (d, J = 7.8 Hz, 2 H), 6.23 (s, 1 H), 3.88 (s, 3 H), 3.74 (s, 3 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 164.4 (s), 156.6 (s), 147.0 (s), 138.5 (s), 130.9 (s), 129.0 (s, 2 C), 128.3 (s, 2 C), 120.5 (s), 96.3 (s), 57.5 (s), 51.8 (s), 21.2 (s) ppm. MS (EI, 70 eV) m/z (%): 263.0 (17), 262.1 (100), 232.1 (12), 231.2 (86), 229.0 (15), 143.1 (22), 115.0 (11). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_3\text{SH}^+$: 263.0742; Found: 263.07838. IR: $\tilde{\nu}$ = 3116 (w), 3021 (w), 2949 (w), 1719 (s), 1513 (s), 1393 (m), 1274 (s), 1205 (s), 1096 (s), 815 (m), 504 (m) cm^{-1} .

Synthesis of 2-(4-methylphenyl)- Benzo[b]thiophene-3-carboxylic acid methyl ester 3sa



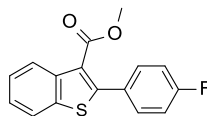
[CAS: 1630132-02-3]

Compound **3sa** was prepared following the general procedure for the *ortho*-Arylation, starting from 1-benzothiophene-3-carboxylic acid (**1s**) (91.9 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3sa** was obtained as yellow oil (120 mg, 0.448 mmol, 90%).

^1H NMR (300 MHz, CDCl_3): δ = 8.30 (dt, J = 7.8, 0.8 Hz, 1 H), 7.75 (dt, J = 7.9, 0.9 Hz, 1 H), 7.30 - 7.46 (m, 4 H), 7.17 - 7.23 (m, 2 H), 3.75 (s, 3 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 164.5 (s), 152.0 (s), 138.9 (s), 138.5 (s), 138.4 (s), 130.9 (s), 129.2 (s, 2 C), 128.8 (s, 2 C), 125.2 (s), 124.8 (s), 124.4 (s), 122.5 (s), 121.6 (s), 51.5 (s), 21.3 (s) ppm. MS (EI, 70 eV) m/z (%): 3059 (w), 2995 (w), 1706 (s), 1496 (m), 1432 (s), 1202 (s), 1019 (m), 813 (m),

503 (m). HRMS-ESI (m/z): $[M+H^+]$ calcd. for $C_{17}H_{14}O_2SH^+$: 283.0793; Found: 283.0780. IR: $\tilde{\nu} = 282.0$ (100), 251.1 (89), 223.2 (13), 221.1 (15), 208.1 (13) cm^{-1} .

Synthesis of 2-(4-fluorophenyl)-Benzo[b]thiophene-3-carboxylic acid methyl ester 3sd

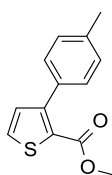


[CAS: 1630132-00-1]

Compound **3sd** was prepared following the general procedure for the *ortho*-Arylation with 1 mol% $Rh_2(OAc)_4$ (2.21 mg, 0.005 mmol), starting from 1-benzothiophene-3-carboxylic acid (**1s**) (91.9 mg, 0.50 mmol) and 1-bromo-4-fluorobenzene (**2d**) (113 mg, 0.75 mmol). After purification, **3sd** was obtained as orange solid (127.0 mg, 0.466 mmol, 93%).

m.p.: 79-81 °C. 1H NMR (300 MHz, $CDCl_3$): $\delta = 8.25 - 8.47$ (m, 1 H), 7.75 - 7.95 (m, 1 H), 7.34 - 7.62 (m, 4 H), 7.14 (t, $J = 8.7$ Hz, 2 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 8.25 - 8.47$ (m, 1 H), 7.75 - 7.95 (m, 1 H), 7.34 - 7.62 (m, 4 H), 7.14 (t, $J = 8.7$ Hz, 2 H), 3.79 164.8 (s), 164.2 (s), 161.5 (s), 150.8 (s), 138.4 (d), 131.3 (d, 2 C), 130.0 (s), 125.5 (s), 125.1 (s), 124.7 (s), 123.1 (s), 121.7 (s), 115.2 (d, 2 C), 51.6 (s) ppm. ^{19}F NMR (41 MHz, $CDCl_3$): $\delta = -117.33$ ppm. MS (EI, 70 eV) m/z (%): 286.0 (77), 255.0 (100), 226.2 (17), 183.2 (19). HRMS-ESI (m/z): $[M+H^+]$ calcd. for $C_{16}H_{11}FO_2SH^+$: 287.0542; Found: 287.0537. IR: $\tilde{\nu} = 3066$ (w), 3025 (w), 3005 (w), 2951 (w), 1714 (s), 1495 (m), 1431 (m), 1202 (s), 991 (m), 750 (s), 519 (m) cm^{-1} .

Synthesis of 3-(4-methylphenyl)-2-Thiophenecarboxylic acid methyl ester 3ta



[CAS: 91902-81-7]

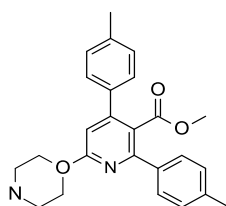
Compound **3ta** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% $Rh_2(OAc)_4$ (8.84 mg, 0.02 mmol), starting from 2-thiophenecarboxylic acid (**1t**) (64.7 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **3ta** was obtained as colorless solid (31 mg, 0.134 mmol, 27%).

m.p.: 75 °C. 1H NMR (400 MHz, $CDCl_3$): $\delta = 7.50$ (d, $J = 5.1$ Hz, 1 H), 7.37 (d, $J = 8.1$ Hz, 1 H), 7.23 (d, $J = 8.1$ Hz, 2 H), 7.09 (d, $J = 5.1$ Hz, 1 H), 3.79 (s, 3 H), 2.41 (s, 3 H) ppm. ^{13}C

EXPERIMENTELLER TEIL

NMR (75 MHz, CDCl₃): δ = 162.5 (s), 148.8 (s), 137.8 (s), 132.7 (s), 131.6 (s), 130.1 (s), 129.1 (s, 2 C), 128.6 (s, 2 C), 126.5 (s), 51.9 (s), 21.3 (s) ppm. MS (EI, 70 eV) m/z (%): 233.0 (19), 232.1 (100), 231.2 (17), 201.0 (78), 173.1 (38), 129.1 (15), 45.0 (13). HRMS-ESI (m/z): [M+H⁺] calcd. for C₁₃H₁₂O₂SH⁺: 233.0636; Found: 233.0629. IR: $\tilde{\nu}$ = 3022 (w), 2949 (w), 1716 (s), 1504 (m), 1434 (m), 1274 (m), 1220 (s), 1068 (s), 819 (m), 771 (s) cm⁻¹.

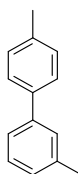
*Synthesis of 6-(4-morpholinyl)-2,4-bis(4-methylphenyl)-3-Pyridinecarboxylic acid methyl ester **3ua***



Compound **3ua** was prepared following the general procedure for the *ortho*-Arylation with 4 mol% Rh₂(OAc)₄ (8.84 mg, 0.02 mmol), starting from 6-(4-morpholinyl)-3-pyridinecarboxylic acid (**1u**) (70 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (218 mg, 1.25 mmol). After purification, **3ua** was obtained as colorless solid (138 mg, 0.343 mmol, 69%).

m.p.: 152 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.48 - 7.58 (m, 2 H), 7.25 - 7.34 (m, 2 H), 7.18 - 7.25 (m, 4 H), 3.81 (dd, J =5.8, 3.9 Hz, 4 H), 3.64 (dd, J =6.0, 3.9 Hz, 4 H), 3.45 (s, 3 H), 2.40 (s, 3 H), 2.39 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ = 170.0 (s), 158.4 (s), 155.8 (s), 150.9 (s), 138.3 (s), 138.0 (s), 137.6 (s), 136.7 (s), 129.1 (s), 128.8 (s), 128.2 (s), 127.6 (s), 118.1 (s), 105.0 (s), 66.6 (s), 51.8 (s), 45.2 (s), 21.2 (s), 21.2 (s) ppm. MS (EI, 70 eV) m/z (%): 401.8 (44), 401.0 (32), 372.0 (40), 371.1 (100), 357.1 (44), 345.1 (47), 344.1 (25). HRMS-ESI (m/z): [M+H⁺] calcd. for C₂₅H₂₆N₂O₃H⁺: 403.2021; Found: 403.2014. IR: $\tilde{\nu}$ = 3023 (w), 2963 (w), 2856 (w), 1731 (m), 1568 (s), 1433 (m), 1225 (s), 1114 (s), 967 (m), 825 (s) cm⁻¹.

