Dissertation zur Erlangung des Doktorgrades
der Fakultät für Chemie und Pharmazie
der Ludwig-Maximilians-Universität München

Benzylic Arylation of Heterocycles Using TMP-Bases and Cross-Coupling Reactions between Aromatic Halides and Aromatic Grignard Reagents Catalyzed by Alternative Metals

von

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aus Dillingen an der Donau

2014

Erklärung

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. Novemver 2011 von Herrn Prof. Dr. Paul Knochel betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde selbständig und ohne unerlaubte Hilfe erarbeitet.

München, am 24. April 2014

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Dissertation eingereicht am 02. Mai 2014

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Mündliche Prüfung am 08. Juli 2014

This work was carried out from January 2011 to April 2014 under the guidance of Prof. Dr. Paul Knochel at the Department Chemie und Pharmazie of the Ludwig-Maximilians-Universität, Munich.

Firstly, I would like to express my appreciation to Prof. Dr. Paul Knochel for giving me the great opportunity to do my Ph.D. in his group and for his guidance and support in the course of my scientific research.

I am also very grateful to Prof. Dr. Manfred Heuschmann for agreeing to be my "Zweitgutachter" as well as Prof. Dr. Anja Hoffmann-Röder, Prof. Dr. Heinz Langhals, Prof. Dr. Konstantin Karaghiosoff and Dr. Thomas Magauer for their interest shown in this manuscript by accepting to be referees.

I really would like to thank Robert Greiner and Julia Nafe for the careful correction of this manuscript.

I thank all past and present co-workers I have met in the Knochel group for their kindness and their help. Special thanks to my actual and former lab mates Dr. Coura Diene, Dr. Tobias Thaler, Dr. Stephanie Seel, Dr. Christoph Sämann, Dr. Andreas Unsinn, Dr. Andreas Wagner, Dr. Ilaria Tirotta, Dr. Cora Dunst, Dr. Sophia Manolikakes, Julia Nafe, Nadja Barl and Olesya Kuzmina.

I would like to thank Dr. Tobias Thaler, Dr. Kimihiro Komeyama, Dr. John Markiewicz and especially Olesya Kuzmina for the fruitful collaboration in the field of organo-iron chemistry and Dr. Stephanie Duez for their great support in the area of benzylic metalations.

I would also like to thank Dr. Vladimir Malakhov, Simon Matthe, Renate Schröder and Yulia Tsvik for their help in organizing everyday life in the lab and in the office, as well as the analytical team of the LMU for their invaluable help.

I thank Mario Ellwart, Min Zhang, Andreas Hader and Patrick Jüstel for their contributions to this work in course of their internship in the Knochel group.

I would like to thank my parents and grandparents for their great support, throughout my studies and my Ph.D.

Parts of this Ph.D. thesis have been published

1) Steib, A. K., Kuzmina, O. M., Fernandez, S., Flubacher, D. & Knochel, P., Efficient Chromium(II)-Catalyzed Cross-Coupling Reactions between Csp^2-Centers. *J. Am. Chem. Soc.* **135** (2013), 15346.
2) Kuzmina, O. M., Steib, A. K., Markiewicz, J. T., Flubacher, D. & Knochel, P., Ligand-Accelerated Fe- and Co-Catalyzed Cross-Coupling Reactions between *N*-Heterocyclic Halides and Aryl Magnesium Reagents. *Angew. Chem. Int. Ed.* **52** (2013), 4945.
3) Kuzmina, O. M., Steib, A. K., Flubacher, D. & Knochel, P., Iron-Catalyzed Cross-Coupling of *N*-Heterocyclic Chlorides and Bromides with Arylmagnesium Reagents. *Org. Lett.* **14** (2012), 4818.
4) Duez, S., Steib, A. K. & Knochel, P., Benzylic Arylation of 2-Methyl-5-membered Heterocycles Using TMP-Bases. *Org. Lett.* **14** (2012), 1951.
5) Duez, S., Steib, A. K., Manolikakes, S. M. & Knochel, P., Lewis Acid Promoted Benzylic Cross-Coupling of Pyridines with Aryl Bromides. *Angew. Chem. Int. Ed.* **50** (2011), 7686.

Meinen Eltern

Table of Contents

Abbreviations

A. INTRODUCTION 11

1. Overview 12

2. Preparation of Functionalized Organometallic Reagents 13

2.1. Introduction 13

2.2. Oxidative Insertion of Magnesium Metal into Organic Halides 14

2.3. Halogen-Magnesium Exchange Reaction 16

2.4. Directed Metalation 18

3. Iron-Catalyzed Unsymmetrical Aryl-Aryl Cross-Couplings 20

4. Cobalt-Catalyzed Unsymmetrical Aryl-Aryl Cross-Couplings 24

5. Objectives 28

B. RESULTS AND DISCUSSION 30

1. Benzylic Arylation of Heterocycles 31

1.1. Introduction 31

1.2. Benzylic Cross-Coupling of Pyridines with Aryl Bromides 32

1.3. Benzylic Arylation of 2-Methyl-5-Membered Heterocycles Using TMP-Bases 38

2. Aryl-Aryl Cross-Coupling Reactions Using Alternative Metal Catalysts 43

2.1. Introduction 43

2.2. Iron-Catalyzed Cross-Coupling of *N*-Heterocyclic Chlorides and Bromides with Arylmagnesium Reagents Using *t*BuOMe as Solvent 43

2.3. Ligand-Accelerated Fe- and Co-Catalyzed Cross-Coupling Reactions between *N*-Heterocyclic Halides and Arylmagnesium Reagents 49

2.4. Chromium(II)-Catalyzed Cross-Coupling Reactions between Csp^2-Centers 58

2.5. Regio- and Chemoselective Chromium(II)-Catalyzed Cross-Coupling Reactions of Dihalogenated Heteroaromatics with Aromatic Grignard Reagents 64

3. Summary and Outlook 69

3.1. Lewis-Acid Promoted Benzylic Cross-Couplings of Pyridines with Aryl Bromides 69

3.2. Benzylic Arylation of 2-Methyl-5-Membered Heterocycles using TMP-Bases 71

3.3. Iron-Catalyzed Cross-Coupling of *N*-Heterocyclic Chlorides and Bromides with Arylmagnesium Reagents Using *t*BuOMe as Solvent 72
3.4. Ligand-Accelerated Fe- and Co-Catalyzed Cross-Coupling Reactions between *N*-Heterocyclic Halides and Arylmagnesium Reagents 73
3.5. Chromium(II)-Catalyzed Cross-Coupling Reactions between Csp^2-Centers 74
C. EXPERIMENTAL SECTION 77
1. General Considerations 78
1.1. Solvents 78
1.2. Reagents 78
1.3. Content Determination of Organometallic Reagents 80
1.4. Chromatography 80
1.5. Analytical Data 80
2. Typical Procedures (TP) 81
2.1. Typical Procedure of the Metalation of Methylpyridines and Related *N*-Heterocycles with TMPZnCl·LiCl (**7**) (TP1) 81
2.2. Typical Procedure for Fe-Catalyzed Cross-Coupling Reactions of *N*-Heterocyclic Chlorides and Bromides with Arylmagnesium Reagents Using *t*BuOMe as Solvent (TP2) 81
2.3. Typical Procedure for Fe- or Co-Catalyzed Cross-Coupling Reactions with Isoquinoline (TP3) 81
2.4. Typical Procedure for Cr-Catalyzed Cross-Coupling Reactions between Aryl Halides and Aromatic Grignard Reagents (TP4) 82
2.5. Typical Procedure for Cr-Catalyzed Cross-Coupling Reactions with Imine **47** (TP5) 82
2.6. Typical Procedure for Cr-Catalyzed Cross-Coupling Reactions with Alkenyl Iodide **49** (TP6) 82
2.7. Typical Procedure for Cr-Catalyzed Regio- and Chemoselective Cross-Coupling Reactions in THF as Solvent (TP7) 83
2.8. Typical Procedure for Cr-Catalyzed Regio- and Chemoselective Cross-Coupling Reactions in CPME as Solvent (TP8) 83
3. Benzylic Cross-Coupling of Pyridines with Aryl Bromides 84
4. Benzylic Arylation of 2-Methyl-5-Membered Heterocycles Using TMP-Bases 112

5. Iron-Catalyzed Cross-Coupling of *N*-Heterocylic Chlorides and Bromides with Arylmagnesium Reagents Using *t*BuOMe as Solvent 132
6. Ligand Accelerated Fe- and Co-Catalyzed Cross-Coupling Reactions between *N*-Heterocyclic Halides and Arylmagnesium Reagents 150
6.1. Preparation of the Starting Materials 150
6.2. Preparation of the Title Compounds Using TP3 157
7. Efficient Chromium(II)-Catalyzed Cross-Coupling Reactions Between Csp^2-Centers 180
7.1. Preparation of the Title Compounds Using TP4 180
7.2. Preparation of the Title Compounds Using TP5 194
7.3. Preparation of the Title Compounds Using TP6 196
7.3. Preparation of the Title Compounds Using TP7 and TP8 199

Abbreviations

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*t*-butyloxycarbonyl
br	broad
Bu	butyl
*n*Bu	*n*-butyl
*t*Bu	*t*-butyl
calc.	calculated
conc.	concentrated
Cy	cyclohexyl
δ	chemical shifts in parts per million
d	doublet
Davephos	2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	*trans,trans*-dibenzylideneacetone
DME	dimethoxyethane
DMPU	1,3-dimethyltetrahydropyrimidin-2(1*H*)-one
dppe	diphenylphosphinoethane
dppf	1,1'-bis(diphenylphosphino) ferrocene
E	electrophile
EI	electron-impact ionization
ESI	electrospray ionization
equiv	equivalent
Et	ethyl
FG	functional group
GC	gas chromatography
h	hour
Hal	halogene
(Het)Ar	heteroaryl
HRMS	high resolution mass spectroscopy
LDA	lithium diisopropylamide
M	molarity
m	meta
m	multiplet
Me	methyl
Met/M	metal
min	minute
mmol	millimole
m.p.	melting point
MS	mass spectroscopy
NEP	*N*-ethyl-2-pyrrolidone
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
Piv	pivaloyl
*i*Pr	*iso*-propyl
q	quartet
R	organic substituent
r.t.	room temperature
sat.	saturated
s	singulet
S-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBS	*t*-butyldimethylsilyl
Tf	triflate
tfp	tri-2-furylphosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMHD	2,2,6,6-tetramethyl-3,5-heptane-dionate
TMS	trimethylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
Tol	tolyl
TP	typical procedure
Ts	4-toluenesulfonyl

IR	infra-red	X	halide or pseudohalide
J	coupling constant (NMR)	Xanthphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

A. Introduction

1. Overview

The United States Census Bureau (USCB) estimated the world population to number 7.152 billion in April 2014.[1] Facing this immense number and keeping in mind, that the world population will reach eight billion by 2027, a tremendous increase in global energy consumption is obvious. Besides the need to invent novel energy producing processes, the development of energy saving techniques offers the greatest chances to meet our energy needs in the long run. In the field of industrial and pharmaceutical chemistry, one of the most important branches of the German economy, catalysis is one of the key technologies to save energy. Modern research in catalysis has to achieve many aspects, such as broad applicability, high selectivity, environmental sustainability and cost effectiveness. Organometallic chemistry has shown in the past that it is able to fulfill most of these criteria and a variety of powerful concepts have been developed and reported within the last 40 years.[2] Just in 2010, the importance of organometallic chemistry was once more highlighted by awarding the Nobel price in Chemistry to *Richard F. Heck*, *Ei-ichi Negishi* and *Akira Suzuki* for their work on palladium-catalyzed cross-coupling reactions.[3] Even if palladium-based catalysts have certainly revolutionized organic syntheses, its potential to furnish even more complex molecules has certainly not been exploit yet.[4] Nevertheless, palladium has some drawbacks that cannot be ignored in our modern society of the 21st century. Besides the fact, that palladium is a rare and expensive metal,[5] it is also toxicologically very critical. Also, one must consider that palladium-salts undergo catalytic coupling reactions in general in the presence of ligands, that could be even more expensive and toxic, than the palladium-salt itself. Interestingly, very abundant and low-toxic alternative transition metals, such as iron or cobalt were shown to react without the need of additional ligands in exceptional reaction rates at low temperatures, often even surpassing related palladium-catalyzed coupling reactions.[6]

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[1] www.census.gov; April 4th 2014.
[2] Halpern, J. *Pure Appl. Chem.* **2001**, *73*, 209.
[3] www.nobelprize.org/nobel_prizes/chemistry/laureates/2010; April 4th 2014.
[4] (a) *Cross-Coupling reactions. A Practical Guide*; Miyaura, N., Ed.; Springer, Berlin, 2002. (b) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH, Weinheim, 2004. (c) *Organotransition Metal Chemistry*; Hartwig, J. F., Ed.; University Science Books, Sausalito, California, 2010.
[5] One ounce (about 31 gramm) of palladium-metal costs 555 € (www.wallstreet-online.de/rohstoffe/palladiumpreis, April 4th 2014).
[6] (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Shinokuo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081. (c) Yorimitsu, H.; Oshima, K. *Pure Appl. Chem.* **2006**, *78*, 441. (d) *Iron Catalysis in Organic Chemistry: Reactions and Applications*; Plietker, B., Ed.; Wiley-VCH, Weinheim, **2008**. (e) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3317. (f) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (g) Bolm, C. *Nature Chem.* **2009**, *1*, 420. (h) Fürstner, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 1364. (i) Czaplik, W. M.; Mayer, M.; Cvengros, J.; Jacobi von Wangelin, A. *ChemSusChem* **2009**, *2*, 396. (j) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (k) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293.

The replacement of palladium in transition metal catalyzed reactions by alternative metals like iron or cobalt is certainly one of the big challenges for organometallic chemists of the 21st century.

2. Preparation of Functionalized Organometallic Reagents

2.1. Introduction

The cradle of organometallic chemistry is a Paris military pharmacy in 1760. It was there that *Cadet* worked on sympathetic inks based on cobalt salts. For their preparation, he used cobalt minerals which contain arsenic.[7] In 1827, *Zeise* isolated $Na[PtCl_3C_2H_4]$, called Zeise`s salt, the first olefin complex in history.[8] Another milestone in organometallic chemistry was the first synthesis of diethyl zinc by *Frankland* in 1849.[9] He prepared diethyl zinc by reaction of zinc metal with ethyliodide. About 50 years later, *Grignard* prepared organomagnesium compounds for the very first time and paved the way for modern organometallic chemistry.[10]

Today, almost all metals play a more or less important role in organometallic chemistry. The polarity of the carbon-metal bond of an organometallic reagent displays its reactivity.[11] Therefore, organolithium reagents feature very high reactivity due to their strongly polarized carbon-lithium bond. This high reactivity makes organolithium reagents very nucleophilic, but also incompatible with sensitive functional groups.[12] In contrast, organoboron reagents possess almost covalent carbon-boron bonds and require harsh reaction conditions or sophisticated catalytic systems for successful reactions with appropriate electrophiles.[13] Organomagnesium, -copper and -zinc reagents are a good balance between these two extremes, as they show high reactivity and broad functional group compatibility.[11,14]

There exist various ways to prepare organometallic reagents. In this work, the attention should be focused on oxidative insertion of magnesium metal into organic halides, halogen-magnesium exchange reactions and direct metalation.

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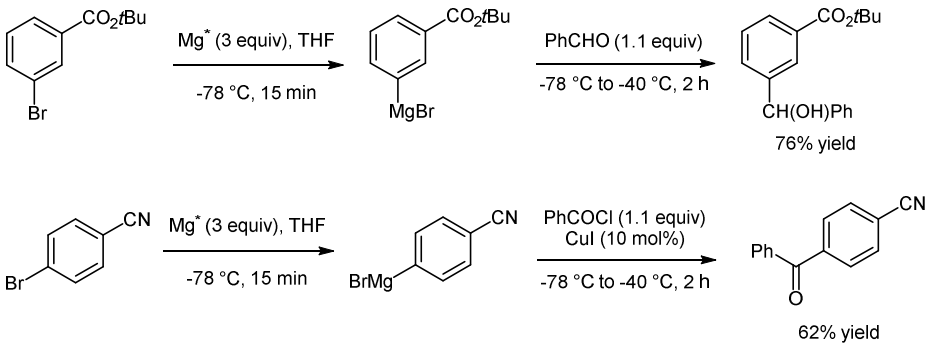
[7] *Organometallics*; Elschenbroich, C., Ed.; Wiley-VCH, Weinheim, **1992**.
[8] (a) Zeise, W. C. *Poggendorf`s Ann. Phys.* **1827**, *9*, 632. (b) Zeise, W. C. *Poggendorf`s Ann. Phys.* **1831**, *21*, 497. (c) Zeise, W. C. *Poggendorf`s Ann. Phys.* **1837**, *40*, 234.
[9] (a) Frankland, E. *Ann. Chem.* **1849**, *71*, 171. (b) Frankland, E. *Ann. Chem.* **1849**, *71*, 213.
[10] Grignard, V. *Compt. Rend. Acad. Sci. Paris*, **1900**, *130*, 1322.
[11] *Handbook of Functionalized Organometallics*, Knochel, P., Ed.; Wiley-VCH, Weinheim, **2005**.
[12] Wu. G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596.
[13] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
[14] Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302.