*Synthesis of 3,4'-dimethyl-1,1'-biphenyl **4ga***



[CAS: 7383-90-6]

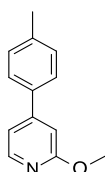
Compound **4ga** was prepared following procedure **B** for the one-pot *ortho*-Arylation and protodecarboxylation, starting from *ortho*-toluic acid (**1g**) (68.1 mg, 0.50 mmol) and 4-

bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **4ga** was obtained as colorless oil (73.0 mg, 0.401 mmol, 80%).

^1H NMR (400 MHz, CDCl_3): δ = 7.57 (d, J = 8.1 Hz, 2 H), 7.44 - 7.51 (m, 2 H), 7.39 (t, J = 7.6 Hz, 1 H), 7.32 (d, J = 8.1 Hz, 2 H), 7.22 (d, J = 7.6 Hz, 1 H), 2.49 (s, 3 H), 2.47 (s, 3 H) ppm.

^{13}C NMR (101 MHz, CDCl_3): δ = 141.1 (s), 138.5 (s), 138.2 (s), 136.9 (s), 129.4 (s, 2 C), 128.6 (s), 127.8 (s), 127.7 (s, 2 C), 127.0 (s), 124.1 (s), 21.5 (s), 21.1 (s) ppm. MS (EI, 70 eV) m/z (%): 183.0 (14), 182.0 (100), 181.0 (31), 167.1 (45), 165.0 (26), 91.0 (9), 89.0 (15). IR: $\tilde{\nu}$ = 3022 (w), 2918 (w), 1606 (m), 1515 (m), 1484 (m), 820 (m), 776 (s), 698 (m) cm^{-1} . The analytical data (NMR) matched those reported in the literature.³²⁶

Synthesis of 4-(2-methoxy-4-pyridinyl)-toluene **4aa**



Compound **4aa** was prepared following procedure **A** for the one-pot *ortho*-Arylation and protodecarboxylation, starting from 2-methoxynicotinic acid (**1a**) (78.9 mg, 0.50 mmol) and 4-bromotoluene (**2a**) (131 mg, 0.75 mmol). After purification, **4aa** was obtained as colorless solid (49.0 mg, 0.246 mmol, 49%).

m.p.: 64 °C. ^1H NMR (400 MHz, CDCl_3): δ = 8.19 (d, J = 5.3 Hz, 1 H), 7.51 (d, J = 8.3 Hz, 2 H), 7.23 - 7.29 (m, 2 H), 7.09 (dd, J = 5.4, 1.6 Hz, 1 H), 6.91 - 6.96 (m, 1 H), 3.98 (s, 3 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (101 MHz, CDCl_3): δ = 164.9 (s), 151.1 (s), 147.1 (s), 139.0 (s), 135.3 (s), 129.7 (s, 2 C), 126.8 (s, 2 C), 115.2 (s), 108.1 (s), 53.4 (s), 21.2 (s) ppm. MS (EI, 70 eV) m/z (%): 200.1 (100), 198.1 (49), 169.2 (13), 168.1 (10), 154.0 (9), 115.1 (8). HRMS-ESI (m/z): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{13}\text{H}_{13}\text{NOH}^+$: 200.1075; Found: 200.1070. IR: $\tilde{\nu}$ = 3035 (w), 2938 (w), 1605 (m), 1386 (m), 1202 (m), 806 (s), 515 (m), 454 (m) cm^{-1} .

7.8 Regiospecific *ortho*-C-H Allylation of Benzoic Acids

7.8.1 General procedure for the *ortho*-allylation

An oven-dried 20 mL vial was charged with [Ru(*p*-cymene)Cl₂]₂ (12.2 mg, 0.02 mmol), K₃PO₄ (76.6 mg, 0.35 mmol) and a benzoic acid (0.50 mmol) and closed with a septum cap. Under exclusion of air and water, 2,2,2-trichloroethanol (0.5 mL) and an allyl acetate (0.75 mmol) were added via syringe. The resulting mixture was stirred at 50 °C or, whenever stated, at 60 °C for 16 h. After the reaction was complete, it was diluted with EtOAc (10 mL) and extracted with aq. K₂CO₃ solution (3×10 mL). The combined aqueous phases were acidified with 2M HCl (pH 1-2), then extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂, ethyl acetate/cyclohexane gradient, 1% HCOOH), yielding the corresponding *ortho*-allylated benzoic acid.

7.8.2 General procedure for the *ortho*-propenylation

An oven-dried 20 mL vial was charged with [Ru(*p*-cymene)Cl₂]₂ (12.2 mg, 0.02 mmol), K₃PO₄ (54.7 mg, 0.25 mmol) and a benzoic acid (0.50 mmol) and closed with a septum cap. Under exclusion of air and water, 2,2,2-trifluoroethanol (0.5 mL) and allyl acetate (82.4 μL, 0.75 mmol) were added via syringe. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was complete, it was diluted with EtOAc (10 mL) and extracted with aq. K₂CO₃ solution (3×10 mL). The combined aqueous phases were acidified with 2M HCl (pH 1-2), then extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO₂, ethyl acetate/cyclohexane gradient, 1% HCOOH), yielding the corresponding *ortho*-propenylated benzoic acid.

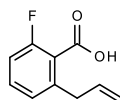
7.8.3 Procedure for the one-pot *ortho*-propenylation and protodecarboxylation

An oven-dried 20 mL vial was charged with [Ru(*p*-cymene)Cl₂]₂ (12.2 mg, 0.02 mmol), K₃PO₄ (54.7 mg, 0.25 mmol) and a benzoic acid (0.50 mmol) and closed with a septum cap. Under exclusion of air and water, 2,2,2-trifluoroethanol (0.5 mL) and allyl acetate (82.4 μL, 0.75 mmol) were added via syringe. The resulting mixture was stirred at 100 °C for 16 h. After the reaction was complete, CuBr (14.6 mg, 0.10 mmol) and bathophenanthroline (34.3 mg, 0.10 mmol) were added under argon atmosphere. NMP (2 mL) was added via syringe and the

resulting mixture was stirred at 190 °C for 18 h. NMP (2 mL) and benzotrifluoride (30 μ L) as internal standard were added to the reaction mixture and 1-fluoro-3-(1-propen-1-yl)benzene **6a** was formed in 72% yield as determined by ^{19}F NMR spectroscopic analysis and confirmed by GC-MS analytics. ^{19}F NMR (235 MHz, DMSO-*d*6) δ = -116.29 ppm.

7.8.4 Synthesis and characterization of products

Synthesis of 2-Allyl-6-fluoro-benzoic acid 3aa

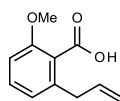


[CAS 1809821-18-8]

Compound **3aa** was prepared following the general procedure for the *ortho*-allylation from 2-fluorobenzoic acid (70.8 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol) and isolated as a white solid (71 mg, 79%).

m.p.: 56 – 57 °C. ^1H NMR (300 MHz, CDCl_3): δ = 11.41 (br s, 1 H), 7.41 (ddd, J = 8.0, 8.0, 5.7 Hz, 1 H), 6.91 - 7.19 (m, 2 H), 5.97 (ddt, J = 16.9, 10.5, 6.5 Hz, 1 H), 4.98 - 5.24 (m, 2 H), 3.63 (dt, J = 6.6, 1.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 170.8 (d, J = 2.2 Hz), 158.9 (d, J = 252.7 Hz), 141.5 (d, J = 1.7 Hz), 136.0 (s), 132.3 (d, J = 9.4 Hz), 125.8 (d, J = 3.3 Hz), 119.9 (d, J = 14.4 Hz), 116.8 (s), 114.1 (d, J = 17.8 Hz), 37.7 (d, J = 2.8 Hz). ^{19}F NMR (235 MHz, CDCl_3): δ = -112.65 (s) ppm. IR: $\tilde{\nu}$ = 3080, 2917, 2849, 1696, 1614, 1460, 1410, 1289, 1249, 1127 cm^{-1} . The analytical data (NMR) matched those reported in the literature.^[327]

Synthesis of Allyl-6-methoxy-benzoic acid 3ba



[CAS: 325172-28-9]

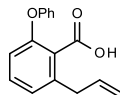
Compound **3ba** was prepared following the general procedure for the *ortho*-allylation from 2-methoxybenzoic acid (76.8 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol) and isolated as a white solid (79 mg, 82%).

m.p.: 89 – 91 °C. ^1H NMR (300 MHz, CDCl_3): δ = 10.77 (br s, 1 H), 7.35 (t, J = 8.1 Hz, 1 H), 6.88 (m, 2 H), 5.98 (ddt, J = 16.9, 10.1, 6.7 Hz, 1 H), 5.04 - 5.19 (m, 2 H), 3.91 (s, 3 H), 3.56 (d, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 172.4 (s), 156.9 (s), 139.8 (s), 136.4 (s), 131.2 (s), 122.3 (s), 121.8 (s), 116.4 (s), 109.3 (s), 56.2 (s), 37.9 (s) ppm. IR: $\tilde{\nu}$ = 3009,

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2967, 2916, 1691, 1582, 1468, 1265, 1074, 912 cm^{-1} . The analytical data (NMR) matched those reported in the literature.²⁶⁰

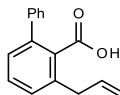
Synthesis of 2-Allyl-6-phenoxybenzoic acid **3ca**



Compound **3ca** was prepared following the general procedure for the *ortho*-allylation from 2-phenoxybenzoic acid (107 mg, 0.50 mmol) and allyl acetate (82.4 μL , 0.75 mmol) and isolated as a white solid (105 mg, 83%).

m.p.: 93 – 94 °C. ^1H NMR (300 MHz, CDCl_3): δ = 9.93 (br s, 1 H), 7.26 - 7.39 (m, 3 H), 6.97 - 7.17 (m, 4 H), 6.79 (dd, J = 8.4, 1.1 Hz, 1 H), 5.98 (ddt, J = 16.9, 10.2, 6.6 Hz, 1 H), 4.92 - 5.24 (m, 2 H), 3.57 (dt, J = 6.6, 1.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 172.6 (s), 157.0 (s), 154.8 (s), 139.3 (s), 136.1 (s), 131.1 (s), 129.7 (s), 124.7 (s), 124.5 (s), 123.7 (s), 119.2 (s), 116.7 (s), 116.65 (s), 37.8 (s) ppm. IR: $\tilde{\nu}$ = 3082, 2916, 1696, 1576, 1490, 1470, 1248, 1205, 995, 911 cm^{-1} . MS (EI-TOF) m/z (%): 254 (18) [M^+], 239 (15), 236 (63), 235 (27), 221 (100), 219 (20), 209 (10), 207 (14). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{16}\text{H}_{14}\text{O}_3$: 254.0943; found: 254.0934.

Synthesis of 2-Allyl-6-phenylbenzoic acid **3da**



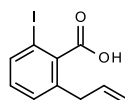
Compound **3da** was prepared following the general procedure for the *ortho*-allylation from 2-phenylbenzoic acid (101 mg, 0.50 mmol) and allyl acetate (82.4 μL , 0.75 mmol) and isolated as a white solid (98 mg, 82%).

Gram-scale synthesis of **3da**: An oven-dried 100 mL vial was charged with $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (245 mg, 0.40 mmol), K_3PO_4 (1.53 mg, 7.00 mmol) and 2-phenylbenzoic acid (2.02 g, 10.0 mmol) and closed with a septum cap. Under exclusion of air and water, 2,2,2-trichloroethanol (8 mL) and allyl acetate (1.65 mL, 15.0 mmol) were added via syringe. The resulting mixture was stirred at 50 °C for 16 h. After the reaction was complete, it was diluted with EtOAc (30 mL) and extracted with aq. K_2CO_3 solution (3 \times 30 mL). The combined aqueous phases were acidified with 2M HCl (pH 1-2), then extracted with EtOAc (3 \times 50 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO_4 , filtered, and the volatiles were removed under reduced pressure. The residue was purified by column

chromatography (SiO₂, ethyl acetate/cyclohexane gradient, 1% HCOOH) and **3da** was isolated in 62% yield (1.47 g).

m.p.: 116 – 118 °C. ¹H NMR (300 MHz, CDCl₃): δ = 10.08 (br s, 1 H), 7.35 - 7.47 (m, 6 H), 7.24 - 7.31 (m, 2 H), 5.90 - 6.07 (m, 1 H), 5.04 - 5.17 (m, 2 H), 3.55 (d, *J* = 6.8 Hz, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 174.4 (s), 140.6 (s), 140.5 (s), 137.5 (s), 136.4 (s), 131.8 (s), 129.9 (s), 128.6 (s), 128.4 (s), 128.3 (s), 128.1 (s), 127.6 (s), 116.6 (s), 38.0 (s). IR: $\tilde{\nu}$ = 3061, 2979, 2918, 1692, 1459, 1300, 1132, 919, 761, 698 cm⁻¹. MS (EI-TOF) *m/z* (%): 238 (27) [M⁺], 223 (32), 220 (100), 205 (28), 189 (30), 178 (13), 165 (39), 152 (22). HRMS (EI-TOF): [M⁺] calcd. for: C₁₆H₁₄O₂: 238.0994; found: 238.0993.

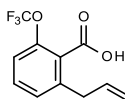
Synthesis of 2-Allyl-6-iodo-benzoic acid **3ea**



Compound **3ea** was prepared following the general procedure for the *ortho*-allylation (at T = 60 °C) from 2-iodobenzoic acid (124 mg, 0.50 mmol) and allyl acetate (82.4 μL, 0.75 mmol) and isolated as a white solid (106 mg, 74%).

m.p.: 84 – 85 °C. ¹H NMR (300 MHz, CDCl₃): δ = 11.11 (br s, 1 H), 7.77 (d, *J* = 7.7 Hz, 1 H), 7.25 - 7.32 (m, 1 H), 7.11 (dt, *J* = 7.9, 1.0 Hz, 1 H), 5.81 - 6.11 (m, 1 H), 5.01 - 5.30 (m, 2 H), 3.54 (d, *J* = 6.6 Hz, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 174.2 (s), 138.74 (s), 138.69 (s), 137.3 (s), 135.6 (s), 131.2 (s), 129.3 (s), 117.2 (s), 91.9 (s), 38.4 (s) ppm. IR: $\tilde{\nu}$ = 3002, 2958, 2919, 2852, 2648, 2361, 1696, 1440, 1388, 1277, 990, 921, 583, 539, 503 cm⁻¹. MS (EI-TOF) *m/z* (%): 288 (55) [M⁺], 272 (98), 244 (13), 230 (20), 215 (53), 149 (30), 127 (68), 115 (100). HRMS (EI-TOF): [M⁺] calcd. for: C₁₀H₉O₂I: 287.9647; found: 287.9661.

Synthesis of 2-Allyl-6-(trifluoromethoxy)benzoic acid **3fa**



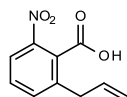
Compound **3fa** was prepared following the general procedure for the *ortho*-allylation (at T = 60 °C) from 2-(trifluoromethoxy)benzoic acid (107 mg, 0.50 mmol) and allyl acetate (82.4 μL, 0.75 mmol) and isolated as a pale yellow oil (98 mg, 80%).