2.2. Oxidative Insertion of Magnesium Metal into Organic Halides

The most common preparation method for organomagnesium compounds is the direct insertion of magnesium metal into organic halides.[15] Even if the entire mechanism of this reaction has still not been elucidated completely, radical pathways are generally accepted.[16] The direct insertion of magnesium metal into organic halides usually proceeds under reflux conditions, which limits its functional group compatibility and its application in plant scale, due to safety issues.[17] *Rieke* and coworkers observed that the reaction of lithium naphthalide with magnesium salts furnishes highly reactive magnesium powder (Mg^*; so called Rieke magnesium) that can undergo oxidative insertion reactions into organic halides at very low temperatures, tolerating many sensitive functional groups, such as esters or nitriles (Scheme 1).[18]



Scheme 1. Low-temperature formation of functionalized Grignard reagents.

Even if this method proved to be very efficient for the preparation of functionalized Grignard reagents, it still has some drawbacks, namely cryogenic conditions and separate preparation of the highly active magnesium. *Knochel* and coworkers could bypass these drawbacks elegantly by adding stoichiometric amounts of LiCl to the insertion reaction of magnesium metal into organic halides.[19] LiCl not only accelerates the insertion progress significantly, it also leads to higher solubility and reactivity of the organomagnesium reagent in organic solvents.[20] Using

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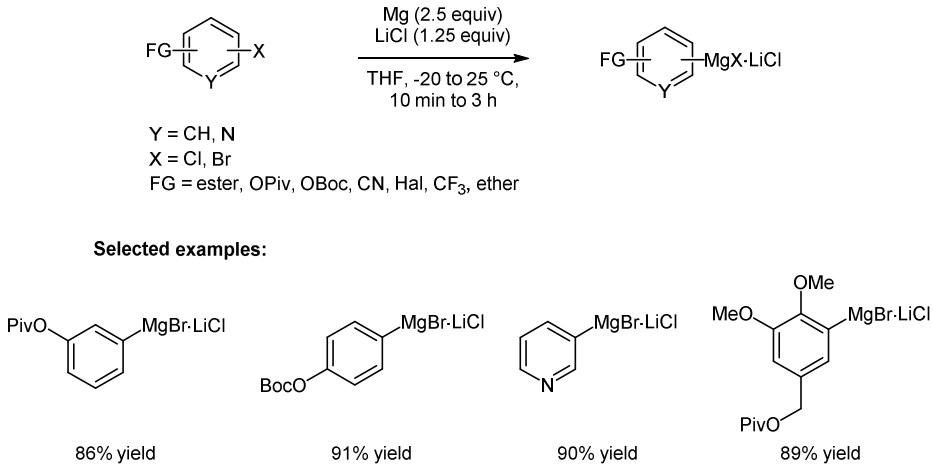
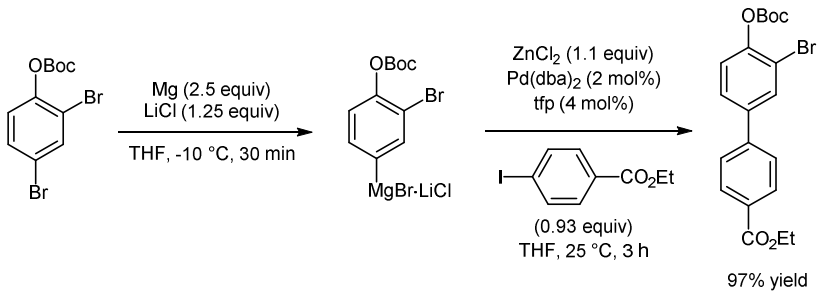
[15] *Handbook of Grignard Reagents*, Silverman, G. S.; Rakita, P. E., Eds.; Marcel Dekker, New York, **2000**.
[16] (a) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286. (b) Garst, J. F. *Acc. Chem. Res.* **1991**, *24*, 95. (c) Garst, J. F.; Soriaga, M. P. *Coord. Chem. Rev.* **2004**, *248*, 623.
[17] Jones, M. C. *Plant and Operations Progress*, **1989**, *8*, 200.
[18] (a) Rieke, R. D. *Science*, **1989**, 246, 1260. (b) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925. (c) Lee, J.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428. (d) Rieke, R. D. *Aldrichchim. Acta* **2000**, *33*, 52.
[19] (a) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 6802. (b) Piller, F. M.; Metzger, A.; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 7192.
[20] *Solvents and Solvent Effects in Organic Chemistry*, Reichardt, C., Ed.; Wiley-VCH, Weinheim, **2003**.

this LiCl-mediated magnesium insertion, functionalized aryl and heteroaryl magnesium compounds can be prepared under mild reaction conditions in high yields (Scheme 2).



Scheme 2. LiCl-mediated insertion of magnesium metal into (hetero)aromatic halides.

Knochel and coworkers could also perform highly regioselective magnesium-directed insertion reactions using this LiCl-mediated insertion reaction. Reaction of *tert*-butyl (2,4-dibromophenyl) carbonate with Mg/LiCl (THF, -20 °C) led to magnesium insertion exclusively in the *para*-position (Scheme 3). Related Zn insertion reactions provide the respective *ortho*-metalated compound.[21] This behavior can be explained by assuming that zinc insertion requires coordination to the directing group, whereas magnesium metal, which has a much stronger reducing power, does not need this *ortho*-coordination site and prefers to insert into the least sterically hindered carbon-bromine bond.[19]

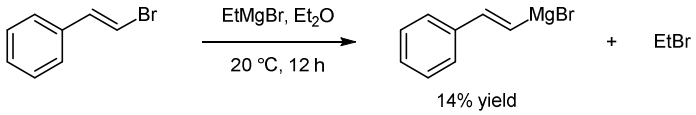


Scheme 3. Regioselective LiCl-mediated magnesium insertion.

[21] Boudet, N.; Sase, S.; Sinha, P.; Liu, C.-Y.; Krasovskiy, A.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 12358.

2.3. Halogen-Magnesium Exchange Reaction

An alternative, very straightforward way to prepare organomagnesium reagents from the respective halides is to use another organomagnesium reagent that undergoes a halogen-magnesium exchange reaction with the halide. The driving force for this kind of transformation is the higher stability of the produced organomagnesium compound compared to the exchange reagent itself. The order of stability of organometallic reagents with respect to the hybridization of the connected carbon atom is the following: $C_{sp} > C_{sp^2\,vinyl} > C_{sp^2\,aryl} > C_{sp^3\,primary} > C_{sp^3\,secondary}$.[22] The first example of a bromine-magnesium exchange reaction was reported by *Prévost* in 1931.[23] Cinnamyl bromide was reacted with ethylmagnesium bromide to furnish cinnamylmagnesium bromide in low yield (Scheme 4).

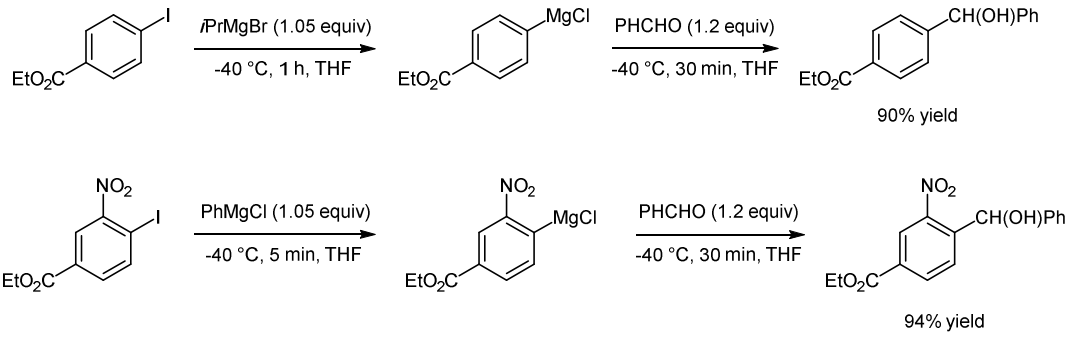


Scheme 4. First example of halogen-magnesium exchange reaction.

Over the last decades, this kind of reaction was studied intensively and nowadays several applications, even on industrial scale exist.[14] Even if the detailed mechanism of these halogen-magnesium exchange reactions is still not completely understood, a halogen ate complex is assumed to be operative in this process.[24] The nature of the halide and the electronic properties of the organic substrate play important roles for the rate of halogen-magnesium exchange reactions.[25] In general, iodides undergo the halogen-magnesium exchange reaction faster than bromides, and bromides exchange faster than chlorides. Furthermore, the rate is higher, if the organic substrate bears electron-withdrawing groups. *Knochel* and coworkers could establish the reagents *i*PrMgBr and PhMgCl as widely used halogen-metal exchange reactions in organic synthesis.[14,26] These reagents tolerate various functional groups and allow the preparation of a broad range of organomagnesium reagents from the respective iodides (Scheme 5).

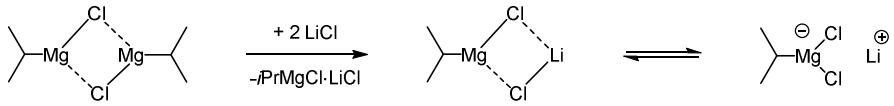
---

[22] Hauk, D.; Lang, S.; Murso, A. *Org. Process Res. Dev.* **2006**, *10*, 733.
[23] Prévost, C. *Bull. Soc. Chim. Fr.* **1931**, *49*, 1372.
[24] (a) Hoffmann, R. W.; Brönstrup, M.; Müller, M. *Org. Lett.* **2003**, *5*, 313. (b) Böhm, V. P. W.; Schulze, V.; Brönstrup, M.; Müller, M.; Hoffmann, R. W. *Organometallics* **2003**, *22*, 2925.
[25] Tamborski, C.; Moore, G. J. *J. Organomet. Chem.* **1971**, *26*, 153.
[26] (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem. Int. Ed.* **1998**, *37*, 1701. (b) Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 1610.



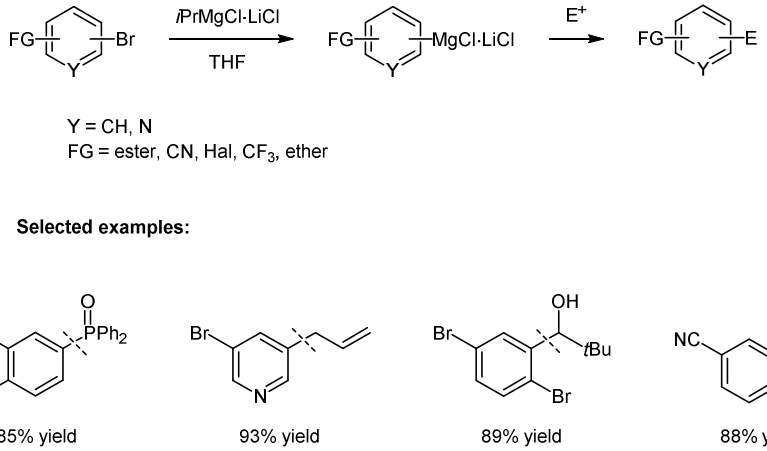
Scheme 5. Examples of halogen-magnesium exchange reactions using *i*PrMgBr and PhMgCl.

Knochel further improved the halogen-magnesium exchange reaction by introducing the so called Turbo-Grignard reagent *i*PrMgCl·LiCl. Stoichiometric amounts of LiCl are able to break aggregates of *i*PrMgCl and lead to an increased reactivity and solubility of the Grignard reagent by formation of a magnesium-lithium ate complexe (Scheme 6).[27]



Scheme 6. Effect of LiCl on *i*PrMgCl aggregates.

Using the Turbo-Grignard reagent *i*PrMgCl·LiCl, now highly functionalized aromatic and heteroaromatic bromides undergo very efficiently the halogen-magnesium exchange reaction to furnish the corresponding magnesiated reagents (Scheme 7).[28]



Scheme 7. Bromine-magnesium exchange reactions using *i*PrMgCl·LiCl.

[27] Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[28] Barl, N. M.; Werner, V., Sämann, C.; Knochel, P. *Heterocycles*, **2014**, *88*, 827.

2.4. Directed Metalation

A third way to produce magnesiated compounds involves the direct metalation of organic substrates. No halide like iodide or bromide is necessary for this kind of reaction. Simply a C-H bond having a pk_a-value lower than the metalation agent is required for this reaction to be operative. Historically, lithium-reagents like *n*BuLi[29] or EtLi[30] have been used to metalate organic substrates. In the following decades, less nucleophilic sterically hindered lithium amide bases like LDA and TMPLi have been developed.[31] Although many organic molecules were lithiated successfully with these lithium-amide bases, the high reactivity of these bases has precluded the use of many functionalized substrates. The resulting highly reactive aryllithium compounds obtained after metalation are usually only stable at low temperature and react with important functional groups such as esters or nitriles even under these mild conditions.[32] Therefore, respective magnesium amide bases have been established that display a much higher functional group tolerance.[33] However, due to aggregation of the magnesium amides low solubility in organic solvents and low kinetic basicity was observed. To overcome these problems, *Knochel* and coworkers broke these aggregates by addition of stoichiometric amounts of LiCl. The most prominent example of such a monomeric highly active mixed Mg/Li-base is TMPMgCl·LiCl, that can be prepared by reaction of TMPH with *i*PrMgCl·LiCl.[34] Besides outstanding advantages like high solubility (up to 1.3 M in THF) and excellent kinetic basicity, TMPMgCl·LiCl is stable at room temperature for many months under an inert atmosphere. Using this magnesium-amide base, various functionalized (hetero)aromatic systems can be magnesiated with excellent regio- and chemoselectivity at convenient temperatures (Scheme 8).[35]

Recently, *Knochel* and coworkers further improved the scope of direct magnesiation reactions by establishing $TMP_2Mg·2LiCl$ as a chemoselective base for less activated substrates.[36]

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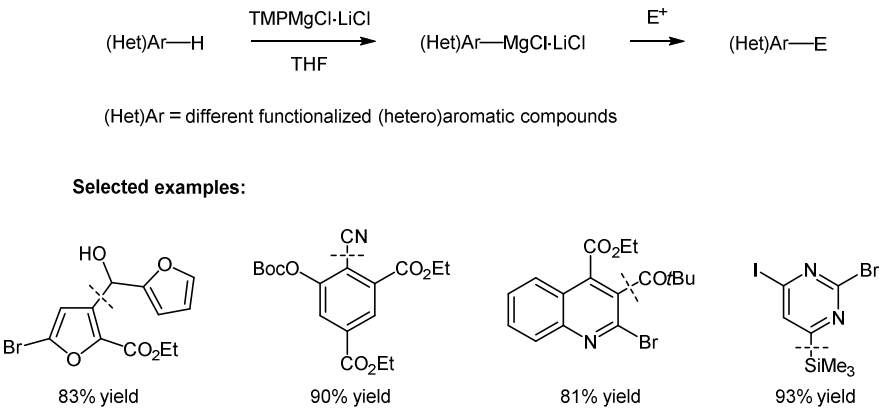
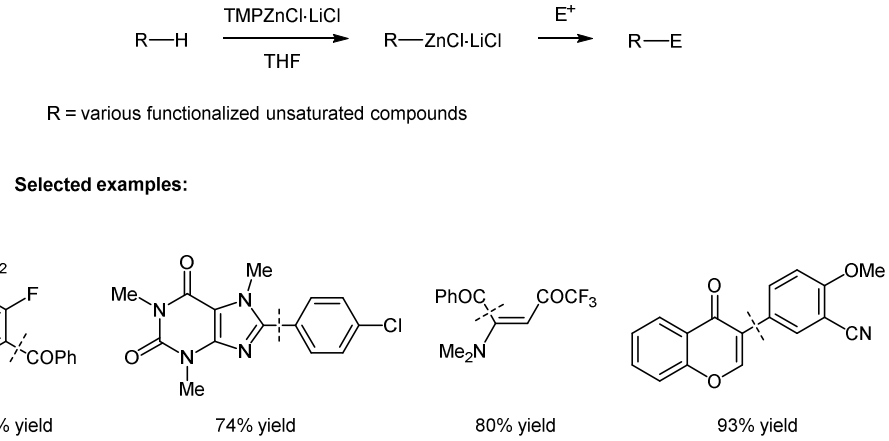
[29] Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109.
[30] Schlenk, W., Bergmann, E. *Ann. Chem.* **1928**, *463*, 98.
[31] (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376.
[32] Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 9794.
[33] (a) Hauser, C. R.; Walker, H. W. *J. Am. Chem. Soc.* **1947**, *69*, 295. (b) Eaton, P. E.; Lee. C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (c) Schlecker, W.; Huth A.; Ottow, E.; Mulzer, J. *J. Org. Chem.* **1995**, *60*, 8414.
[34] Krasovskiy. A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
[35] (a) Lin, W.; Baron, P.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673. (b) Boudet, N.; Lachs, J. R.; Knochel, P. *Org. Lett.* **2007**, *9*, 5525. (c) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497.
[36] (a) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681. (b) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem. Int. Ed*. **2008**, *47*, 1503.



Scheme 8. Regio- and chemoselective functionalizations using TMPMgCl·LiCl.

Organic compounds that contain very sensitive functional groups like nitro or aldehyde functionalities could not be compatible with magnesiation conditions. Therefore, milder bases, like TMPZnCl·LiCl[37] (Scheme 9) and $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$[38] have been developed. Zinc-amide bases also offer the advantage, that once the substrates are zincated, they can undergo directly palladium-catalyzed cross-coupling reactions with aromatic halides.[4]

The concept of mixed Li/metal amide bases was further extended to alternative metals like Al, Mn, Fe, Zr and La.[32]



Scheme 9. Regio -and chemoselective functionalizations using TMPZnCl·LiCl.

[37] (a) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837. (b) Bresser, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 1914. (c) Klier, L.; Bresser, T.; Nigst, T. A.; Karaghiosoff, K.; Knochel, P. *J. Am. Chem. Soc.* **2012**, *134*, 13584.

[38] (a) Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7685; (b) Dong, Z.; Clososki, G. C.; Wunderlich, S. H.; Unsinn, A.; Li, J.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 457.

3. Iron-Catalyzed Unsymmetrical Aryl-Aryl Cross-Couplings

Palladium, nickel and copper constitute the metals of choice, if chemists aim to synthesize complex and functionalized organic molecules involving cross-coupling reactions. Numerous applications document their advantageous use with respect to generality and functional-group tolerance.[6i] Nevertheless, the high prize of palladium and its complexes,[5] as well as toxicological issues associated with nickel and copper,[39] have prompted the search for alternative metals that combine ecological and economical aspects with high catalytic activity and chemical selectivity.

Iron-catalyzed carbon-carbon bond-forming reactions have emerged from exotic phenomenas to indispensable tools in organic synthesis over the last decades.[6] Whereas alkyl-aryl,[40] alkyl-alkenyl,[41] aryl-alkenyl,[41b,41c,41k,42] as well as alkynyl coupling reactions are well

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[39] (a) *Handbook of the Toxikology of Metals*; Friberg, L.; Nordberg, G. F.; Vouk, V. B.; Eds.; Elsevier, Amsterdam, **1986**. (b) Hughes, M. N. *Compr. Coord. Chem.* **1987**, *67*, 643. (c) *Nickel and the Skin: Absorption, Immunology, Epidermology, and Metallurgy*; Hostynek, J.J.; Maibach, H. I.; Eds.; CRC Press, Boca Raton, **2002**.

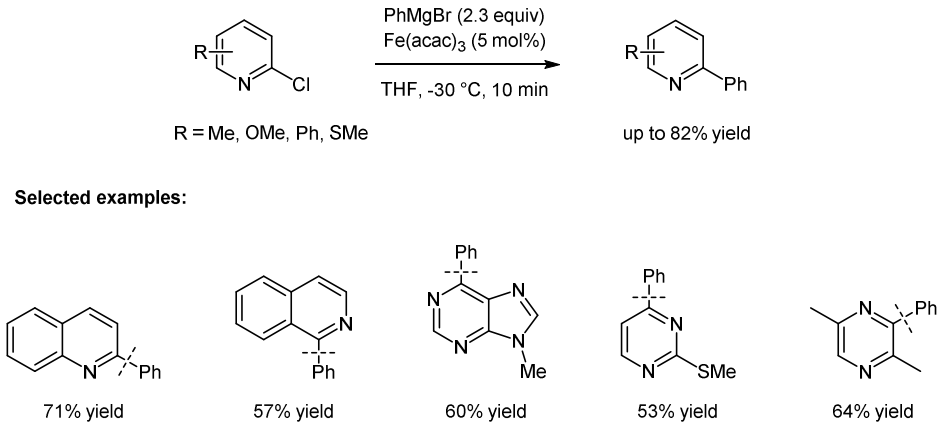
[40] (a) Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955. (d) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297. (e) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (f) Bedford, R. B.; Bruce, D. W.; Frost, R. M.; Goodby, J. W.; Hird, M. *Chem. Commun.* **2004**, *40*, 2822. (g) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, *11*, 1794. (h) Bedford, R. B.; Betham, M.; Bruce, D. W.; Danopoulos, A. A.; Frost, R. M.; Hird, M. *J. Org. Chem.* **2006**, *71*, 1104. (i) Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4364. (j) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773. (k) Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 607. (l) Bedford, R. B.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, *45*, 600. (m) Cahiez, G.; Foulgoc, L.; Moyeux, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 2969. (n) Noda, D.; Sunada, Y.; Hatakeyama, T.; Nakamura, M.; Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 6078. (o) Ito, S.; Fujiwara, Y.-i.; Nakamura, E.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4306. (p) Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4886. (q) Kawamura, S.; Ishizuka, K.; Takaya, H.; Nakamura, M. *Chem. Commun.* **2010**, *46*, 6054. (r) Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674. (s) Steib, A. K.; Thaler, T.; Komeyama, K.; Mayer, P.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 3303. (t) Yamaguchi, Y.; Ando, H.; Nagaya, M.; Hinago, H.; Ito, T.; Asami, M. *Chem. Lett.* **2011**, *40*, 983. (u) Jin, M.; Nakamura, M. *Chem. Lett.* **2011**, *40*, 1012. (v) Hatakeyama, T.; Fujiwara, Y.-i.; Okada, Y.; Itoh, T.; Hashimoto, T.; Kawamura, S.; Ogata, K.; Takaya, H.; Nakamura, M. *Chem. Lett.* **2011**, *40*, 1030. (w) Kawamura, S.; Kawabata, T.; Ishizuka K.; Nakamura, M. *Chem. Commun.* **2012**, *48*, 9376. (x) Silberstein, A. L.; Ramgren, S. D.; Garg, N. K. *Org. Lett.* **2012**, *14*, 3796. (y) Agrawal, T.; Cook, S. P. *Org. Lett.* **2013**, *15*, 96.

[41] (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Fabre, J.-L.; Julia, M.; Verpeaux, J.-N. *Tetrahedron. Lett.* **1982**, *23*, 2469. (c) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943. (d) Cahiez, G.; Duplais, C.; Moyeux, A. *Org. Lett.* **2007**, *9*, 3253. (e) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 6521. (f) Cahiez, G.; Habiak, V.; Gager, O. *Org. Lett.* **2008**, *10*, 2389. (g) Hatakeyama, T.; Nakagawa, N.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4496. (h) Li, B.-J.; Xu, L.; Wu, Z.-H.; Guan, B.-T.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *J. Am. Chem. Soc.* **2009**, *131*, 14656. (i) Nishikado, H.; Nakatsuji, H.; Ueno, K.; Nagase, R.; Tanabe, Y. *Synlett* **2010**, *14*, 2087. (j) Hashimoto T.; Hatakeyama T.; Nakamura M. *J. Org. Chem.* **2012**, *77*, 1168. (k) Cahiez, G.; Gager, O.; Buendia, J. Patinote, C. *Chem. Eur. J.* **2012**, *18*, 5860.

[42] (a) Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E. *Tetrahedron Lett.* **1983**, *24*, 5449. (b) Itami, K.; Higashi, S.; Mineno, M.; Yoshida, J.-i. *Org. Lett.* **2005**, *7*, 1219.

documented,[43] the corresponding aryl-aryl cross-coupling reactions are much more challenging due to unsufficient catalytic activity of the iron-catalyst and due to undesired homo-coupling side-reaction of the organometallic species.[44]

The first example of an unsymmetrical biaryl-formation mediated by an iron-catalyst was reported by *Fürstner* in 2002.[40b] Heteroaromatic chlorides were treated with non-functionalized (hetero)aryl Grignard reagents (2.3 equiv) at low temperatures (-30 °C) in the presence of 5 mol% of $Fe(acac)_3$ in THF. Interestingly, this reaction reached full conversion in only 10 min reaction time, revealing the high activity of the iron-catalyst. The excess of Grignard reagent was found to be necessary, as large amounts of homo-coupling byproducts resulting from the Grignard reagent are observed (Scheme 10).



Scheme 10. Iron-catalyzed aryl-aryl bond-formation reported by *Fürstner et al.*[40b]

Figadère[45] and *Plé* [46] further investigated this iron-catalyzed aryl-aryl cross-coupling reaction between *N*-heterocyclic halides and simple unfunctionalized aromatic Grignard reagents by testing various solvents and additives, showing that the conditions reported by *Fürstner* were indeed optimum. Later, *Knochel* reported an example using catalytic amounts of iron powder for efficient cross-coupling between 2-chloroquinoline and phenylmagnesium bromide

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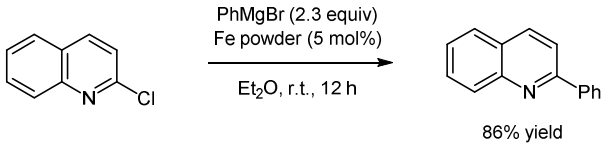
[43] (a) Hatakeyama, T.; Yoshimoto, Y.; Gabriel, T.; Nakamura, M. *Org. Lett.* **2008**, *10*, 5341. (b) Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. *ChemCatChem* **2011**, *3*, 135. (c) Hatakeyama, T.; Okada, Y.; Yoshimoto, Y.; Nakamura, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 10973.

[44] For Fe-catalyzed homo-coupling reactions, see: (a) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316. (b) H. Felkin, H.; Meunier, B. *J. Organomet. Chem.* **1978**, *146*, 169. (c) Nagano, T.; Hayashi, T. *Org. Lett.* **2005**, *7*, 491. (d) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943. (e) Xu, X.; Cheng, D.; Pei, W. *J. Org. Chem.* **2006**, *71*, 6637. (f) Liu, W.; Lei, A. *Tetrahedron Lett.* **2007**, *49*, 610. (g) Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788. (h) Kiefer, G.; Jeanbourquin, L.; Severin, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 6302. (i) Toummini, D.; Ouzzani, F.; Taillefer, M. *Org. Lett.* **2013**, *15*, 4690.

[45] Quintin, J.; Franck, X.; Hocquemiller, R.; Fidagère, B. *Tetrahedron Lett.* **2002**, *43*, 3547.

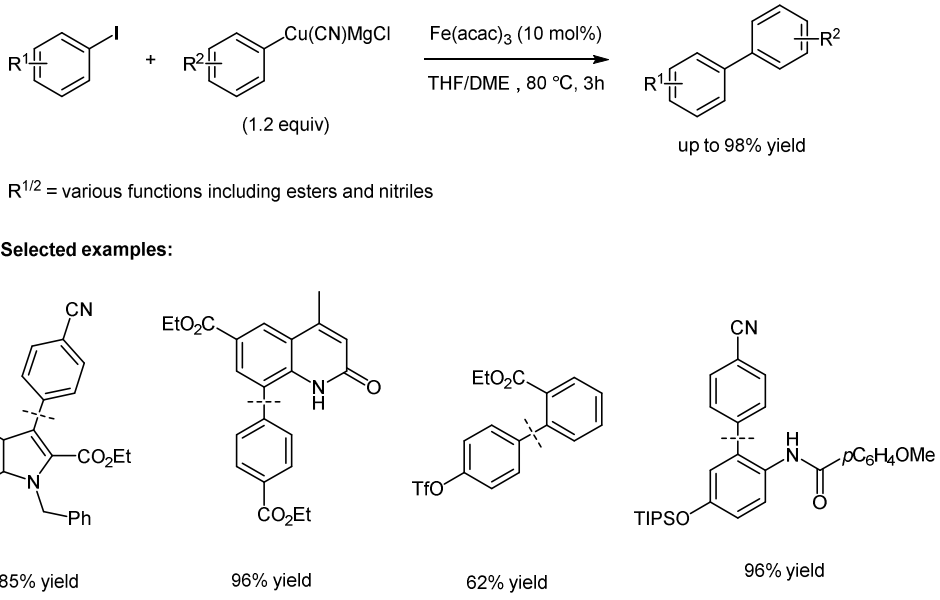
[46] Boully, L.; Darabantu, M.; Turck, A. Plé, N. *J. Heterocycl. Chem.* **2005**, *42*, 1423.

(Scheme 11).[47] This observation supports the involvement of reduced ferrate species in this cross-coupling.



Scheme 11. Heteroaryl-aryl bond-formation catalyzed by iron powder.

Knochel and coworkers also demonstrated that the undesired homo-coupling side-reaction can be suppressed by using organocopper reagents instead of aryl Grignard reagents. Transmetalation of functionalized Grignard reagents with CuCN·2LiCl furnishes the respective arylcopper reagents that undergo iron-catalyzed coupling reactions with various aromatic iodides in the presence of $Fe(acac)_3$ in THF/DME at elevated temperatures (Scheme 12).[48]

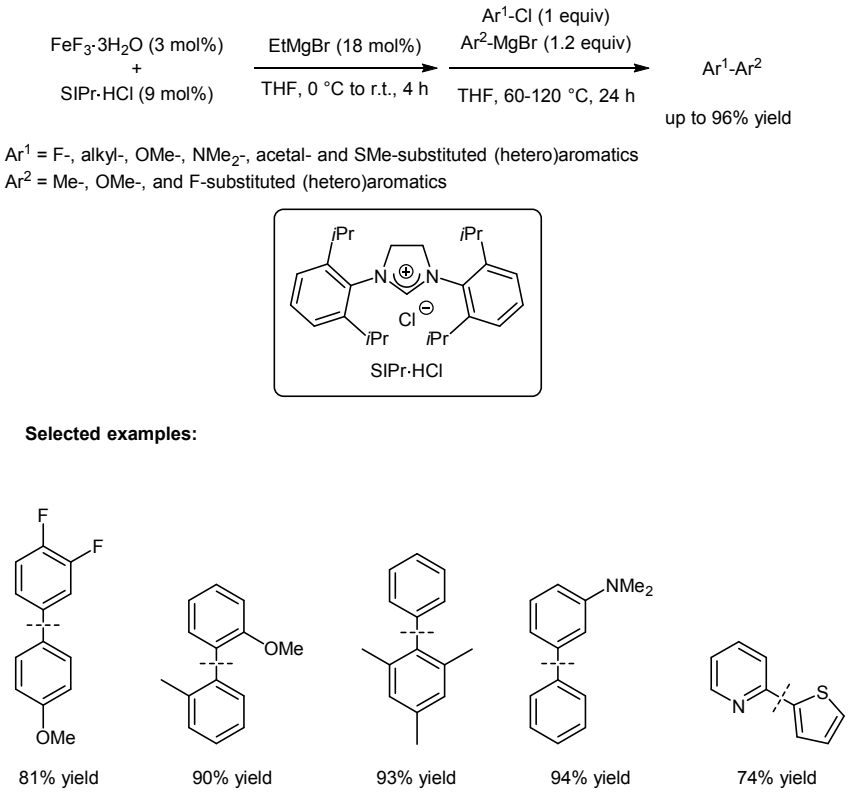


Scheme 12. Organocopper reagents in iron-catalyzed aryl-aryl cross-coupling reactions.

In 2007, *Nakamura et al.* showed that aromatic Grignard reagents can in fact undergo iron-catalyzed cross-coupling reactions with aromatic halides by using a novel catalytic system

[47] Korn, T. J.; Cahiez, G.; Knochel, P. *Synlett* **2003**, 1892.
[48] (a) Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 1654. (b) Kofink, C. C.; Blank, B.; Pagano, S.; Götz, N.; Knochel, P. *Chem. Commun.* **2007**, 1954.

based on $FeF_3 \cdot 3H_2O$ and *N*-heterocyclic carbene ligands.[49] Under optimized conditions, the iron-catalyst $FeF_3 \cdot 3H_2O$ (3 mol%) and the carbene ligand precursor SIPr·HCl (1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride; 9 mol%) have to be pre-treated with EtMgBr to produce the active iron species. Subsequently, the electrophile and the desired aromatic Grignard reagent have to be added and the reaction mixture has to be stirred at 60-120 °C for 24 h to produce the respective biaryl coupling product with negligible amounts of homo-coupling byproducts (Scheme 13).



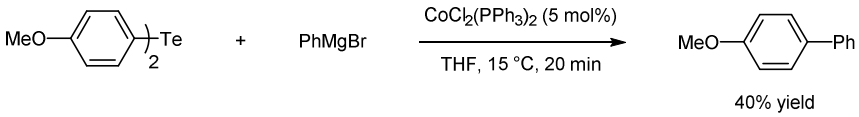
Scheme 13. Iron-carbene catalyst for unsymmetrical biaryl formation reactions.

Even if the authors could improve the iron-catalyzed aryl-aryl cross-coupling reaction dramatically by suppressing the undesired homo-coupling reaction significantly, this method suffers some disadvantages. First, an expensive *N*-heterocyclic carbene ligand has to be used in combination with toxic iron fluoride salts. Second, the reaction requires high temperatures of up to 120 °C and long reaction times. And third, the substrate scope is rather limited.

[49] (a) Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 9844. (b) Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc*. **2009**, *131*, 11949.