¹H NMR (300 MHz, CDCl₃): δ = 9.85 (br s, 1 H), 7.43 (t, *J* = 8.1 Hz, 1 H), 7.20 - 7.28 (m, 2 H), 5.96 (ddt, *J* = 16.8, 10.3, 6.6 Hz, 1 H), 4.97 - 5.25 (m, 2 H), 3.58 (dt, *J* = 6.6, 1.7 Hz, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 171.4 (s), 146.3 (q, *J* = 1.7 Hz), 140.4 (s), 135.5 (s),

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131.3 (s), 128.2 (s), 126.6 (s), 118.7 (q, $J = 258.7$ Hz), 118.68 (q, $J = 1.0$ Hz), 117.2 (s), 37.7 (s) ppm. ^{19}F NMR (235 MHz, CDCl_3): $\delta = -57.31$ ppm. IR: $\tilde{\nu} = 3087, 3018, 2922, 1704, 1466, 1400, 1246, 1208, 1161, 1067$ cm^{-1} . MS (EI-TOF) m/z (%): 246 (10) [M^+], 244 (100), 231 (17), 217 (27), 211 (63), 189 (56), 160 (22), 145 (20), 123 (20), 115 (42). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{11}\text{H}_9\text{O}_3\text{F}_3$: 246.0504; found: 246.0517

Synthesis of 2-Allyl-6-nitro-benzoic acid **3ga**

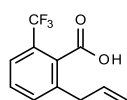


[CAS: 1809821-19-9]

Compound **3ga** was prepared following the general procedure for the *ortho*-allylation (at $T = 60$ °C) from 2-nitrobenzoic acid (83.6 mg, 0.50 mmol) and allyl acetate (82.4 μL , 0.75 mmol) and isolated as a white solid (41 mg, 41%).

m.p.: 122 – 124 °C. ^1H NMR (300 MHz, CDCl_3): $\delta = 9.43$ (br s, 1 H), 8.07 (dd, $J = 7.9, 1.5$ Hz, 1 H), 7.52 - 7.67 (m, 2 H), 5.97 (ddt, $J = 16.8, 10.2, 6.7$ Hz, 1 H), 5.08 - 5.26 (m, 2 H), 3.62 (dt, $J = 6.6, 1.6$ Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 171.2$ (s), 146.3 (s), 139.6 (s), 135.6 (s), 134.8 (s), 130.4 (s), 128.2 (s), 122.4 (s), 118.0 (s), 37.2 (s) ppm. IR: $\tilde{\nu} = 2961, 2922, 2853, 1700, 1613, 1343, 1287, 922$ cm^{-1} . The analytical data (NMR) matched those reported in the literature.³²⁷

Synthesis of 2-Allyl-6-(trifluoromethyl)benzoic acid **3ha**



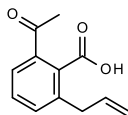
[CAS: 1344667-72-6]

Compound **3ha** was prepared following the general procedure for the *ortho*-allylation (at $T = 60$ °C) from 2-(trifluoromethyl)benzoic acid (97 mg, 0.50 mmol) and allyl acetate (82.4 μL , 0.75 mmol) and isolated as a white solid (62 mg, 54%).

m.p.: 85 – 86 °C. ^1H NMR (300 MHz, CDCl_3): $\delta = 10.56$ (br s, 1 H), 7.57 - 7.66 (m, 1 H), 7.47 - 7.57 (m, 2 H), 5.96 (ddt, $J = 16.6, 10.4, 6.7$ Hz, 1 H), 5.02 - 5.23 (m, 2 H), 3.57 (dt, $J = 6.6, 1.5$ Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 173.3$ (s), 138.3 (s), 135.3 (s), 133.4 (s), 130.5 (q, $J = 2.2$ Hz), 130.1 (s), 127.8 (q, $J = 32.1$ Hz), 124.4 (q, $J = 4.4$ Hz), 124.2 (q, $J = 273.0$ Hz), 117.4 (s), 37.6 (s) ppm. ^{19}F NMR (235 MHz, CDCl_3): $\delta = -59.32$ (s) ppm. IR: $\tilde{\nu} = 3013,$

2922, 2853, 2657, 1706, 1397, 1314, 1283, 1166, 1127, 1100, 930 cm^{-1} . The analytical data matched those reported in the literature.³²⁸

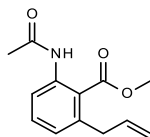
Synthesis of 2-Acetyl-6-allyl-benzoic acid 3ia



Compound **3ia** was prepared following the general procedure for the *ortho*-allylation (at T = 60 °C) from 2-acetylbenzoic acid (82.9 mg, 0.50 mmol) and allyl acetate (82.4 μL , 0.75 mmol) and isolated as a colorless oil (50 mg, 49%).

^1H NMR (300 MHz, CDCl_3): δ = 7.60 (t, J = 7.2 Hz, 1 H), 7.41 (dd, J = 7.5, 0.9 Hz, 1 H), 7.35 (dd, J = 7.5, 0.9 Hz, 1 H), 5.94 (ddt, J = 16.9, 10.2, 6.7 Hz, 1 H), 5.00 - 5.16 (m, 2 H), 3.70 - 3.84 (m, 2 H), 1.85 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 168.6 (s), 150.5 (s), 141.5 (s), 135.6 (s), 134.7 (s), 131.1 (s), 122.9 (s), 119.9 (s), 116.8 (s), 104.8 (s), 34.7 (s), 26.1 (s) ppm. IR: $\tilde{\nu}$ = 3348, 2954, 2922, 2853, 1734, 1460, 1377, 1182, 1024 cm^{-1} . MS (EI) m/z (%): 186 (83) [$\text{M}-\text{H}_2\text{O}$], 171 (100), 168 (22), 158 (22), 141 (31), 127 (78), 115 (89). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{12}\text{H}_{12}\text{O}_3$: 204.0786; found: 204.0790.

Synthesis of Methyl 2-acetamido-6-allyl-benzoate 3ja

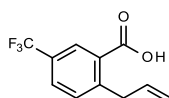


Compound **3ja** was prepared following the general procedure for the *ortho*-allylation (at T = 60 °C) from N-acetylanthranilic acid (90.5 mg, 0.50 mmol) and allyl acetate (82.4 μL , 0.75 mmol). Due to low solubility, the acid form was not suitable for NMR analysis, thus it was isolated as methyl ester. After the allylation step was complete, NMP (2 mL), K_2CO_3 (207 mg, 1.50 mmol) and MeI (156 μL , 2.5 mmol) were added and the mixture was stirred at 50 °C for 2 h. The reaction mixture was diluted with EtOAc (20 mL) and the resulting mixture was washed with water and 10% LiCl solution (3 \times 10 mL each). The combined organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (SiO_2 , ethyl acetate/cyclohexane gradient), yielding the corresponding *ortho*-allylated methyl benzoate as a yellow oil (92 mg, 79%).

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^1H NMR (300 MHz, CDCl_3): δ = 9.29 (br s, 1 H), 8.14 (d, J = 7.7 Hz, 1 H), 7.33 (t, J = 8.0 Hz, 1 H), 6.96 (d, J = 7.7 Hz, 1 H), 5.86 (ddt, J = 16.8, 10.4, 6.4 Hz, 1 H), 4.88 - 5.07 (m, 2 H), 3.87 (d, J = 0.9 Hz, 3 H), 3.52 (dt, J = 6.4, 1.8 Hz, 2 H), 2.13 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 169.0 (s), 169.4 (s), 140.1 (s), 137.8 (s), 136.7 (s), 131.6 (s), 126.0 (s), 120.4 (s), 120.2 (s), 115.8 (s), 52.0 (s), 39.3 (s), 24.8 (s) ppm. IR: $\tilde{\nu}$ = 3023, 2979, 2331, 1698, 1644, 1401, 1303, 925 cm^{-1} . MS (EI) m/z (%): 233 (7) [M^+], 201 (33), 186 (13), 159 (100), 131 (41), 115 (14), 103 (11). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{12}\text{H}_{11}\text{NO}_2$: 233.1052; found: 233.1051.