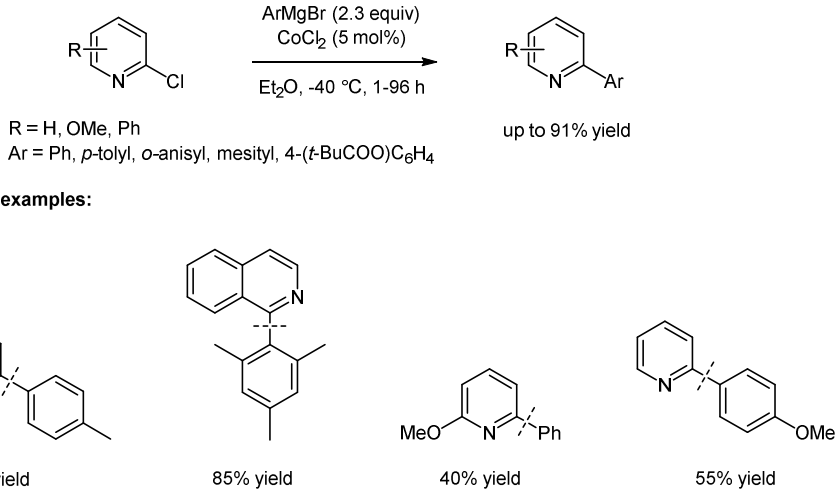
4. Cobalt-Catalyzed Unsymmetrical Aryl-Aryl Cross-Couplings

The first report on a cobalt-catalyzed cross-coupling reaction goes back to 1939, when *Gilman* and *Lichtenwalter* described the nearly quantitative formation of homo-coupling products from aromatic Grignard reagents by treating them with cobalt chloride.[50] Comparable to iron-catalysis, the formation of those homo-coupling products is undesired, if on attempts to perform a cobalt-catalyzed cross-coupling reaction between an aromatic halide and an aromatic organometallic reagent. *Uemura* described the first cobalt-catalyzed synthesis of unsymmetrical biaryls via reaction of diaryltellurides with aromatic organomagnesium reagents (Scheme 14).[51]



Scheme 14. Cobalt-catalyzed cross-coupling reaction between diaryltelurides and aromatic Grignard reagents.

Knochel and *Cahiez* significantly improved this reaction by coupling activated heteroaromatic halides with arylmagnesium reagents in the presence of catalytic amounts of cobalt chloride. Interestingly, stericially hindered Grignard reagents like mesitylmagnesium bromide react smoothly under the described conditions (Scheme 15).[47]



Scheme 15. $CoCl_2$-catalyzed cross-coupling reactions between heteroaryl chlorides and aromatic Grignard reagents.

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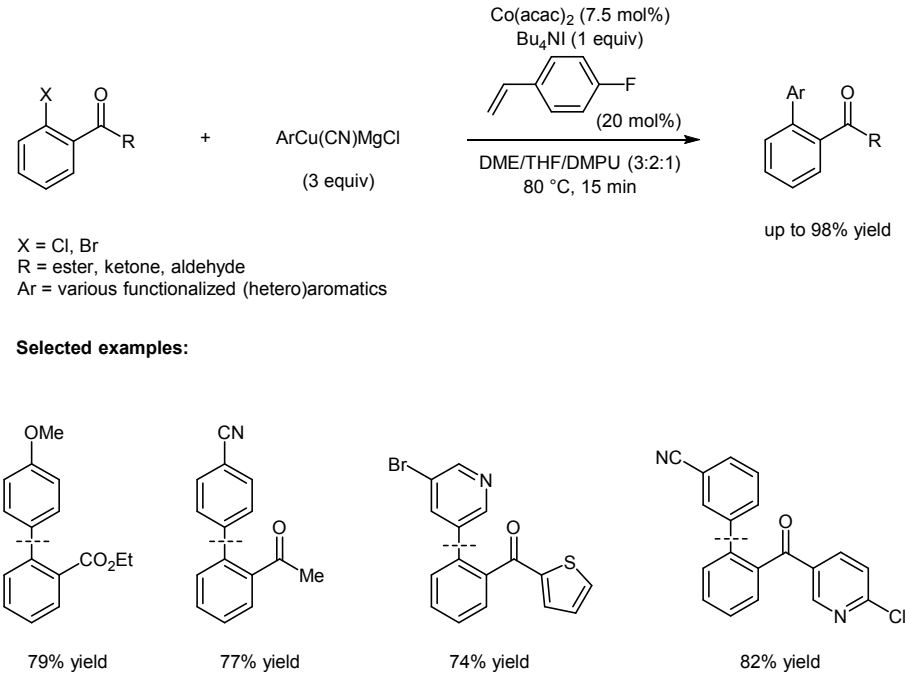
[50] Gilman, G.; Lichtenwalter, M. *J. Am. Chem. Soc.* **1939**, *61*, 957.
[51] (a) Uemura, S.; Fukuzawa, S.-I. *Tetrahedron Lett.* **1982**, *23*, 1181. (b) Uemura, S.; Fukuzawa, S.-I.; Path, S. R. *J. Organomet. Chem.* **1983**, *243*, 9.

The same authors also reported that cobalt powder can be used as catalyst in some cases.[47] Furthermore, *Knochel* has shown that also *ortho*-bromo or *ortho*-chloro aromatic ketones, esters and even aldehydes can be coupled using a cobalt catalyst. Regarding this, the aromatic Grignard reagent has to be transmetalated to the respective organocopper reagent using CuCN·2LiCl. To reach full conversion, a THF/DME/DMPU solvent mixture has to be prepared and additives like Bu_4NI and 4-fluorostyrene were found to be crucial.[52] Numerous polyfunctional biaryls could be synthesized following this procedure (Scheme 16).



Scheme 16. Cobalt-catalyzed cross-coupling of polyfunctional aryl copper reagents with aryl bromides and chlorides.

This cobalt-catalyzed reaction could also be extended to aromatic tosylates and even fluorides.[53] Noteworthy, especially aryl fluorides are usually not very reactive using traditional metals like palladium or nickel, due to the inherent strength of the C-F bond that prevents metal insertion into this bond. Using pentafluorobenzophenones, the two *ortho*-fluorides could be functionalized selectively using an excess of arylcopper reagents (Schemes 17 and 18).[54]

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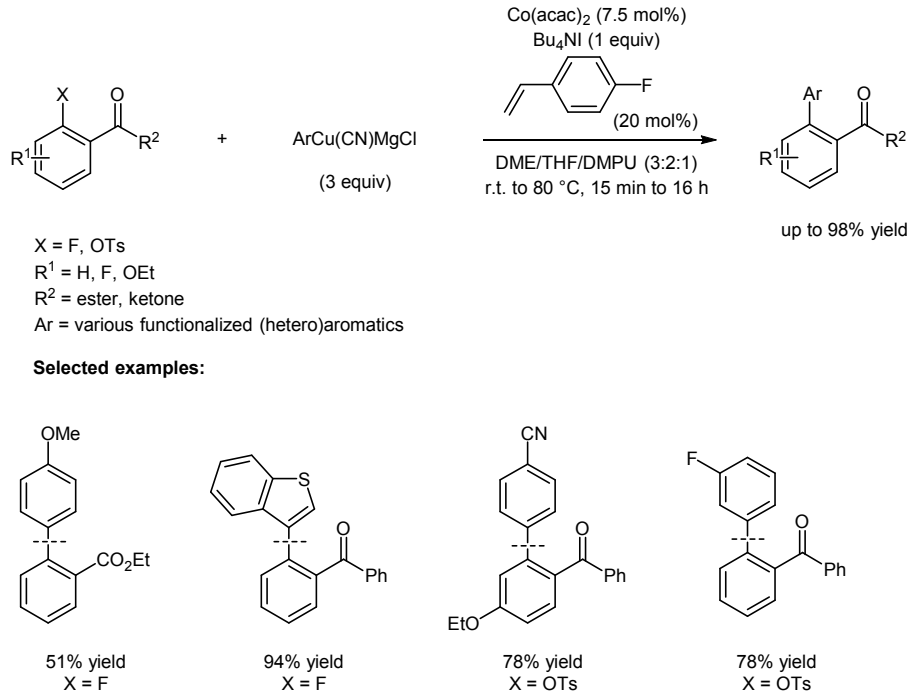
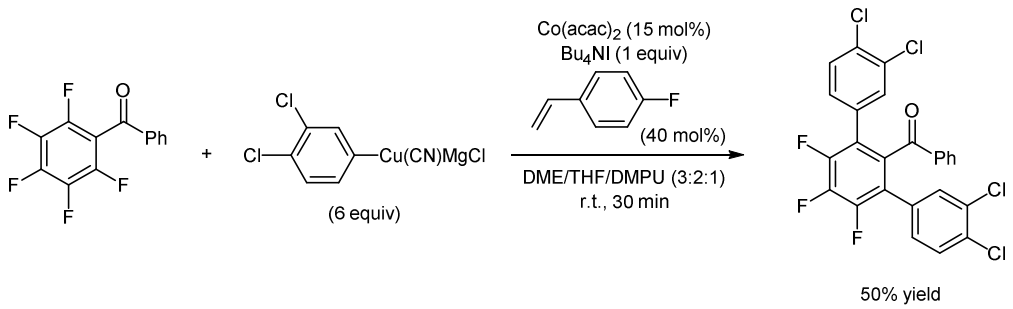
[52] Korn, T. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 2947.
[53] Korn, T. J.; Schade, M. A.; Wirth, S.; Knochel, P. *Org. Lett.* **2006**, *8*, 725.
[54] Korn, T. J.; Schade, M. A.; Cheemala, M. N.; Wirth, S.; Guevara, S. A.; Cahiez, G.; Knochel, P. *Synthesis* **2006**, 3547.



Scheme 17. Cobalt-catalyzed cross-couplings of aryl fluorides and tosylates.

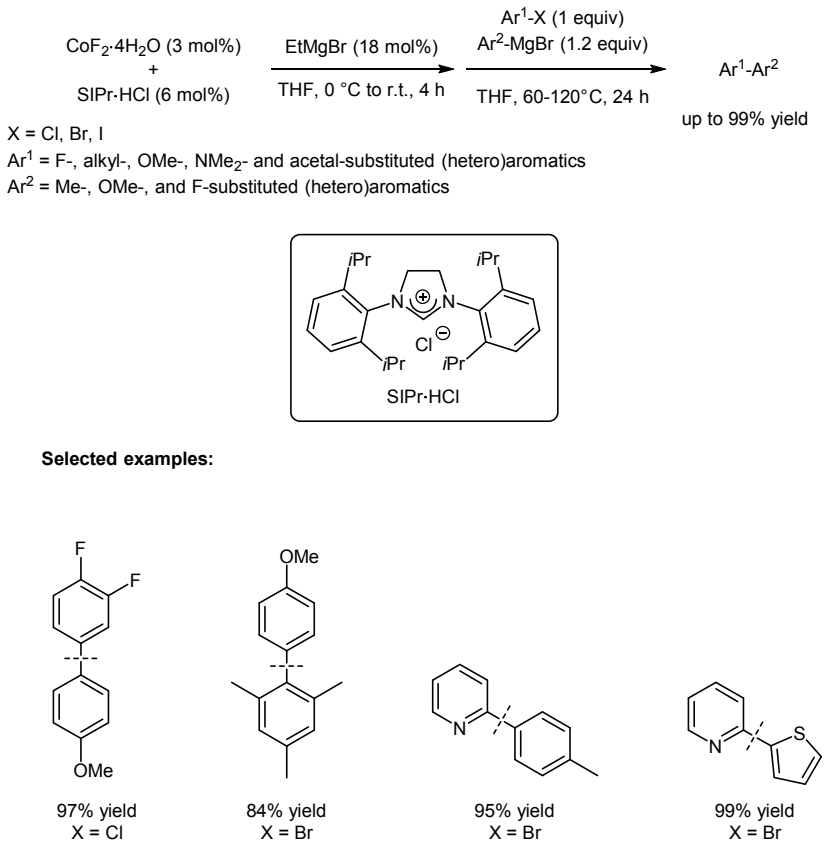


Scheme 18. Example for cobalt-catalyzed cross-coupling of pentafluorobenzophenone.

Nakamuras method using metal fluorides and *N*-heterocyclic carbene ligands could also be applied to cobalt, resulting in various aryl-aryl coupling products via reaction of an aromatic Grignard reagent with aromatic halides (Scheme 19).[49b] With cobalt fluoride, better results are obtained with aromatic iodides and bromides as electrophiles, whereas with iron fluoride higher yields are obtained using aryl chlorides.[55]

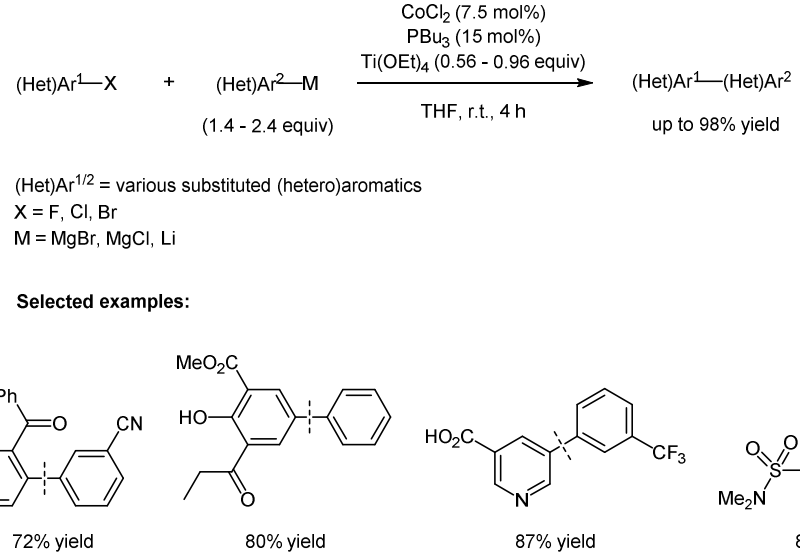
In 2013, *Duan* presented a novel cobalt-catalyzed cross-coupling reaction between aryl halides and aromatic magnesium and lithium reagents. The presence of 40 mol% of $Ti(OEt)_4$ was found to suppress undesired homo-coupling side-products from the organometallic

[55] Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *110*, 1435.



Scheme 19. Cobalt-carbene catalyst for unsymmetrical biaryl formation reactions.

reagent. Interestingly, the reaction can also take place in the presence of a free carboxylic acid, a hydroxyl or an amide residue (Scheme 20).[56] Even if this reaction displays a broad functional group tolerance, a large excess of Ti-salts is present in the reaction mixture and toxicological anxious PBu_3 is used.

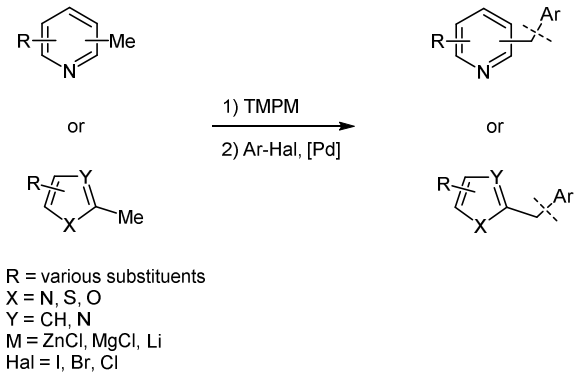


Scheme 20. Co/Ti cooperatively catalyzed biaryl couplings.

[56] Zeng, J.; Liu, K. M.; Duan, X. F. *Org. Lett.* **2013**, *15*, 5342.

5. Objectives

The benzylic arylation of pyridines and related *N*-heterocycles is an important synthetic challenge due to their important biological or material properties.[57] So far, the arylation of methyl-substituted 5- and 6-membered heterocycles is an unsolved problem. Hence, benzylic metalation of a range of methyl-substituted heterocycles should be developed, using the direct metalation method described in Chapter 2.4. Subsequent cross-coupling reactions of the resulting benzylic organometallic reagents should furnish benzylic arylated heterocycles (Scheme 21).[58]



Scheme 21. Intended benzylic arylation of heterocycles.

Furthermore, the regioselectivity of benzylic metalation of lutidines should be investigated. Examination of Lewis acidic additives should be undertaken and the effect of these additives on the regioselectivity of the metalation should be studied (Scheme 22).

Another project should focus on iron- and cobalt-catalyzed aryl-aryl cross-coupling reactions. As described in Chapter 3 and 4, the formation of unsymmetrical biaryls is still dominated by palladium and nickel catalysts. Due to ecological and economical reasons, the replacement of these metals by more abundant metals like iron or cobalt is highly desired. Previous reports on

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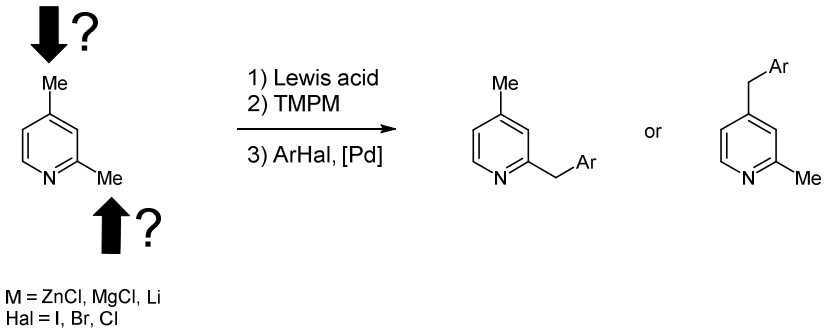
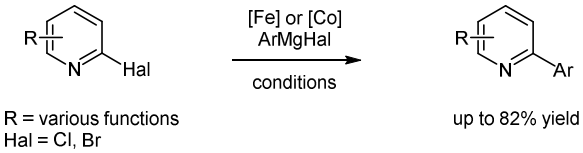
[57] Nicolaou, K. C.; Scarpelli, R.; Bollbuck, B.; Werschkun, B.; Pereira, M. M. A.; Wartmann, M.; Altmann, K.-H.; Zaharevitz, D.; Gussio, R.; Giannakakou, P. *Chem. Biol.* **2000**, *7*, 593. (b) Oliva, B.; Miller, K.; Caggiano, N.; O´Neill, A. J.; Cuny, G. D.; Hoemann, M. Z.; Hauske, J. R.; Chopra, I. *Antimicrob. Agents Chemother.* **2003**, *47*, 458. (c) Bouillon, A.; Voisin, A. S.; Robic, A.; Lancelot, J.-C.; Collot, V.; Rault, S. *J. Org. Chem.* **2003**, *68*, 10178. (d) Nolan, E. M.; Jaworski, J.; Okamoto, K.-I.; Hayashi, Y.; Sheng, M.; Lippard, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 16812. (e) Hayashi, A.; Arai, M.; Fujita, M.; Kobayashi, M. *Biol. Pharm. Bull.* **2009**, *32*, 1261. (f) Quiroga, J.; Trilleras, J.; Insuasty, B.; Abonia, R.; Nogueras, M.; Marchal, A.; Cobo, J. *Tetrahedron Lett.* **2010**, *51*, 1107. (g) Laird, T. *Org. Process Res. Dev.* **2006**, *10*, 851. (h) Yurovskaya, M. A.; Karchava, A. V. *Chem. Heterocycl. Compd.* **1994**, *30*, 1331. (i) Baxter, P. N. W.; Lehn, J.-M.; Fischer, J.; Youinou, M.-T. *Angew. Chem. Int. Ed.* **1994**, *33*, 2284. (j) Lehn J.-M. *Science* **2002**, *295*, 2400. (k) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (l) Burton, P. M.; Morris, J. A. *Org. Lett.* **2010**, *12*, 5359.

[58] This project was developed in cooperation with Duez, S. and Manolikakes, S. M.



Scheme 22. Regioselective benzylic arylation of 2,4-lutidine.

these Csp^2-Csp^2 cross-coupling reactions using iron or cobalt salts have shown that the key to success is the suppression of undesired homo-coupling side products arising from the organo-metallic reagent. Therefore, conditions for efficient iron- and cobalt-catalyzed cross-coupling reactions between *N*-heterocyclic halides and aromatic Grignard reagents should be developed. The Grignard reagents should be prepared according to Chapters 2.2 and 2.3 (Scheme 23).[59]



Scheme 23. Attempted iron- and cobalt-catalyzed cross-coupling reactions.

Furthermore, this coupling reaction should be extended to aromatic halides like 2-chlorobenzophenone or 2-halogenated protected benzaldehydes as well as to alkenyl halides. Alternative metal salts like chromium-, vanadium- or molybdenum-chlorides and -bromides should also be tested for their efficiency in similiar Csp^2-Csp^2 cross-coupling reactions.[59]

[59] This project was developed in cooperation with Kuzmina, O. M.; Markiewicz, J. T.; Flubacher, D. and Fernandez, S.

B. Results and Discussion

1. Benzylic Arylation of Heterocycles

1.2. Introduction

The functionalization of pyridines and related heterocycles is very important due to their biological or material properties.[57] Especially, the benzylic arylation of pyridines is a challenging synthetic problem. Pd-catalyzed arylations of 2-picoline involving a direct C-H activation[60] have no generality and only scarce examples have been reported. Thus, azaarenes bearing electron-withdrawing groups may be arylated at 100 °C with a Pd-catalyst.[61] Several alternative procedures involving the fragmentation of a 2-(2-pyridyl)ethanol,[62] the arylation of *N*-oxides[63] or *N*-iminopyridinium ylides[64] have been described. These methods, although displaying now a good generality, require modified *N*-heterocyclic precursors. Also, whereas 2-picoline (**1a**) can be functionalized in this way, no arylation on 4-picoline (**2a**) has been described. The difficulty for forming a new carbon-carbon bond with metalated 2-picoline (**3**) (or 4-picoline) may be due to the nature of the palladium complexes[65] (**4a-c**) resulting from a reaction with ArPdX (Scheme 24). All these possible structures would be reluctant to undergo a reductive elimination due to the chelation of the heterocyclic nitrogen with the Pd-center. *Hartwig* has already shown that Pd-catalyzed aminations are accelerated by a Lewis-Acid (BEt_3).[66] *Nolan* has also reported that reductive eliminations of Pd-complexes are accelerated by $AlCl_3$.[67] The presence of an appropriate Lewis-Acid (LA) complexing this heterocyclic nitrogen should lead to a new Pd-intermediate such as **5** which will now be prone to undergo a fast reductive elimination leading to the cross-coupling product **6**. A similar behavior may be expected for the arylation of 4-picoline (Scheme 24). The beneficial effect of Lewis-acids for performing additions of 2-picoline to imines and enones has already been demonstrated.[68,69]

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[60] (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) For a special issue on Selective Functionalization of C-H Bonds: *Chem. Rev.* **2010**, *110*, 575. (c) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (d) *Activation of Unreactive Bonds and Organic Synthesis*, Murai, S., Ed.; Springer-Verlag, Berlin Heidelberg, **1999**. (e) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439; (f) Schlosser, M.; Mongin, F. *Chem. Soc. Rev.* **2007**, *36*, 1161. (g) Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 2373.

[61] Burton, P. M.; Morris, J. A. *Org. Lett.* **2010**, *12*, 5359.

[62] Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 2643.

[63] (a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (b) Schipper, D. J.; Campeau, L.-C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155.

[64] Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641.

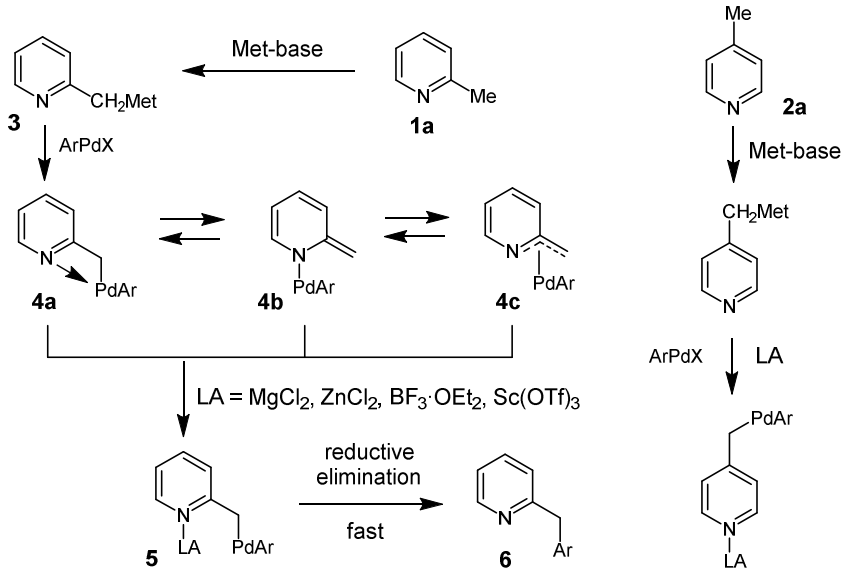
[65] For structures of palladium picolyl derivatives, see: (a) Onishi, M.; Hiraki, K.; Maeda, K.; Itoh, T. *J. Organomet. Chem.* **1980**, *188*, 245. (b) Isobe, K.; Nakamura, Y.; Kawaguchi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1802. (c) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650.

[66] Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734.

[67] Huang, J.; Haar, C. M.; Nolan, S. P. *Organometallics* **1999**, *18*, 297.

[68] For additions to imines, see: (a) Qian, B.; Guo, S.: Xia, Huang, H. *Adv. Synth. Catal.* **2010**, *352*, 3195. (b) Rueping, M.; Tolstoluzhsky, N. *Org. Lett.* **2011**, *13*, 1095.

[69] For additions to enones, see: Komai, H.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Org. Lett.* **2011**, *13*, 1706.



Scheme 24. Lewis-acid (LA) promoted benzylic cross-coupling.

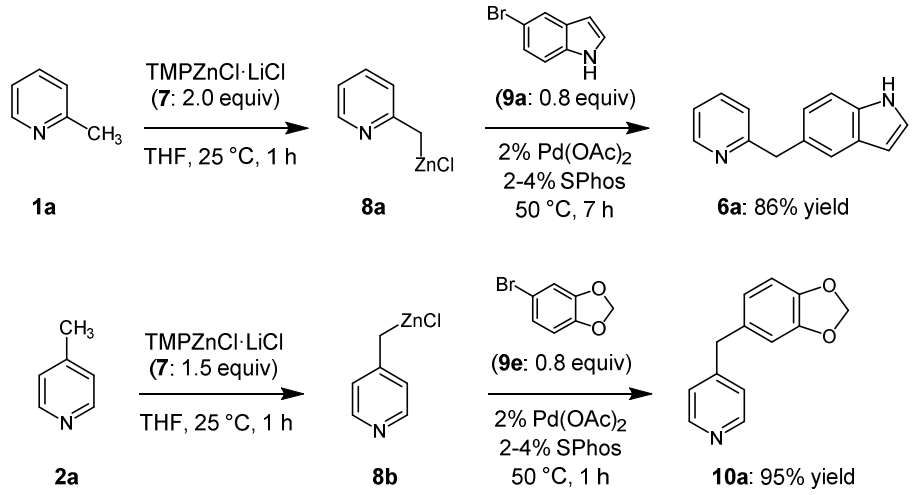
Thus, the use of bases (Met-base) bearing a Lewis-acid metal centre for performing the metalation was attempted to be investigated. TMPZnCl·LiCl (**7**) displays a high chemoselectivity in various directed zincations of aromatics and heterocycles. Besides, TMPZnCl·LiCl (**7**) proved to be an excellent base for the generation of nitrile and ester enolates.[70,71] Moreover, TMPZnCl·LiCl is compatible with additional strong Lewis-acids ($MgCl_2$, $BF_3 \cdot OEt_2$) forming frustrated Lewis pairs.[72] The goal of the following investigation was to examine, if Lewis-acids such as $ZnCl_2$, $MgCl_2$, $BF_3 \cdot OEt_2$ or $Sc(OTf)_3$ can be combined with TMPZnCl·LiCl to promote efficiently the Negishi cross-coupling[73] of various methyl-substituted *N*-heterocycles.

1.2. Benzylic Cross-Coupling of Pyridines with Aryl Bromides

At first, it was examined, if TMPZnCl·LiCl is able to metalate picolines. Thus, the zincation of 2-picoline (**1a**) with TMPZnCl·LiCl (**7**: 2.0 equiv)[74] gives the zincated picoline **8a** (THF,

[70] (a) Hlavinka, M. L.; Hagadorn, J. R. *Tetrahedron Lett.* **2006**, *47*, 5049. (b) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics*, **2007**, *26*, 4105.
[71] Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming, F. F.; Knochel, P. *Org. Lett.* **2011**, *13*, 1690.
[72] (a) Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 5451. (b) For an excellent review see: Stephan, D. W.; Erker, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 46.
[73] (a) Erdik, E. *Tetrahedron*. **1992**, *48*, 9577. (b) Negishi, E.-i.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298; (c) Negishi, E.-i. *Acc. Chem. Res.* **1982**, *15*, 340.
[74] Usually, 1.5 equiv of base (**7**) is used. In this case, 2.0 equiv of base are used due to the presence of the indole NH-group.

25 °C, 1 h). Its cross-coupling with 5-bromoindole (**9a**: 0.8 equiv) using 2% $Pd(OAc)_2$ and 2-4% SPhos[75] (50 °C, 7 h) affords the desired pyridine **6a** in 86% yield (Scheme 25).



Scheme 25. Pd-catalyzed direct cross-coupling of picolines **1a** and **2a**.

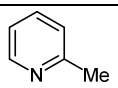
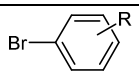
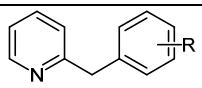
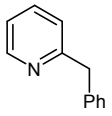
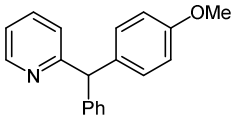
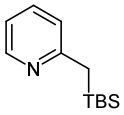
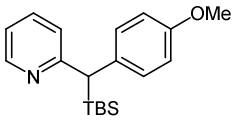
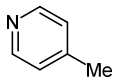
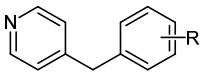
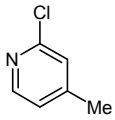
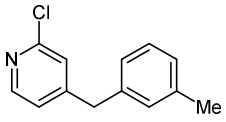
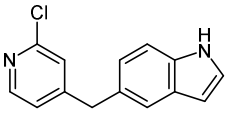
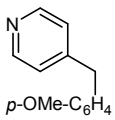
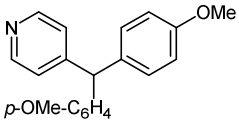
Such cross-coupling reactions can be extended to various substituted aryl bromides (**9b-d**) leading to products **6b-d** in 66 to 95% yield (Table 1, entries 1-3). Also, 2-substituted pyridines such as **1b-c** are metalated with TMPZnCl·LiCl (**7**) under the same conditions and provide the desired products (**6e-f**) with 4-bromoanisole (**9b**) in very high yields (92-99%, entries 4-5). No arylation of 4-picoline (**2a**) has been reported in the literature so far. However, with TMPZnCl·LiCl (**7**: 1.5 equiv), a smooth zincation of **2a** proceeds readily (25 °C, 1 h) and the Pd-catalyzed cross-coupling of **8b** with various aryl bromides (**9b**, **9e-i**) furnishes the 4-substituted pyridines **10a-f** in 70 to 98% yield (Scheme 25 and entries 6-10). Also, 2-chloro-4-methylpyridine (**2b**) similarly reacts and produces the arylated products **10g** and **10h** in 69% yield (entries 11-12). Cross-coupling of the 4-substituted pyridine (**10b**) with 4-bromoanisole (**9b**) leads to the desired product (**10i**) in high yield (entry 13).

These smooth cross-couplings may be explained by the role that $ZnCl_2$ plays as Lewis-acid. Interestingly, the use of TMPZnCl·$MgCl_2$·2LiCl (prepared from TMPMgCl·LiCl and $ZnCl_2$) leads to even faster cross-couplings (at least 6 times faster). However, the reaction is complicated by increased amounts of bis-arylation[76] making a general use of this Lewis-acid

[75] (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (c) Altman, R. A.; Buchwald, S. L. *Nat. Protocols* **2007**, *2*, 3115. (d) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

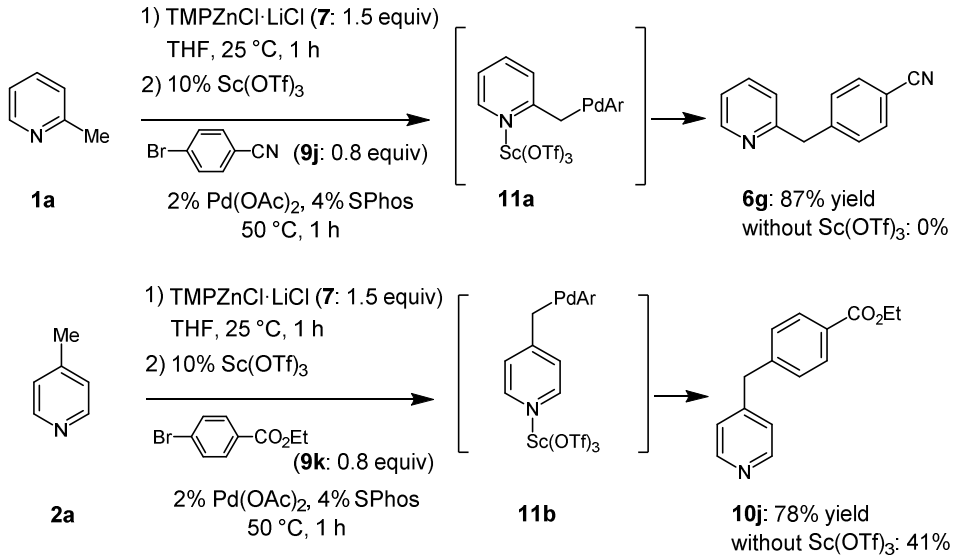
[76] Pd-catalyzed arylation of 2-picoline (**1a**) with 3-chlorobromobenzene (**9d**) proceeds in 1 h using TMPZnCl·$MgCl_2$·LiCl instead of 6 h when using TMPZnCl·LiCl (**7**) but led to less product **6d** (61%) due to the formation of 17% of di-arylated product.

Table 1: Direct benzylic cross-coupling of 2- and 4-picoline.