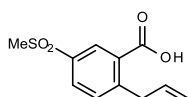
Synthesis of 2-Allyl-5-(trifluoromethyl)benzoic acid **3ka**



Compound **3ka** was prepared following the general procedure for the *ortho*-allylation (at T = 60 °C) from 3-(trifluoromethyl)benzoic acid (97.0 mg, 0.50 mmol) and allyl acetate (82.4 μL , 0.75 mmol) and isolated as a white solid (80 mg, 70%).

m.p.: 71 – 72 °C. ^1H NMR (300 MHz, CDCl_3): δ = 11.15 (br s, 1 H), 8.09 - 8.41 (m, 1 H), 7.68 (ddd, J = 8.1, 1.8, 0.7 Hz, 1 H), 7.28 - 7.51 (m, 1 H), 5.95 (ddt, J = 16.9, 10.3, 6.5 Hz, 1 H), 4.76 - 5.21 (m, 2 H), 3.82 (dt, J = 6.5, 1.6 Hz, 2 H). ^{13}C NMR (75 MHz, CDCl_3): δ = 171.9 (s), 146.9 (s), 136.1 (s), 131.9 (s), 129.5 (q, J = 33.2 Hz), 129.4 (q, J = 3.9 Hz), 128.74 (s), 128.73 (q, J = 4.4 Hz), 126.7 (q, J = 272.6 Hz), 116.8 (s), 38.4 (s). ^{19}F NMR (235 MHz, CDCl_3): δ = -62.73 (s) ppm. IR: $\tilde{\nu}$ = 3087, 2927, 2859, 2632, 1701, 1410, 1335, 1308, 1251, 1183, 1124, 1092, 921 cm^{-1} . MS (EI-TOF) m/z (%): 230 (35) [M^+], 215 (100), 202 (15), 184 (15), 173 (18), 164 (11), 145 (16), 115 (47). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{11}\text{H}_9\text{F}_3\text{O}_2$: 230.0555; found: 240.0566.

Synthesis of 2-Allyl-5-methylsulfonyl-benzoic acid **3la**

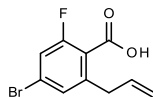


Compound **3la** was prepared following the general procedure for the *ortho*-allylation (at T = 60 °C) from 2-(methylsulfonyl)benzoic acid (105 mg, 0.50 mmol) and allyl acetate (82.4 μL , 0.75 mmol) and isolated as a white solid (72 mg, 60%).

m.p.: 149 – 150 °C. ^1H NMR (300 MHz, CDCl_3): δ = 9.96 (br s, 1 H), 8.63 (d, J = 2.0 Hz, 1 H), 8.07 (dd, J = 8.2, 2.1 Hz, 1 H), 7.57 (d, J = 8.1 Hz, 1 H), 6.02 (ddt, J = 16.9, 10.2, 6.5 Hz, 1 H), 4.99 - 5.02 (m, 2 H), 3.93 (dt, J = 6.6, 1.3 Hz, 2 H), 3.11 (s, 3 H) ppm. ^{13}C NMR (75

MHz, CDCl₃): δ = 170.8 (s), 149.0 (s), 139.0 (s), 135.6 (s), 132.5 (s), 131.3 (s), 130.8 (s), 129.5 (s), 117.3 (s), 44.5 (s), 38.4 (s) ppm. IR: $\tilde{\nu}$ = 3203, 3013, 2925, 1725, 1293, 1203, 1132, 1106 cm⁻¹. MS (EI-TOF) m/z (%): 240 (6) [M⁺], 196 (100), 168 (13). HRMS (EI-TOF): [M⁺] calcd. for: C₁₁H₁₂O₄S: 240.0456; found: 240.0464.

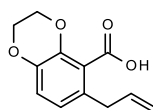
Synthesis of 2-Allyl-4-bromo-6-fluoro-benzoic acid 3ma



Compound **3ma** was prepared following the general procedure for the *ortho*-allylation (at T = 60 °C) from 4-bromo-2-fluorobenzoic acid (112 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol) and isolated as a white solid (90 mg, 70%).

m.p.: 97 – 98 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.19 - 7.27 (m, 2 H), 5.93 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1 H), 4.92 - 5.24 (m, 2 H), 3.59 (d, *J* = 6.6 Hz, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.1 (s), 160.4 (d, *J* = 258.7 Hz), 143.2 (d, *J* = 1.7 Hz), 135.1 (s), 129.1 (d, *J* = 3.3 Hz), 125.7 (d, *J* = 10.5 Hz), 118.8 (d, *J* = 13.8 Hz), 117.9 (d, *J* = 25.4 Hz), 117.6 (s), 37.5 (d, *J* = 2.2 Hz). ¹⁹F NMR (235 MHz, CDCl₃): δ = -109.59 (s) ppm. IR: $\tilde{\nu}$ = 3078, 2917, 2849, 1691, 1596, 1419, 1398, 1299, 1266, 1248, 1130, 1008, 916, 604, 575, 524 cm⁻¹. MS (EI-TOF) m/z (%): 260 (20) [M⁺ (⁸¹Br)], 258 (21) [M⁺ (⁷⁹Br)], 243 (100), 201 (10), 133 (60), 107 (11). HRMS (EI-TOF): [M⁺] calcd. for: C₁₀H₈O₂⁷⁹Br: 257.9692 and C₁₀H₈O₂⁸¹Br: 259.9671; found: 257.9676 and 259.9654.

Synthesis of 6-Allyl-2,3-dihydro-1,4-benzodioxine-5-carboxylic acid 3na



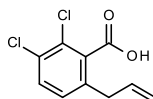
Compound **3na** was prepared following the general procedure for the *ortho*-allylation from 2,3-dihydro-1,4-benzodioxine-5-carboxylic acid (91.0 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol) and isolated as a white solid (94 mg, 85%).

m.p.: 97 – 97 °C. ¹H NMR (300 MHz, CDCl₃): δ = 10.31 (br s, 1 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 6.67 (d, *J* = 8.4 Hz, 1 H), 5.87 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1 H), 4.89 - 5.07 (m, 2 H), 4.13 - 4.32 (m, 3 H), 3.40 (d, *J* = 6.6 Hz, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 171.3 (s), 141.9 (s), 141.3 (s), 136.8 (s), 131.7 (s), 122.7 (s), 121.3 (s), 119.2(s), 116.1 (s), 64.7 (s), 64.0 (s), 37.5 (s) ppm. IR: $\tilde{\nu}$ = 3007, 2987, 2883, 1679, 1487, 1445, 1288, 1071 cm⁻¹. MS (EI-TOF) m/z

EXPERIMENTELLER TEIL

(%): 220 (59) [M⁺], 205 (100), 202 (80), 175 (14), 163 (49), 146 (96), 121 (12), 118 (62), 89 (24). HRMS (EI-TOF): [M⁺] calcd. for: C₁₂H₁₂O₄: 220.0736; found: 220.0729.

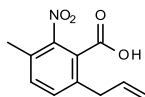
Synthesis of 2-Allyl-5,6-dichloro-benzoic acid **3oa**



Compound **3oa** was prepared) following the general procedure for the *ortho*-allylation (at T = 60 °C) from 2,3-dichlorobenzoic acid (97.5 mg, 0.50 mmol) and allyl acetate (82.4 μL, 0.75 mmol) and isolated as a white solid (97 mg, 80%).

m.p.: 90 – 92 °C. ¹H NMR (300 MHz, CDCl₃): δ = 10.13 (br s, 1 H), 7.49 (d, *J* = 8.3 Hz, 1 H), 7.15 (d, *J* = 8.3 Hz, 1 H), 5.92 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1 H), 5.01 - 5.22 (m, 2 H), 3.48 (dt, *J* = 6.6, 1.6 Hz, 2 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 171.5 (s), 137.2 (s), 135.0 (s), 134.2 (s), 131.4 (s), 129.2 (s), 129.0 (s), 128.9 (s), 117.6 (s), 37.5 (s) ppm. IR: $\tilde{\nu}$ = 3015, 2922, 2648, 2559, 1704, 1420, 1288, 1231, 917, 820, 689, 606 cm⁻¹. MS (EI-TOF) *m/z* (%): 234 (15), [M⁺ (³⁷Cl)], 230 (4) [M⁺ (³⁵Cl)], 215 (100), 201 (26), 186 (26), 173 (49), 149 (67), 115 (39). HRMS (EI-TOF): [M⁺] calcd. for: C₁₀H₈O₂³⁵Cl₂: 229.9901 and C₁₀H₈O₂³⁷Cl₂: 233.9842; found: 229.9899 and 233.9858.