Entry	Picoline[a]	Aryl-Br	Product	Yield (%)[b]
				
1	**1a** (3)	**9b**:R = 4-OMe	**6b**:R = 4-OMe	95
2	**1a** (6)	**9c**:R = 4-F	**6c**:R = 4-F	78
3	**1a** (6)	**9d**:R = 3-Cl	**6d**:R = 3-Cl	66
				
4	**1b** (20)	**9b**	**6e**	99
				
5	**1c** (11)	**9b**	**6f**	92
				
6	**1a** (1)	**9b**	**10b**: R = 4-OMe	98[c]
7	**2a** (1)	**9f**: R = 3-Me	**10c**:R = 3-Me	82
8	**2a** (1)	**9g**:R = 4-NMe_2	**10d**:R = 4-NMe_2	70
9	**2a** (1)	**9h**:R = 4-OH	**10e**:R = 4-OH	84[c]
10	**2a** (1)	**9i**: R = 4-OPiv	**10f**:R = 4-OPiv	81[c]
				
11	**2b** (1)	**9f**	**10g**	69[d]
				
12	**2b** (1)	**9a**	**10h**	69
				
13	**10b** (3)	**9b**	**10i**	93

(a) Reaction time (h) for the arylation in brackets. (b) Isolated yield of analytically pure product. (c) $Pd(OCOCF_3)_2$ was used as the Pd-source. (d) 2% $Pd(OAc)_2$, 4% PCy_3 was used.

undesirable. A further hint showing the importance of Lewis-acids via a tentative Pd-intermediate of type **5** (Scheme 24) is found in the cross-coupling reaction of picolines (**1a** or **2a**) with electron-deficient aryl bromides. Such substrates like 4-bromobenzonitrile (**9j**) or ethyl 4-bromobenzoate (**9k**) gave disappointing results in the presence of $ZnCl_2$ or $MgCl_2$ as Lewis-acids. Therefore, we have screened other powerful alternative Lewis-acids[77] such as $ScCl_3$, $Sc(OTf)_3$,[78] $Yb(OTf)_3$,[79] $Y(OTf)_3$.[77a] Thus, the direct cross-coupling of zincated 2-picoline (**8a**) with 4-bromobenzonitrile (**9j**) gave no product (even after an additional Pd-ligand screening)[80] (Scheme 26). However, in the presence of 10% $Sc(OTf)_3$, an efficient Pd-catalyzed cross-coupling took place and afforded the coupling product **6g** in 87% yield (Scheme 26). Similarly, 4-picoline (**2a**) gave the cross-coupling product **10j** only in 41% yield without $Sc(OTf)_3$, but the addition of 10% $Sc(OTf)_3$ increased the cross-coupling yield to 78% (Scheme 26). The effect of $Sc(OTf)_3$ may be best explained by an acceleration of the



Scheme 26. $Sc(OTf)_3$ catalyzed cross-coupling of 2-picoline (**1a**) and 4-picoline (**2a**) with electron-withdrawing substituted aryl bromides (**9j-k**).

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[77] (a) *Lewis Acid reagents: a practical approach*, Yamamoto, H.; Ed.; Oxford University Press, New York, **1999**. (b) *Selectivities in Lewis acid promoted reactions*, Schinzer, D.; Ed.; Kluwer Academic, Dordrecht, **1989**. (c) *Lanthanides: Chemistry and Use in Organic Synthesis*, Kobayashi, S.; Ed.; Springer-Verlag, Berlin Heidelberg, **1999**. (d) *Acid Catalysis in Modern Organic Synthesis, Vol. 2*, Shibasaki, M.; Matsunaga, S.; Kumagai, N.; Eds.; Wiley: Weinheim, Germany, **2008**, p. 635.

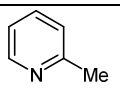
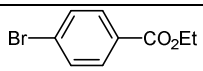
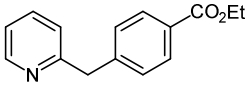
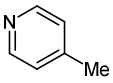
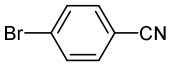
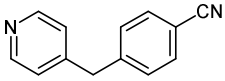
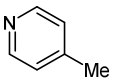
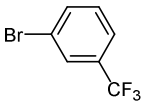
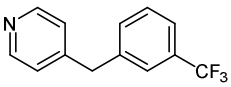
[78] (a) *Acid Catalysis in Modern Organic Synthesis, Vol 2*, Ogawa, C.; Gu, Y.; Boudou, M.; Kobayashi, S.; Eds.; Wiley-VCH Weinheim, Germany, **2008**, p. 589. (b) *Lewis Acids in Organic Synthesis, Vol. 2*, Kobayashi; S.; Ed.; Wiley: Weinheim, Germany, **2000**, p. 883. (c) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755.

[79] (a) *Transition Metals for Organic Synthesis, Vol. 1*, Kobayashi, S.; Ed.; Wiley: Weinheim, Germany, **1998**, p. 285. (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. L. *Chem. Rev.* **2002**, *102*, 2227.

[80] Screenings of various Pd sources such as $Pd(OAc)_2$, $Pddba_2$, $Pd(OCOCF_3)_2$ in combination with ligands like SPhos, Xantphos, Davephos, BINAP, tfp, PCy_3, P*t*Bu_3 as well as PEPPSI, $Pd(PPh_3)_4$, $PdCl_2$(dppf) have been examined without giving satisfactory results.

cross-coupling reductive elimination step due to a complexation of $Sc(OTf)_3$ at the heterocyclic nitrogen (see **11a-b**, Scheme 26). It is anticipated that electron-withdrawing substituents lead to Pd-intermediates of type **4** (Scheme 24) which are especially reluctant to undergo a reductive elimination. The effect of a Lewis-acid seems to be crucial in these cases. Thus, the cross-couplings of picolines **1a** and **2a** with various electron-deficient aryl bromides (**9j-l**) are dramatically improved by the presence of 10% $Sc(OTf)_3$ affording the cross-coupling products **6h** and **10k-l** in 75-85% yield. In the absence of $Sc(OTf)_3$, the yields of cross-coupling lay between 0-51% (Table 2, entries 1-3).

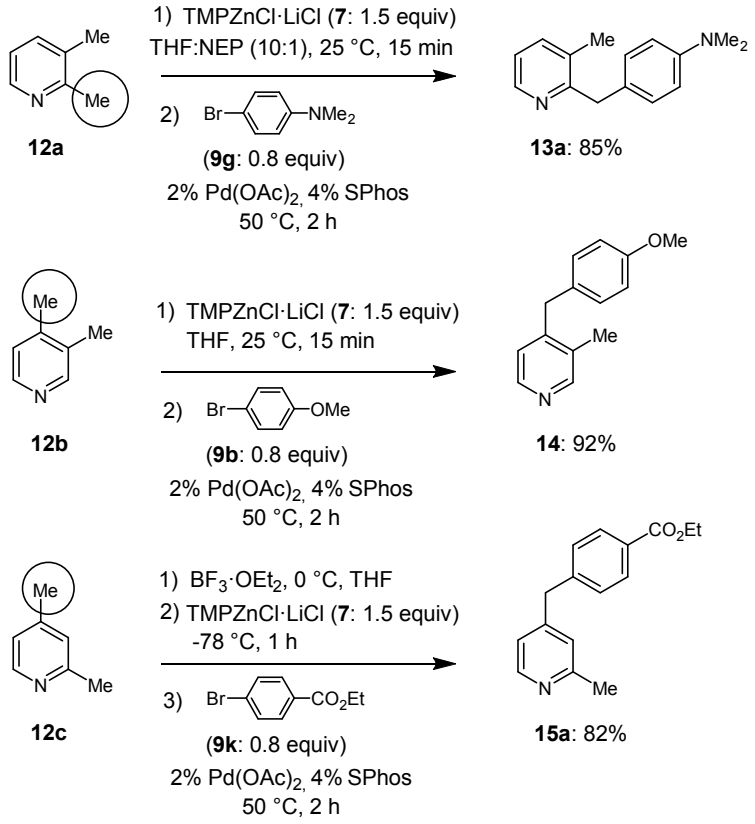
Table 2: Effect of $Sc(OTf)_3$ on the benzylic cross-coupling of 2- and 4-picoline with electron-deficient electrophiles.

Entry	Picoline[a]	Aryl-Br	Product[b]
			
1	**1a**	**9k**	**6h**: 85% (31%)[c]
			
2	**2a**	**9j**	**10k**: 75% (0%)[c]
			
3	**2a**	**9l**	**10l**: 78% (51%)[c]

(a) Conditions: 50 °C, 1 h. (b) Isolated yield of analytically pure product. (c) Isolated yield of reaction performed without $Sc(OTf)_3$.

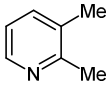
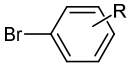
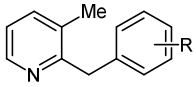
The mild zincation of picolines and efficient subsequent cross-coupling allows now to tackle regioselectivity issues in the arylation of dimethylpyridines. Thus, the arylation of 2,3-, 3,4- and 2,4-lutidines (**12a-c**) was examined. With 2,3-lutidine (**12a**), an exclusive zincation with TMPZnCl·LiCl (**7**) occurs at position 2 leading after Pd-catalyzed arylation with 4-bromo-*N*,*N*-dimethylaniline (**9g**) to the disubstituted pyridine (**13a**) in 85% yield (Scheme 27). Further arylations proceed in excellent yields and are described in Table 3, entries 1-3. In the case of 3,4-lutidine (**12b**), a complete regioselective metalation is observed at position 4 leading after a cross-coupling with 4-bromoanisole (**9b**) to the disubstituted pyridine **14** in 92% yield (Scheme 27). The regioselective arylation of 2,4-lutidine (**12c**) is more challenging since a direct zincation with TMPZnCl·LiCl (**7**) produces a 2:1 mixture of regioisomers. However, the addition of $BF_3 \cdot OEt_2$[72a] prior to TMPZnCl·LiCl (**7**) directs the zincation only at

position 4 since the complexation of **12c** with $BF_3 \cdot OEt_2$ at the heterocyclic nitrogen hampers the metalation by TMPZnCl·LiCl (**7**) at position 2 for steric factors. Therefore the zincation occurs at position 4 leading after cross-coupling with ethyl 4-bromobenzoate (**9k**) to the pyridine (**15a**) in 82% yield. This behavior is general and several typical aryl bromides, chlorides and a triflate (**9b, i, j, n-q**) undergo regioselective arylations at position 4 leading to products **15b-g** in 77-98% yield (entries 4-10).[81]



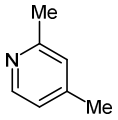
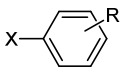
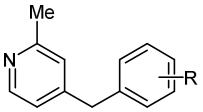
Scheme 27. Selective cross-couplings of lutidines (**12a-12c**).[82]

Table 3: Selective benzylic cross-couplings of lutidines with various aryl bromides, chlorides and a triflate.

Entry	Lutidine[a]	Aryl-X	Product	Yield (%)[a]
				
1	**12a**	**9b**	**13b**: R = 4-OMe	90
2	**12a**	**9f**	**13c**: R = 3-Me	91

[81] Interestingly, a less hindered base $(i\text{Pr})_2\text{NZnCl}\cdot\text{LiCl}$ is not compatible with the Lewis-acid $BF_3 \cdot OEt_2$, since it forms a stable complex $(i\text{Pr})_2\text{NBF}_3\text{ZnCl}$ which does not dissociate reversibly under the reaction conditions, unlike the frustrated Lewis-acid pair $\text{TMPBF}_3\text{ZnCl}$.[72b]

[82] the presence of *N*-ethylpyrrolidinone (NEP) leads to shorter reaction times (3 times faster).

3	**12a**	**9m**: R = 4-CF_3	**13d**: R = 4-CF_3	88
				
4	**12c**	**9b**	**15b**: R = 4-OMe	92[b]
5	**12c**	**9i**	**15c**: R = 4-OPiv	82[b]
6	**12c**	**9j**	**15d**: R = 4-CN	77[b]
7	**12c**	**9n**: X = OTf, R = 4-OMe	**15b**: R = 4-OMe	98[b]
8	**12c**	**9o**: X = Br, R = 2-OMe	**15e**: R = 2-OMe	92[b]
9	**12c**	**9p**: X = Cl, R = 3-OMe	**15f**: R = 3-OMe	86[b]
10	**12c**	**9q**: X = Cl, R = 4-CF_3	**15g**: R= 4-CF_3	88[b]

(a) Isolated yield of the analytically pure product. (b) $BF_3 \cdot OEt_2$ was added prior to TMPZnCl·LiCl.

1.3. Benzylic Arylation of 2-Methyl-5-Membered Heterocycles Using TMP-Bases

Next, the arylation of methyl-substituted 5-membered heterocycles was envisioned, as this remained by far an unsolved problem.[83] The arylation of 1,2-dimethylimidazole (**16**) occurs usually at position 5 and no "benzylic" C-H activation followed by cross-couplings has been reported.[84,85] Only alkylation reactions on the methyl group have been performed successfully after deprotonation with *n*BuLi.[86] Also, the benzylic metalation and subsequent arylation of 2-methylbenzothiophenes[87] and 2-methylbenzofurans[87b] has not yet been described. Therefore, a

[83] (a) Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. *J. Am. Chem. Soc.* **2011**, *133*, 12439. (b) Ackermann, L.; Barfüsser, S.; Kornhaass, C.; Kapdi, A. R. *Org. Lett.* **2011**, *13*, 3082. (c) Fleming, P.; O`Shea, D. F. *J. Am. Chem. Soc.* **2011**, *133*, 1698. (d) Lei, A.; Liu, W.; Liu, C.; Chen M. *Dalton Trans.* **2010**, *39*, 10352. (e) Ackermann, L. *Modern Arylation Methods*, Wiley-VCH Weinheim, Germany, **2009**. (f) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.

[84] (a) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Otha, A. *Heterocycles* **1992**, *33*, 257. (b) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, 71, 467. (c) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (d) Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *J. Org. Chem* **2005**, *70*, 3997. (e) Bellina, F.; Cauteruccio, S.; Di Fiore, A.; Rossi, R. *Eur. J. Org. Chem.* **2008**, 5436. (f) Bellina, F.; Cauteruccio, S.; Di Fiore, A.; Marchetti, C.; Rossi, R. *Tetrahedron* **2008**, *64*, 6060. (g) Toure, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979. (h) Liégaut, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (i) Roger, J.; Doucet, H. *Tetrahedron* **2009**, *65*, 9772. (j) Laidaoui, N.; Miloudi, A.; El Abed, D.; Doucet, H. *Synthesis* **2010**, *15*, 2553.

[85] Song, G.; Su, Y.; Gong, X.; Han, K.; Li, X. *Org. Lett.* **2011**, *13*, 1968.

[86] (a) Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P. *Dalton Trans.* **2009**, *18*, 3599. (b) Oxenford, S. J.; Wright, J. M.; O'Brien, P.; Panday, N.; Shipton, M. R. *Tetrahedron Lett.* **2005**, *46*, 8315. (c) Sagae, T.; Ogawa, S.; Furukawa, N. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 3179.

[87] For benzylic functionalization of 2-methylbenzofuran see: (a) Setoh, M.; Kouno, M.; Miyanohana, Y.; Kori M. (Takeda Pharmaceutical Company Limited), US 2010/41891, **2010**. (b) Ellingboe, J. W.; Alessi, T. R.; Dolak, T. M.; Nguyen, T. T.; Tomer, J. D.; Guzzo, F.; Bagli, J. F.; McCaleb, M. L. *J. Med. Chem.* **1992**, *35*, 1176. (c) Alvarez, M.; Bosch, J.; Feliz, M. *J. Heterocycl Chem.* **1978**, *15*, 1089.

direct benzylic arylation on a variety of different methyl-substituted 5-membered heterocycles, including 2-methyl-imidazoles, -benzothiophenes and -benzofurans and related 5-membered heterocycles using TMP-bases should be investigated. Thus, by using the magnesium base TMPMgCl·LiCl (**17**) and subsequent transmetalation with $ZnCl_2$, we were able to zincate 1,2-dimethylimidazole (**16**) *selectively* at the 2-methyl position. The resulting zincated reagent **18** was used successfully to perform cross-coupling reactions with various aryl bromides of type **9** affording 2-benzylated imidazoles (**19**) in 71-91% yield (Table 4). For example, the magnesiation of 1,2-dimethylimidazole (**16**) with TMPMgCl·LiCl (**17**: 1.5 equiv) in THF is complete within 3 h at 25 °C.[88] After transmetalation with $ZnCl_2$ (1.5 equiv, 25 °C, 15 min), the zincated imidazole derivative (**18**) is treated with ethyl 4-bromobenzoate (**9k**: 0.8 equiv) in the presence of 2% $Pd(dba)_2$ and 4% SPhos to provide the desired arylated 1,2-dimethylimidazole (**19a**) at 50 °C within 2 h in 85% yield without the formation of a 5-arylated imidazole derivative (Table 4, entry 1). Similarly, cyano and trifluoromethyl substituted aryl bromides (**9j/l**) can be successfully converted leading to the imidazole derivatives (**19b-c**, 71-77%, entries 2 and 3). Also, electron-rich aryl bromides bearing alkoxy, pivaloxy, methyl or amino substituents undergo the cross-coupling in excellent yields (71-91% yields, entries 4-8) showing the broad scope of this arylation.

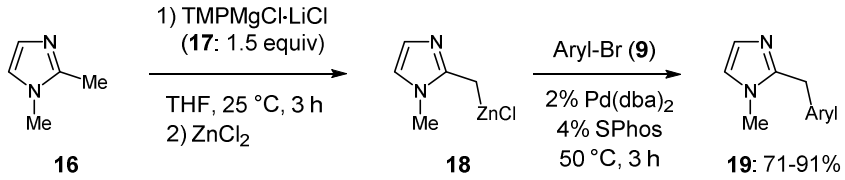
Efforts were made to extend this method to even less acidic methyl-substituted 5-membered heterocycles. It was found that 2-methyl benzothiophene (**20**) was readily metalated with TMPLi[89] (**21**: 1.15 equiv, -78 °C, 15 min) in THF.[90] After transmetalation with $ZnCl_2$, the resulting heterocyclic benzylic reagent (**22**) was smoothly arylated with various aryl bromides using 2% $Pd(OAc)_2$ and 4% SPhos (50 °C, 2 h) leading to the benzothiophenes (**23a-h**) in 68-98% yield (Table 5, entries 1-8). Interestingly, the 2,3-dimethylbenzothiophene (**20b**) undergoes an exclusive lithiation at position 2 providing after cross-coupling the 2-benzylated product (**23i)** in 87% yield (entry 9).

[88] The direct zincation with TMPZnCl·LiCl (**7**) is too sluggish at 25 °C.

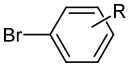
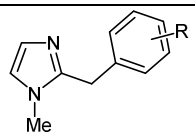
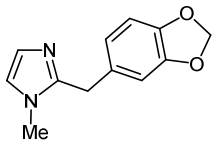
[89] (a) Mulvey, R. E. *Acc. Chem. Res.* **2009**, *42*, 743. (b) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.

[90] Metalation with TMPMgCl·LiCl (**17**) can only proceed at elevated temperatures and the yield of the subsequent cross-coupling proved to be less high, compared to initial metalation with TMPLi (**21**).

Table 4: Pd-catalyzed benzylic arylation of 1,2-dimethylimidazole (**16**) leading to products of type **19**.



16 **18** **19**: 71-91%

Entry	Aryl-Br [a]	Product	Yield (%)[a]
			
1	**9k**	**19a** R = 4-CO_2Et	85
2	**9j**	**19b** R = 4-CN	71
3	**9l**	**19c** R = 3-CF_3	77
4	**9b**	**19d** R = 4-OMe	74
5	**9i**	**19e** R = 4-OPiv	91
6	**9f**	**19f** R = 3-Me	83
7	**9g**	**19g** R = 4-NMe_2	79
			
8	**9e**	**19h**	71

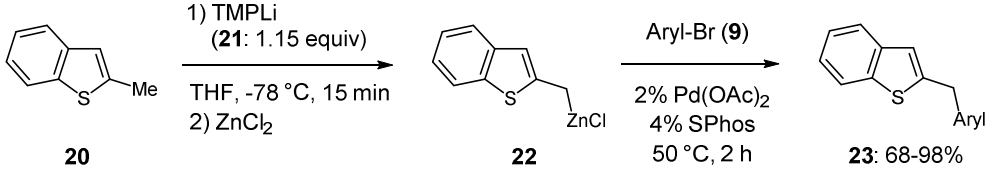
(a) Isolated yield of analytically pure product.

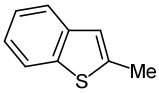
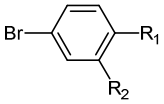
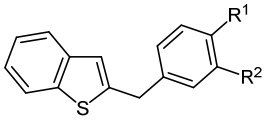
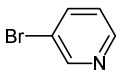
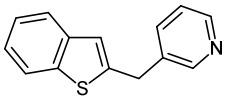
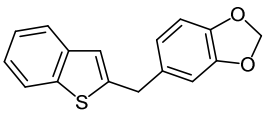
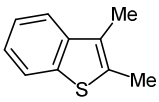
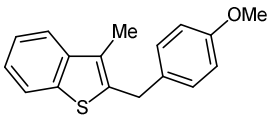
A further extension to the 2-methylbenzofuran scaffold was successful using similar conditions. The lithiation of 2-methylbenzofuran (**24**) was complete within 1 h at -78 °C. After transmetalation with $ZnCl_2$ and cross-coupling with various aryl bromides, methyl-substituted benzofurans (**26a-d**) were obtained in 52-75% yield (Table 6). In the case of cyano-substituted aryl bromides (**9j** and **9r**) we have found, that the addition of 10% $Sc(OTf)_3$ improves the cross-coupling yield.

The generality of this approach is demonstrated by performing the arylation of other related 5-membered heterocycles such as the 2-methyl-indole derivative **27**[91] and the 2-methyl-benzimidazole **28**. In these cases, TMPZnCl·LiCl (**7**) proved to be the suitable base and a complete zincation could be obtained within 1 h at 25 °C. Thus, cross-coupling of 2-methyl-

[91] For preparation of **27**, see: Macor, J. E.; Ryan, K.; Newman, M. E. *J. Org. Chem.* **1989**, *54*, 4785.

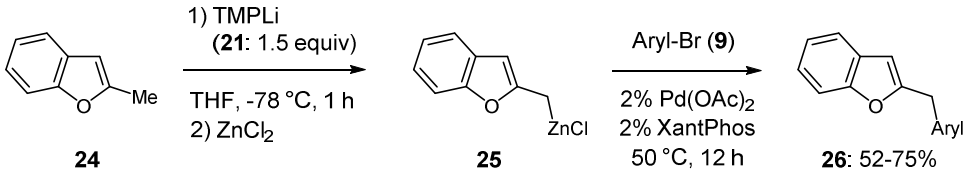
Table 5: Benzylic cross-coupling of 2-methylbenzo[*b*]thiophene (**20**).



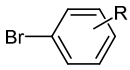
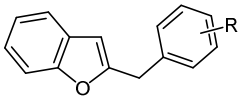
Entry	Substrate[a]	Aryl-Br	Product	Yield (%)[a]
				
1	**20a**	**9k**	**23a** $R_1 = CO_2Et$, $R_2 = H$	86
2	**20a**	**9m**	**23b** $R_1 = CF_3$, $R_2 = H$	90
3	**20a**	**9b**	**23c** $R_1 = OMe$, $R_2 = H$	98
4	**20a**	**9r** $R_1 = OMe$; $R_2 = CN$	**23d** $R_1 = OMe$, $R_2 = CN$	78
5	**20a**	**9i**	**23e** $R_1 = OPiv$, $R_2 = H$	97
6	**20a**	**9g**	**23f** $R_1 = NMe_2$, $R_2 = H$	93
				
7	**20a**	**9s**	**23g**	68
				
8	**20a**	**9e**	**23h**	87
				
9	**20b**	**9b**	**23i**	86

(a) Isolated yield of analytically pure product.

Table 6: Benzylic arylation of 2-methylbenzofuran (**24**).

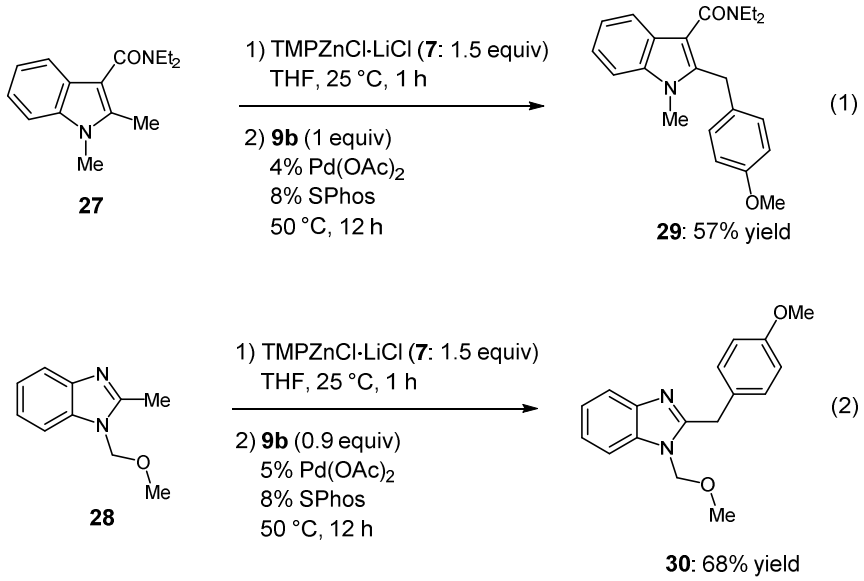


24 **25** **26**: 52-75%

Entry	Aryl-Br [a]	Product	Yield (%)[a]
			
1	**9k**	**26a** R = 4-CO_2Et	64
2	**9j**	**26b** R = 4-CN	52[b]
3	**9r**	**26c** R = 3-CN 4-OMe	74[b,c]
4	**9b**	**26d** R = 4-OMe	75[d]

(a)Isolated yield of analytically pure product. (b) 10% $Sc(OTf)_3$ was added. (c) 2% $Pd(dba)_2$ and 4% SPhos was used. (d) 2% $Pd(dba)_2$ and 2% Xantphos was used.

indole **27** with 4-bromoanisole **9b** gave the indole **29** in 57% yield (Scheme 28). This example represents the first benzylic cross-coupling on a 2-methyl-indole. Also, 2-methyl-benzimidazole (**28**) can be arylated successfully after zincation with TMPZnCl·LiCl (**7**) with 4-bromoanisole (**9b**) to yield the benzoimidazole derivative **30** in 68% yield (Scheme 28).



Scheme 28. Benzylic cross-coupling of indole **27** and benzo[*d*]imidazole **28**.

2. Aryl-Aryl Cross-Coupling Reactions Using Alternative Metal Catalysts

2.1. Introduction

Iron-catalyzed cross-coupling reactions have attracted a lot of attention during the last decade, especially because of their economic and ecological advantages over other transition metal-catalyzed couplings. Moreover, iron catalysts reveal characteristic reactivities and selectivities, which cannot be easily obtained with more classical Ni- or Pd-catalysts. Whereas iron salts have been employed successfully in various kinds of coupling reactions, sp^2-sp^2 cross-coupling reactions remain a major challenge due to the formation of symmetrical biaryls via undesired homocoupling as by-products. Therefore, conditions for iron- and related cobalt-catalyzed coupling reactions between *N*-heterocyclic halides and aromatic Grignard reagents should be examined.

2.2. Iron-Catalyzed Cross-Coupling of *N*-Heterocyclic Chlorides and Bromides with Arylmagnesium Reagents Using *t*BuOMe as Solvent

In preliminary experiments, the cross-coupling between 2-chloropyridine (**31a**) and PhMgCl (**32a**) was examined. Thus, catalytic amounts (5 mol%) of various iron salts like $Fe(acac)_2$, $Fe(acac)_3$ or the related $Fe(TMHD)_3$ (entries 1-3 of Table 7) and iron halides such as $FeCl_2$, $FeCl_3$, $FeBr_2$ or $FeBr_3$ (entries 4-7) as well as $Fe(OTf)_3$ (entry 8) gave only moderate yields of the desired cross-coupling product **33a** (46-63%) in THF at room temperature. Also, the use of iron fluorides and iodide led to only traces of product at room temperature (entries 9-11). Polar co-solvents like NMP hampered the cross-coupling (entry 12). Unpolar solvents like *n*-hexane or toluene did not display any considerable improvement (entries 13-14).[92] However, ethereal solvents such as diethyl ether or *t*BuOMe dramatically increased the GC-yield up to 87% affording after isolation the arylated pyridine **33a** in 84% yield (entries 15-16). Since comparable yields are obtained using *t*BuOMe or Et_2O, we have pursued our investigations using the industry-friendly solvent *t*BuOMe.

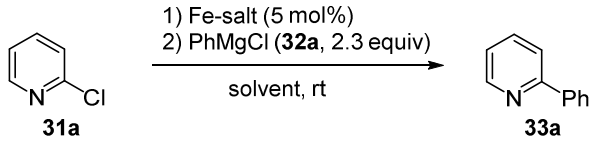
The use of such ethereal solvents proved to be a key determinant and allowed us to extend this cross-coupling to various other *N*-heterocycles. In order to study the reaction scope, we have first varied the *N*-heterocyclic chlorides or bromides and determined their reactions with PhMgCl (**32a**) in *t*BuOMe at room temperature.[93] Thus, we observed that 2-bromopyridine

[92] The low yields in entries 1-14 of Table 7 are due to the fact that the reaction conversion never reaches 100% for these substrates.

[93] Since PhMgCl is prepared in THF, the cross-coupling reaction is in fact performed in a mixture of THF and *t*BuOMe (ca. 2:5).

(**1b**) reacted with PhMgCl at a faster rate for completion than 2-chloropyridine (70 min instead of 90 min) and produced **33a** in the same yield (83%, entry 2 of Table 8). Substituted bromo- or chloro-pyridines such as 2-chloro-4-picoline (**31c**) and 2-bromo-5-chloropyridine (**31d**) reacted smoothly with similar reaction times leading to the pyridines **33b** and **33c** in 78-84% yield (entries 3 and 4). Interestingly, the presence of a *tert*-butoxycarbonyl group in position 3 (**31e**) dramatically increased the reaction rate leading to full conversion within

Table 7: Optimization of the conditions for reaction of pyridyl chloride (**31a**) with PhMgCl (**32a**) in the presence of various Fe-salts.



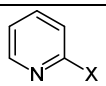
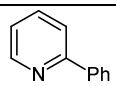
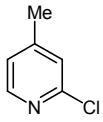
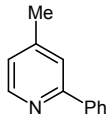
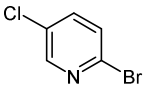
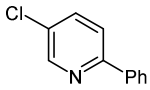
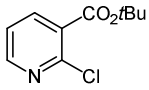
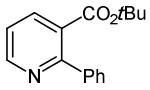
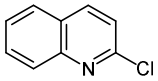
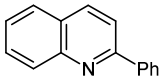
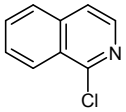
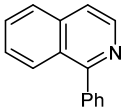
31a **33a**

Entry	Fe-salt[a]	Solvent	Reaction time[b]	Yield (%)[c]
1	$Fe(acac)_2$	THF	2 h	46
2	$Fe(acac)_3$	THF	2 h	55
3	$Fe(TMHD)_3$	THF	2 h	53
4	$FeCl_2$	THF	5 h	56
5	$FeCl_3$	THF	2 h	55
6	$FeBr_2$	THF	2 h	62
7	$FeBr_3$	THF	1.5 h	63
8	$Fe(OTf)_3$	THF	5 h	60
9	FeF_2	THF	20 h	traces[d]
10	FeF_3	THF	20 h	traces[d]
11	FeI_2	THF	20 h	traces[d]
12	$FeBr_3$	THF/NMP[e]	2 h	traces
13	$FeBr_3$	*n*-hexane	2 h	53
14	$FeBr_3$	toluene	1.5 h	14
15	$FeBr_3$	Et_2O	1.5 h	73, 87,[f] (84)[f]
16	$FeBr_3$	*t*-BuOMe	1.5 h	75, 85,[f] (82)[f]

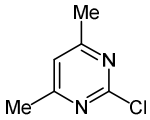
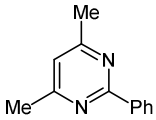
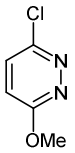
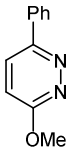
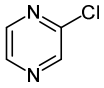
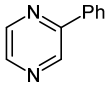
(a) 5 mol% of Fe-salt was used. (b) Reaction time until reaction completion according to GC analysis. (c) Calibrated GC-yield using undecane ($C_{11}H_{24}$) as internal standard. Numbers in brackets indicate isolated yields. (d) Starting material was not consumed even after 20 h. (e) A mixture of THF/NMP (5:1) was used. The reaction of PhMgCl with NMP was dominant. (f) 3 mol% of $FeBr_3$ was used.

5 min (entry 5). The cross-coupling product **33d** was isolated in 60% yield. No starting chloride was detected and the relatively moderate yield may be due to a polymerization of **31e**. The annulation of the pyridine ring with a benzene moiety also accelerated the reaction rate and the cross-couplings of PhMgCl with 2-chloroquinoline (**31f**) or 1-chloroisoquinoline (**31g**) were completed in 5 min and gave the expected phenylated *N*-heterocycles **33e** and **33f** in 88-90% yield (entries 6 and 7). The cross-coupling was also extended to diazines. Whereas the 2-chloropyrimidine derivative **31h** reacted with PhMgCl within 2 h providing the arylated pyrimidine **33g** in 76% yield (entry 8), the more sensitive chloro-pyridazine **31i** and pyrazine **31j** required 3-5 h for the reaction to go to completion, but led to the phenylated products in only 22-24% yield (entries 9 and 10).[94]

Table 8: Scope of iron-catalyzed cross-coupling of *N*-heteroarylchlorides and -bromides **31a-31j** with PhMgCl (**32a**).

Entry[a]	Substrate	Reaction time	Product	Yield (%)[b]
				
1	**31a**: X = Cl	1.5 h	**33a**	82
2	**31b**: X = Br	70 min	**33a**	83
				
3	**31c**	2 h	**33b**	84
				
4	**31d**	70 min	**33c**	78
				
5	**31e**	5 min	**33d**	60
				
6	**31f**	5 min	**33e**	88
				

[94] The use of other heterocyclic halides, like 3- and 4-chloropyridine, 2-chlorothiophene or 2-bromofuran as well as standard haloarenes resulted in only low yields.