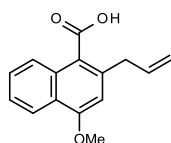
Synthesis of 2-Allyl-5-methyl-6-nitrobenzoic acid **3pa**



Compound **3pa** was prepared following the general procedure for the *ortho*-allylation from 3-methyl-2-nitrobenzoic acid (92.4 mg, 0.50 mmol) and allyl acetate (82.4 μL, 0.75 mmol) and isolated as a white solid (62 mg, 56%).

m.p.: 133 – 135 °C. ¹H NMR (300 MHz, CDCl₃): δ = 10.19 (br s, 1 H), 7.37 (s, 2 H), 5.93 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1 H), 5.04 - 5.19 (m, 2 H), 3.61 (dt, *J* = 6.6, 1.6 Hz, 2 H), 2.42 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.6 (s), 149.7 (s), 138.4 (s), 135.3 (s), 134.1 (s), 132.9 (s), 129.6 (s), 125.9 (s), 117.5 (s), 37.4 (s), 18.2 (s) ppm. IR: $\tilde{\nu}$ = 3010, 2987, 2851, 2664, 2561, 2361, 1696, 1535, 1284, 920 cm⁻¹. MS (EI-TOF) *m/z* (%): 203 (70) [M-H₂O], 189 (28), 158 (47), 145 (37), 128 (100), 115 (62). HRMS (EI-TOF): [M-H₂O] calcd. for: C₁₁H₉NO₂: 203.0582; found: 203.0593.

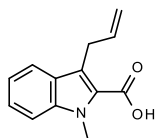
Synthesis of 2-Allyl-4-methoxy-naphthalene-1-carboxylic acid **3qa**



Compound **3qa** was prepared following the general procedure for the *ortho*-allylation from 4-methoxy-1-naphthoic acid (104 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol) and isolated as a white solid (86 mg, 71%).

m.p.: 152 – 153 °C. ^1H NMR (300 MHz, CDCl_3): δ = 11.76 (br s, 1 H), 8.03 - 8.24 (m, 2 H), 7.32 - 7.55 (m, 2 H), 6.62 (s, 1 H), 6.00 (ddt, J = 16.9, 10.2, 6.5 Hz, 1 H), 4.96 - 5.17 (m, 2 H), 3.95 (s, 3 H), 3.68 (d, J = 6.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 175.0 (s), 157.2 (s), 138.5 (s), 136.7 (s), 131.7 (s), 127.9 (s), 125.2 (s), 124.9 (s), 124.3 (s), 122.1 (s), 120.9 (s), 116.4 (s), 105.6 (s), 55.7 (s), 39.4 (s) ppm. IR: $\tilde{\nu}$ = 3005, 2967, 2922, (2851), 1678, 1587, 1510, 1263, 1116 cm^{-1} . MS (EI-TOF) m/z (%): 242 (29) [M^+], 224 (100), 198 (27), 181 (82), 165 (21), 152 (46). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{15}\text{H}_{14}\text{O}_3$: 242.0943; found: 242.0944.

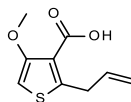
Synthesis of 3-Allyl-1-methyl-indole-2-carboxylic acid **3ra**



Compound **3ra** was prepared following the general procedure for the *ortho*-allylation (at T = 60 °C) from methylindole-2-carboxylic acid (78.0 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol) and isolated as a white solid (25 mg, 26%).

m.p.: 137 – 138 °C. ^1H NMR (300 MHz, CDCl_3): δ = 7.76 (dt, J = 8.1, 1.1 Hz, 1 H), 7.37 - 7.47 (m, 2 H), 7.14 - 7.23 (m, 1 H), 6.00 - 6.22 (m, 1 H), 4.99 - 5.21 (m, 2 H), 4.09 (s, 3 H), 4.01 (dt, J = 6.2, 1.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 168.2 (s), 139.4 (s), 137.0 (s), 126.5 (s), 126.0 (s), 125.2 (s), 123.6 (s), 121.2 (s), 120.1 (s), 114.9 (s), 110.3 (s), 32.3 (s), 29.8 (s) ppm. IR: $\tilde{\nu}$ = 3005, 2923, 2602, 1661, 1523, 1446, 1364, 1274, 1245, 1139, 914 cm^{-1} . MS (EI-TOF) m/z (%): 215 (100) [M^+], 197 (19), 188 (19), 170 (58), 154 (19), 144 (14). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{13}\text{H}_{13}\text{NO}_2$: 215.0946; found: 215.0942.

Synthesis of 2-Allyl-4-methoxy-thiophene-3-carboxylic acid **3sa**

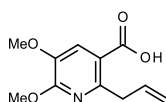


EXPERIMENTELLER TEIL

Compound **3sa** was prepared following the general procedure for the *ortho*-allylation (at T = 60 °C) from 4-methoxythiophene-3-carboxylic acid (83.3 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol) and isolated as off-white solid (36 mg, 36%).

m.p.: 71 – 72 °C (decomp.). ^1H NMR (300 MHz, CDCl_3): δ = 6.23 (s, 1 H), 6.00 (ddt, J = 17.1, 10.1, 6.8, Hz, 1 H), 5.12 - 5.26 (m, 2 H), 3.91 - 4.04 (m, 5 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 162.4 (s), 156.9 (s), 155.1 (s), 134.3 (s), 118.0 (s), 117.0 (s), 95.2 (s), 58.2 (s), 34.9 (s) ppm. IR: $\tilde{\nu}$ = 3119, 2935, 1701, 1665, 1549, 1464, 1204, 1080, 923 cm^{-1} . MS (EI-TOF) m/z (%): 198 (56) [M^+], 183 (38), 180 (89), 165 (100), 151 (11), 137 (41), 121 (19), 109 (26). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_9\text{H}_{10}\text{O}_3\text{S}$: 198.0351; found: 198.0353.

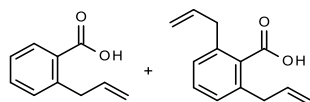
Synthesis of 2-Allyl-5,6-dimethoxy-pyridine-3-carboxylic acid **3ta**



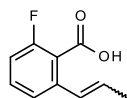
Compound **3ta** was prepared following the general procedure for the *ortho*-allylation (at T = 60 °C) from 5,6-dimethoxynicotinic acid (91.6 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol) and isolated as a white solid in a mixture of 10:1 with its regioisomer (25.0 mg, 22%).

m.p.: 154 – 155 °C. ^1H NMR (300 MHz, CDCl_3): δ = 8.70 (s, 0.1 H-(C_4)), 7.69 (s, 1 H), 6.14 (s, 1 H), 5.85 - 6.04 (m, 0.1 H-(C_4)), 4.96 - 5.17 (m, 2 H), 4.09 (s, 3 H), 3.88 - 3.96 (m, 5 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 171.9 (s), 156.1 (s), 153.0 (s), 141.7 (s), 136.1 (s), 119.6 (s), 116.4 (s), 115.6 (s), 55.9 (s), 54.2 (s), 40.5 ppm. IR: $\tilde{\nu}$ = 3077, 2944, 1694, 1567, 1487, 1401, 1273, 1226, 989 cm^{-1} . MS (EI-TOF) m/z (%): 223 (100) [M^+], 205 (94), 190 (25), 176 (37), 166 (45), 151 (14), 145 (11), 136 (14). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{11}\text{H}_{13}\text{NO}_4$: 223.0845; found: 223.0847.

Synthesis of a mixture of 2-allylbenzoic acid **3ua** and 2,6-diallylbenzoic acid **3va**

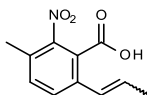


The mixture of **3ua** and **3va** was prepared following the general procedure for the *ortho*-allylation from benzoic acid (61.7 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol). After aqueous work-up, the volatiles were removed and toluene (54 μ L, 1 equiv.) was added as internal standard. The crude mixture was analyzed via ^1H NMR without further purification (ratio of **3ua** and **3va** 1:1.7).

Synthesis of 2-Fluoro-6-(prop-1-enyl)benzoic acid 4aa

Compound **4aa** was prepared following the general procedure for the *ortho*-propenylation from 2-fluorobenzoic acid (70.8 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol) and isolated as a white solid (64.0 mg, 71%, *E/Z* 30:1).

m.p.: 77 – 78 °C. ^1H NMR (300 MHz, CDCl_3): δ = 10.88 (br s, 1 H), 7.29 - 7.48 (m, 2 H), 7.01 (m, 1 H), 6.76 (dq, J = 15.6, 1.8 Hz, 1 H), 6.18 - 6.39 (m, 1 H), 1.94 (dd, J = 6.7, 1.7 Hz, 3 H-*E*), 1.79 (dd, J = 7.1, 1.9 Hz, 0.1 H-*Z*) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 171.1 (s), 160.4 (d, J = 253.8 Hz), 139.4 (d, J = 2.2 Hz), 132.0 (d, J = 9.4 Hz), 130.8 (s), 127.3 (d, J = 2.8 Hz), 121.7 (d, J = 3.3 Hz), 118.4 (d, J = 14.9 Hz), 114.0 (d, J = 22.1 Hz), 18.7 (s) ppm. ^{19}F NMR (235 MHz, CDCl_3): δ = -113.32 (s) ppm. IR: $\tilde{\nu}$ = 3009, 2916, 2849, 2661, 2554, 1695, 1609, 1467, 1407, 1292, 1263, 1243, 1127, 1003, 954, 917 cm^{-1} . MS (EI-TOF) m/z (%): 180 (47) [M^+], 165 (100), 151 (11), 133 (52), 123 (12), 109 (11). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{10}\text{H}_9\text{O}_2\text{F}$: 180.0587; found: 180.0581.

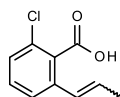
Synthesis of 3-Methyl-2-nitro-6-(prop-1-enyl)benzoic acid 4na

Compound **4na** was prepared following the general procedure for the *ortho*-propenylation from 3-methyl-2-nitrobenzoic acid (92.4 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol) and isolated as a white solid (64 mg, 58%, *E/Z* 2.7:1).

m.p.: 127 – 128 °C. ^1H NMR (300 MHz, CDCl_3): δ = 8.23 (br s, 1 H-*E+Z*), 7.28 - 7.63 (m, 2 H-*E+Z*), 6.71 (d, J = 15.4 Hz, 0.7 H-*E*), 6.62 (d, J = 10.8 Hz, 0.3 H-*Z*), 6.15 - 6.38 (m, 0.7 H-*E*), 5.97 (dq, J = 11.5, 7.1 Hz, 0.3 H-*Z*), 2.41 (s, 0.9 H-*Z*), 2.44 (s, 2.1 H-*E*), 2.41 (s, 2 H), 1.93 (d, J = 6.6 Hz, 2.2 H-*E*), 1.75 (dd, J = 7.2, 1.5 Hz, 0.8 H-*Z*) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 149.3 (s, *Z*), 149.1 (s, *E*), 135.9 (s, *E*), 135.5 (s, *Z*), 133.0 (s, *E*), 132.7 (s, *Z*), 132.5 (s, *Z*), 131.0 (s, *E*), 130.0 (s, *Z*), 129.5 (s, *Z*), 129.4 (s, *E*), 128.5 (s, *E*), 126.5 (s, *E*), 126.2 (s, *Z*), 18.7 (s, *E*), 18.1 (s, *E*), 18.1 (s, *Z*), 14.3 (s, *Z*) ppm. IR: $\tilde{\nu}$ = 3025, 2961, 2917, 1705, 1527, 1403, 1361, 1256, 961 cm^{-1} . MS (EI-TOF) m/z (%): 221 (81) [M^+], 203 (36), 189 (29), 177 (21), 161 (35), 145 (40), 134 (34), 128 (83), 115 (100), 103 (58). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{11}\text{H}_{11}\text{NO}_4$: 221.0688; found: 221.0689.

EXPERIMENTELLER TEIL

Synthesis of 2-Chloro-6-(prop-1-enyl)benzoic acid **4wa**

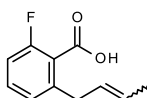


Compound **4wa** was prepared following the general procedure for the *ortho*-propenylation from 2-chlorobenzoic acid (92.4 mg, 0.50 mmol) and allyl acetate (82.4 μ L, 0.75 mmol) and isolated as a white solid (54.0 mg, 55%, *E/Z* 14:1).

m.p.: 86 – 87 °C. ^1H NMR (300 MHz, CDCl_3): δ = 10.69 (br s, 1 H-(*E+Z*)), 7.48 - 7.16 (m, 3 H-(*E+Z*)), 6.43 - 6.61 (m, 1 H-(*E+Z*)), 6.29 (dq, J = 15.6, 6.6 Hz, 0.9 H-(*E*)), 5.86 - 6.03 (m, 0.1 H-(*Z*)), 1.91 (dd, J = 6.6, 1.7 Hz, 2.8 H-(*E*)), 1.77 (dd, J = 7.0, 1.8 Hz, 0.2 H-(*Z*)) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 172.8 (s, *E+Z*), 137.3 (s, *E*), 136.9 (s, *Z*), 132.2 (s, *Z*), 140.0 (s, *E*), 130.8 (s, *E*), 130.70 (s, *Z*), 130.65 (s, *E*), 130.6 (s, *E*), 130.3 (s, *Z*), 127.8 (s, *Z*), 127.7 (s, *Z*), 127.6 (s, *E*), 126.7 (s, *E*), 126.0 (s, *Z*), 123.9 (s, *E*), 123.5 (s, *Z*), 18.7 (s, *E*), 14.5 (s, *Z*) ppm. IR: $\tilde{\nu}$ = 3015, 2913, 2641, 1691, 1590, 1439, 1279, 1184, 1156, 956, 805, 769, 707, 653 cm^{-1} . MS (EI-TOF) m/z (%): 198 (12) [M^+ (^{37}Cl)], 196 (47) [M^+ (^{35}Cl)], 181 (69), 167 (30), 139 (22), 115 (100).

HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{10}\text{H}_9\text{O}_2^{37}\text{Cl}$: 198.0262; found: 198.0276 and for: $\text{C}_{10}\text{H}_9\text{O}_2^{35}\text{Cl}$: 196.0291; found: 196.0279.

Synthesis of 2-(But-2-enyl)-6-fluoro-benzoic acid **3ab**

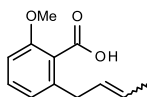


Compound **3ab** was prepared following the general procedure for the *ortho*-allylation from 2-fluorobenzoic acid (70.8 mg, 0.50 mmol) and 1-methylallyl acetate (95.3 μ L, 0.75 mmol) and isolated as a white solid (70.0 mg, 70%, *E/Z* 1:1.5).

m.p.: 48 – 49 °C. ^1H NMR (300 MHz, CDCl_3): δ = 7.29 (ddd, J = 8.0, 8.0, 5.7 Hz, 1 H-(*E+Z*)), 6.86 - 7.03 (m, 2 H-(*E+Z*)), 5.35 - 5.63 (m, 2 H-(*E+Z*)), 3.54 (d, J = 7.0 Hz, 1.2 H-(*Z*)), 3.45 (d, J = 3.7 Hz, 0.8 H-(*E*)), 1.64 (m, J = 6.2 Hz, 1.8 H-(*Z*)), 1.60 (m, 1.2 H-(*E*)) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 171.4 (d, J = 3.4 Hz, *E+Z*), 160.4 (d, J = 253.8 Hz, *E+Z*), 142.5 (d, J = 1.1 Hz, *E*), 142.4 (d, J = 1.1 Hz, *Z*), 132.2 (d, J = 9.4 Hz, *E*), 132.1 (d, J = 9.4 Hz, *Z*), 128.5 (s, *E*), 127.7 (s, *E*), 127.6 (s, *Z*), 126.0 (s, *Z*), 125.6 (d, J = 3.3 Hz, *E*), 125.3 (d, J = 3.3 Hz, *Z*), 120.1 (d, J = 14.4 Hz, *Z*), 120.0 (d, J = 14.9 Hz, *E*), 113.8 (d, J = 23.1 Hz, *E*), 113.7 (d, J = 22.1 Hz, *Z*), 36.6 (d, J = 2.2 Hz, *E*), 31.0 (d, J = 2.2 Hz, *Z*), 17.8 (s, *E*), 12.8 (s, *Z*) ppm. ^{19}F (235 MHz,

CDCl₃): δ = -113.1 (s), -113.2 (s) ppm. IR: $\tilde{\nu}$ = 3028, 2974, 2922, 1693, 1613, 1575, 1475, 1408, 1305, 1289, 1258, 1124, 917, 761 cm⁻¹. MS (EI-TOF) m/z (%): 194 (22) [M⁺], 176 (32), 165 (100), 152 (28), 147 (30), 133 (44), 123 (16), 109 (17). HRMS (EI-TOF): [M⁺] calcd. for: C₁₁H₁₁O₂F: 194.0743; found: 194.0750.

Synthesis of 2-(But-2-enyl)-6-methoxy-benzoic acid 3bb

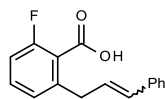


Compound **3bb** was prepared following the general procedure for the *ortho*-allylation from 2-methoxybenzoic acid (76.8 mg, 0.50 mmol) and 1-methylallyl acetate (95.3 μ L, 0.75 mmol) and isolated as a white solid (86 mg, 64%, *E/Z* 1:1.2).

m.p.: 93 – 94°C. ¹H NMR (300 MHz, CDCl₃): δ = 10.83 (br s, 1 H-(*E+Z*)), 7.33 (t, *J* = 8.0 Hz, 1 H-(*E+Z*)), 6.79 - 6.94 (m, 2 H-(*E+Z*)), 5.48 - 5.69 (m, 2 H-(*E+Z*)), 3.90 (s, 3 H-(*E+Z*)), 3.55 (d, *J* = 6.2 Hz, 1.3 H-(*Z*)), 3.47 (d, *J* = 5.0 Hz, 0.7 H-(*E*)), 1.71 - 1.77 (m, 1.9 H-(*Z*)), 1.65 - 1.71 (m, 1.1 H-(*E*)) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 156.8 (s, *E+Z*), 140.8 (s, *E+Z*), 131.13 (s, *Z*), 131.09 (s, *E*), 128.9 (s, *E*), 128.0 (s, *Z*), 127.1 (s, *E*), 125.4 (s, *Z*), 122.2 (s, *E*), 121.9 (s, *Z*), 109.04 (s, *E*), 109.1 (s, *Z*), 56.1 (s, *E+Z*), 36.8 (s, *E*), 31.0 (s, *Z*), 17.8 (s, *E*), 12.8 (s, *Z*) ppm.

IR: $\tilde{\nu}$ = 3016, 2917, 2849, (2657), 1695, 1600, 1471, 1269, 1202, 1077 cm⁻¹. MS (EI-TOF) m/z (%): 206 (40) [M⁺], 188 (79), 177 (100), 169 (35), 155 (27), 145 (49), 129 (41), 115 (76). HRMS (EI-TOF): [M⁺] calcd. for: C₁₂H₁₄O₃: 206.0943; found: 206.0939.

Synthesis of 2-Cinnamyl-6-fluoro-benzoic acid 3ac



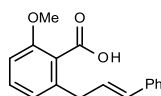
Compound **3ac** was prepared following the general procedure for the *ortho*-allylation from 2-fluorobenzoic acid (70.8 mg, 0.50 mmol) and 1-phenylallyl acetate (130 μ L, 0.75 mmol) and isolated as a colorless oil (100 mg, 78%, *E/Z* 1:1.2).

¹H NMR (300 MHz, CDCl₃): δ = 6.88 - 7.48 (m, 8 H-(*E+Z*)), 6.61 (dt, *J* = 11.4, 2.0 Hz, 0.5 H-(*Z*)), 6.47 (dt, *J* = 15.8, 1.3 Hz, 0.5 H-(*E*)), 6.31 (dt, *J* = 15.8, 6.6 Hz, 0.5 H-(*E*)), 5.79 (dt, *J* = 11.6, 7.3 Hz, 0.5 H-(*Z*)), 3.86 (dd, *J* = 7.3, 1.7 Hz, 1.1 H-(*Z*)), 3.74 (d, *J* = 6.6 Hz, 0.9 H-(*E*)) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.56 (d, *J* = 7.2 Hz, *E+Z*), 162.3 (d, *J* = 253.8 Hz, *E*), 160.0 (d, *J* = 254.3 Hz, *Z*), 142.2 (d, *J* = 1.1 Hz, *E*), 141.8 (d, *J* = 1.1 Hz, *Z*), 137.2 (s, *E*), 136.8 (s, *Z*), 132.4 (d, *J* = 8.9 Hz, *E*), 132.3 (d, *J* = 9.4 Hz, *Z*), 132.1 (s, *E*), 130.9 (s, *Z*), 129.1 (s, *Z*),

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128.6 (s, *Z*), 128.5 (s, *Z*), 128.3 (s, *E*), 127.6 (s, *E*), 127.3 (s, *E*), 127.0 (s, *Z*), 126.2 (s, *E*), 125.8 (d, *J* = 3.3 Hz, *E*), 125.2 (d, *J* = 3.3 Hz, *Z*), 120.0 (d, *J* = 14.4 Hz, *E*), 119.9 (d, *J* = 14.4 Hz, *Z*), 114.3 (d, *J* = 22.1 Hz, *E*), 114.1 (d, *J* = 21.6 Hz, *Z*), 36.9 (d, *J* = 2.2 Hz, *E*), 32.4 (d, *J* = 1.7 Hz, *Z*) ppm. ^{19}F (235 MHz, CDCl_3): δ = -112.31, -112.38 ppm. IR: $\tilde{\nu}$ = 3059, 3028, 2925, 1703, 1613, 1580, 1470, 1250, 1165, 1109, 1062, 1031, 920 cm^{-1} . MS (EI-TOF) m/z (%): 268 (8) [M^+], 237 (58), 209 (43), 189 (15), 165 (100), 152 (34). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{16}\text{H}_{13}\text{O}_2$: 256.0900; found: 256.0902.

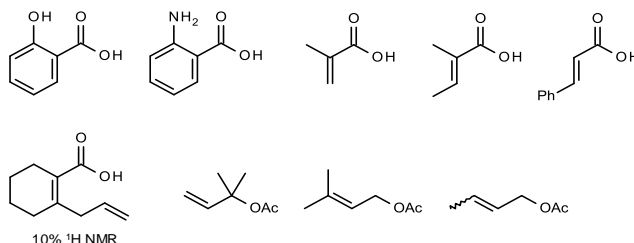
Synthesis of 2-[(*E*)-Cinnamyl]-6-methoxy-benzoic acid **3bc**



Compound **3bc** was prepared following the general procedure for the *ortho*-allylation from 2-methoxybenzoic acid (76.8 mg, 0.50 mmol) and 1-phenylallyl acetate (130 μL , 0.75 mmol) and isolated as a white solid (86 mg, 64%).

m.p.: 133 – 134°C. ^1H NMR (300 MHz, CDCl_3): δ = 7.23 - 7.40 (m, 5 H), 7.13 - 7.22 (m, 1 H), 6.91 - 6.99 (m, 1 H), 6.82 - 6.89 (m, 1 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 6.34 (dt, *J* = 15.8, 6.6 Hz, 1 H), 3.90 (s, 3 H), 3.69 (d, *J* = 6.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 171.8 (s), 157.0 (s), 140.5 (s), 137.8 (s), 131.6 (s), 131.4 (s), 128.4 (s), 128.2 (s), 127.1 (s), 126.2 (s), 122.5 (s), 121.5 (s), 109.4 (s), 56.2 (s), 37.1 (s) ppm. IR: $\tilde{\nu}$ = 3022, 2921, 2850, 1696, 1586, 1474, 1273, 1050 cm^{-1} . MS (EI-TOF) m/z (%): 268 (19) [M^+], 250 (84), 207 (22), 191 (32), 177 (100), 165 (41), 133 (40), 115 (35), 105 (43). HRMS (EI-TOF): [M^+] calcd. for: $\text{C}_{17}\text{H}_{16}\text{O}_3$: 268.1099; found: 268.1091.

7.8.8 Unreactive substrates



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