7	**31g** 	5 min	**33f** 	90
8	**31h** 	2 h	**33g** 	76
9	**31i** 	5 h	**33h** 	22[c]
10	**31j**	3 h	**33i**	24[c]

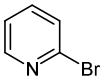
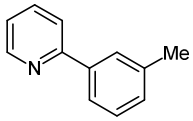
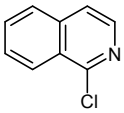
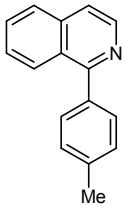
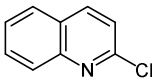
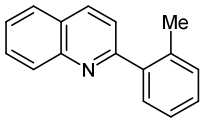
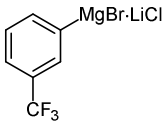
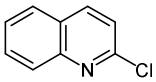
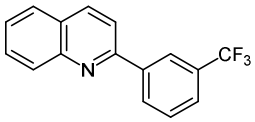
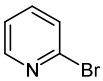
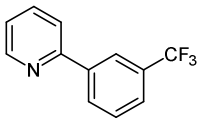
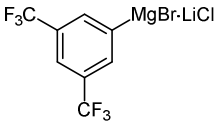
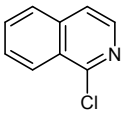
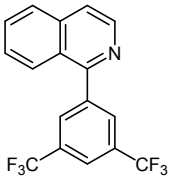
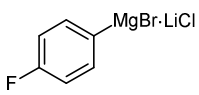
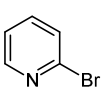
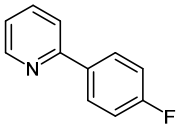
(a) The reaction was performed on a 1 mmol scale with 3 mol% of $FeBr_3$ in THF:*t*BuOMe (ca. 2:5) at room temperature. (b) Isolated yield. (c) GC-yield.

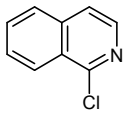
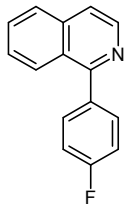
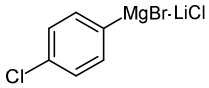
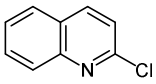
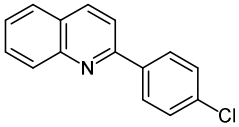
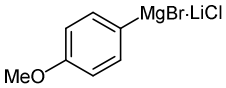
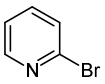
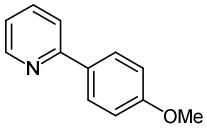
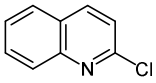
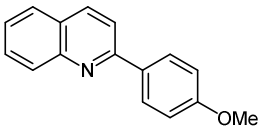
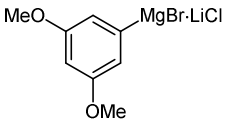
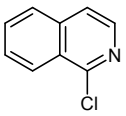
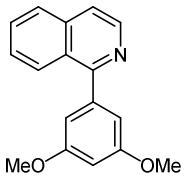
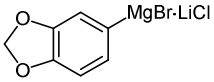
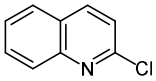
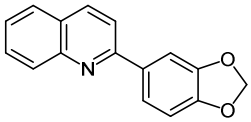
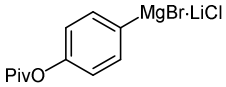
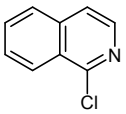
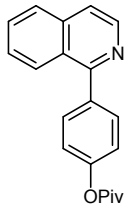
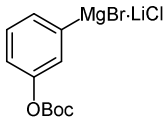
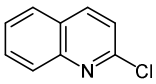
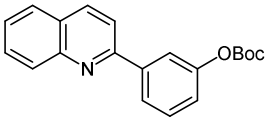
Next, the nature of the Grignard reagent[95] was varied using typical *N*-heterocyclic chlorides and bromides (**31b**, **31f**, **31g**) as electrophiles (Table 9). In all cases, the Fe-catalyzed cross-couplings were fast (2 min to 5 h) and led to complete conversion. Both electron-rich and electron-poor substituents can be present in the Grignard reagent. First, the substitution pattern of the arylmagnesium reagent was examined and it was found that *ortho*-, *meta*- and *para*-substituted Grignard reagents can be used. Whereas *m*-TolMgBr·LiCl (**32b**) and *p*-TolMgBr·LiCl (**32c**) react in similar rates as the unsubstituted magnesium reagent, the presence of an *ortho*-methyl substituent in *o*-TolMgBr·LiCl (**32d**) reduced the reaction rate (compare entry 3 of Table 9 with entry 6 of Table 8). However, in all cases excellent yields (80-93%; entries 1-3 of Table 9) were obtained. Various electron-poor substitutents like a trifluoromethyl group (like in 3-trifluoromethylmagnesium bromide **32e**; and in 3,5-ditrifluoromethylphenylmagnesium bromide **32f**; entries 4-6), a fluorine-group (as in 4-fluorophenylmagnesium bromide **32g**; entries 7 and 8) or a chlorine-goupe (like in **32h**; entry 9) were well tolerated in the cross-couplings providing the expected products in 66-92% yield (entries 4-9). Interestingly, also electron-rich substituents such as methoxy- (see reagents **32i** and **32j**; entries 10-12), methylenedioxy- (see reagent **32k**; entry 13) and pivalate-groups (OPiv; see reagent **32l**; entry 14) were compatible with rapid iron-catalyzed cross-couplings. The more sensitive Boc-protected Grignard reagent **32m** also smoothly underwent the cross-

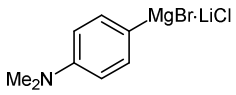
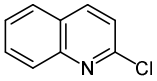
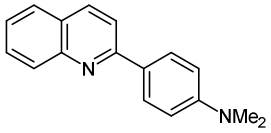
[95] The Grignard reagents were prepared by LiCl-mediated Mg insertion.

coupling with 2-chloroquinoline leading to the 2-arylated quinoline **33x** in 84% yield (entry 15). An amino-substituent did not disturb the cross-coupling and the Grignard reagent **32n** reacted with **31f** within 5 min providing the product **33y** in 82% yield (entry 16).

Table 9: Iron-catalyzed cross-couplings of *N*-heteroarylchlorides and -bromides with various Grignard reagents.

Entry[a]	Grignard reagent	Substrate; Reaction time	Product; Yield[b]
	m-TolMgBr·LiCl		
1	**32b**	**31b**; 1.5 h	**33j**; 80%
	p-TolMgBr·LiCl		
2	**32c**	**31g**; 2 min	**33k**; 93%
	o-TolMgBr·LiCl		
3	**32d**	**31f**; 45 min	**33l**; 84%
			
4	**32e**	**31f**; 15 min	**33m**; 92%
			
5	**32e**	**31b**; 2 h	**33n**; 66%
			
6	**32f**	**31g**; 5 h	**33o**; 75%
			

7	**32g**	**31b**; 5 min	**33p**; 68%
			
8	**32g**	**31g**; 5 min	**33q**; 90%
			
9	**32h**	**31f**; 5 min	**33r**; 84%
			
10	**32i**	**31b**; 10 min	**33s**; 82%
			
11	**32i**	**31f**; 5 min	**33t**; 87%
			
12	**32j**	**31g**; 5 min	**33u**; 71%
			
13	**32k**	**31f**; 5min	**33v**; 81%
			
14	**32l**	**31g**; 15 min	**3w**; 80%
			
15	**32m**	**31f**; 15 min	**33x**; 84%

16	 **32n**	 **31f**; 5 min	 **33y**; 82%	

(a) The reaction was performed on a 1 mmol scale with 3 mol% of $FeBr_3$ in THF:*t*BuOMe (ca. 2:5) at room temperature. (b) Isolated yield.

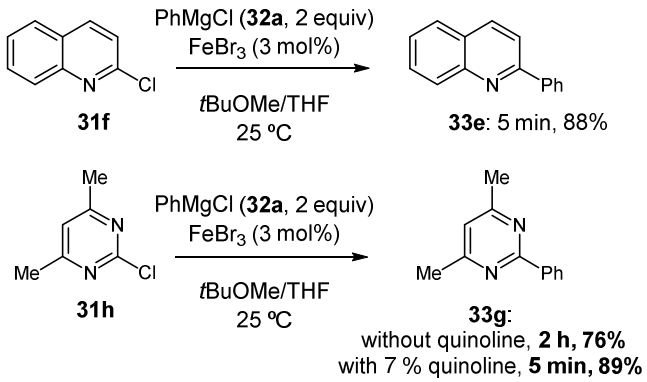
Even though the mechanism of this cross-coupling could not yet be elucidated, we noticed that the use of Fe(II) or Fe(III) salt led to similar results. Reducing the Fe(III)-catalyst *in situ* with *i*PrMgCl prior to cross-coupling, desactivated the catalytic system and hampered the coupling reaction. The use of an apolar co-solvent like *t*BuOMe was found to be vital to achieve high yields mainly by avoiding homo-coupling products.

2.3. Ligand-Accelerated Fe- and Co-Catalyzed Cross-Coupling Reactions between *N*-Heterocyclic Halides and Arylmagnesium Reagents

In Chapter 2.2 one can see that the iron-catalyzed cross-coupling reaction between 2-chloroquinoline (**31f**) and PhMgCl (**32a**) proceeds much faster than the related coupling reaction using 2-chloropyridine (**31a**) as electrophile. Therefore, we were wondering, if the quinoline moiety that is certainly responsible for these fast couplings, could be used as a separate ligand, and if this ligand could accelerate iron-catalyzed cross-coupling reactions of related substrates with arylmagnesium reagents.

The cross-coupling of 2-chloroquinoline (**31f**) with PhMgCl (**32a**) in the presence of 3% $FeBr_3$ in *t*BuOMe:THF is completed at 25 °C in 5 min (producing the phenylated product **33e** in 88% yield; Scheme 29), the cross-coupling of the 2-chloropyrimidine **31h** under the same reaction conditions requires 2 h for completion and provides the arylated pyrimidine **33g** in 76% yield. However, carrying out the same reaction in the presence of 7 mol% quinoline leads to a reaction completion within 5 min (ca. 50 times faster reaction!) and an increased yield of **33g** (89% isolated yield, Scheme 29).

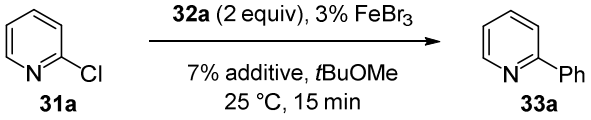
Prompted by these results, a ligand-screening was undertaken. NMP and TMEDA that have been traditionally used for Fe-catalysis had a detrimental effect under our conditions (compare entries 1-4 of Table 10). We systematically examined substituted quinolines. Erosion of the rate enhancement occurs when a methyl group is attached to either the 2- or 8-position (entries 5 and 6), and only a slight improvement can be seen when a methyl group is



Scheme 29. Rate acceleration and improved yield of Fe-catalyzed cross-couplings in the presence of quinoline.

placed at position 6 (entry 7). Benzo[*h*]quinoline and acridine led even to a decrease in yield (entries 8 and 9). Electron-donating groups have a positive effect while electron-withdrawing groups decrease the catalytic activity of the quinoline core (compare entries 10-14). Finally, it was discovered that isoquinoline gave the best results with a 92% yield after 15 min (entry 15). 1-Methyl isoquinoline had a similar catalytic activity as isoquinoline, but surprisingly, electron-rich 1-benzyl-6,7-dimethoxyisoquinoline performed very poorly (compare entries 16 and 17). Two nitrogen-containing heterocycles hindered the reaction (entries 18 and 19).

Table 10: Screening of different additives for Fe-catalyzed cross-coupling reaction of 2-chloropyridine (**31a**) with PhMgCl (**32a**).



Entry	Additive	Yield of 33a (%)[a]
1	without additive	40
2	quinoline	75
3	NMP	0
4	TMEDA	32
5	2-methylquinoline	67
6	8-methylquinoline	48
7	6-methylquinoline	82
8	benzo[*h*]quinoline	30
9	acridine	32
10	4-methoxyquinoline	73

11	6-methoxyquinoline	82
12	4-((*tert*-butyldimethylsilyl)oxy)quinoline	75
13	6-((*tert*-butyldimethylsilyl)oxy)quinoline	83
14	quinoline-3-carbonitrile	43
15	**isoquinoline**	**92 (89)[b]**
16	1-methylisoquinoline	91
17	1-benzyl-6,7-dimethoxyisoquinoline	28
18	2,9-diphenyl-1,10-phenanthroline	27
19	4-(dimethylamino)pyridine	25
20	styrene	40
21	1-methoxy-3-vinylbenzene	67
22	1-methoxy-4-vinylbenzene	68
23	2-vinylpyridine	37

(a) Yield determined after 15 min by integration of a GC-chromatogram and comparison against undecane as a calibrated internal standard. (b) Isolated yield after purification by flash column chromatography.

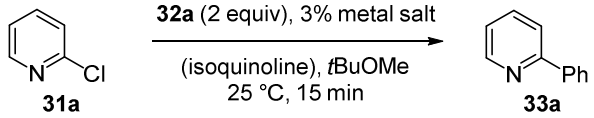
Knochel and coworkers have shown that 4-fluorostyrene promotes Co-catalyzed coupling reactions.[96] However, styrene had no effect (entry 20), and various substituted styrene derivatives caused only a moderate rate enhancement (entries 21-23). Lastly, the amount of isoquinoline was varied from 1-100% and it was found that 10% of the ligand was optimum. It was also noted that isoquinoline (or quinoline) was not consumed during the cross-coupling. With isoquinoline, the ability of other metallic salts to undergo rate-enhanced cross-coupling reactions was tested. In response to the current debate as to whether trace impurities of Cu in commercial samples of Fe salts can be the cause of catalytic activity,[97] $CuBr_2$ was tested and none to minimal activity was found (compare entries 1-2 with 3-4 of Table 11). A mixture of $FeBr_3$ and $CuBr_2$ displayed no synergistic benefit, as the yield was essentially the same as when no Cu is added (entry 5). Vanadium salts also had very little catalytic activity (entries 6-9). But, isoquinoline can also be used as a ligand to enhance the yield of Co-

[96] (a) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79. (b) Rohbogner, C. J.; Diène, C. R.; Korn, T. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 1874.

[97] For the role of metal contaminants in iron catalysis, see: a) Buchwald, S. L.; Bolm, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5586. (b) Larsson, P.-F.; Correa, A.; Carril, M.; Norrby, P.-O.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5691. (c) Thomé, I.; Nijs, A.; Bolm, C. *Chem. Soc. Rev.* **2012**, *41*, 979.

catalyzed reactions (entries 12 and 13).[98] Since both Fe and Co had similar activity, both of these transition metals were utilized, while exploring the scope of this new catalytic system. Using isoquinoline as a ligand (10 mol%), it is possible to obtain the expected cross-coupling products with a variety of chloro- or bromo-substituted pyridines as well as with a fair range of Grignard reagents. Good yields of the substituted pyridines **34a-34h** (65-91%) were obtained especially with electron-rich Grignard reagents (entries 1-6 of Table 12) as well as with electron-poor 4-fluorophenylmagnesium bromide **32g** to give pyridine **34g** (77-79% yield, entry 7). It is possible to couple the polyfunctional pyridine **35h** with the sensitive ester-substituted Grignard compound **32l** to produce pyridine **34h** in 65% yield (entry 8). Often both Co- and Fe-catalyzed couplings proceed with comparable yield, and it is difficult to favour one metallic salt as a superior catalyst for all substrates. Pyrimidines, which are common motifs in pharmaceuticals, can be produced from the same set of Grignard reagents to yield functionalized *N*-heterocycles **34h**-**34n** in 60-95% yield (entries 11-14). Triazines are of great importance as material building blocks and as agrochemicals. This new method allows various chlorotriazines to be cross-coupled with magnesium reagents, leading to the desired products (**34o**-**34r)** in 61-84% yield (entries 15-18).

Table 11: Performance of different transition metals with isoquinoline-promoted cross-coupling reactions.



31a **33a**

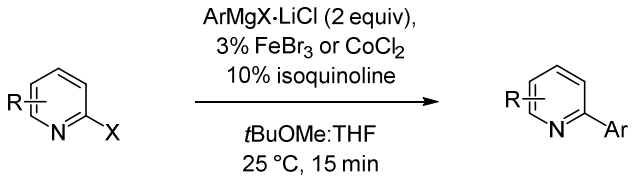
Entry	Metal salt	Isoquinoline (mol%)	Yield of 33a (%)[a]
1	$FeBr_3$	0	40
2	**$FeBr_3$**	**10**	**92 (89)[b]**
3	$CuBr_2$[c]	0	0
4	$CuBr_2$	10	2
5	$FeBr_3$ + $CuBr_2$	10	89
6	VCl_3	0	0

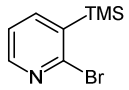
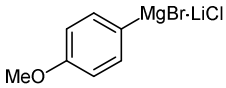
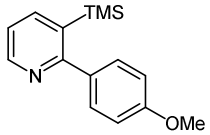
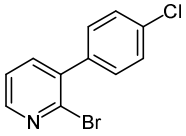
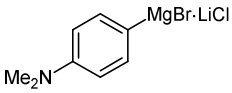
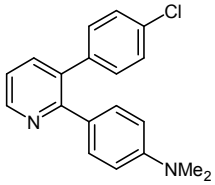
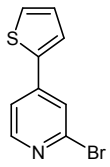
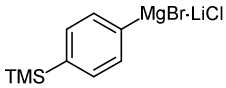
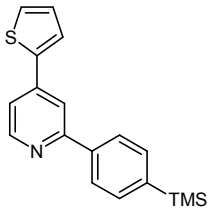
[98] (a) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 1240. (b) Amatore, A.; Gosmini, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 2089. (c) Gosmini, C.; Bégouin, J.-M.; Moncomble, A. *Chem. Commun*. **2008**, 3221. (d) Moncomble, A.; Le Floch, P.; Gosmini, C. *Chem.–Eur. J.* **2009**, 15, 4770. (e) Cahiez, G.; Chaboche, C.; Duplais, C.; Moyeux, A. *Org. Lett.* **2009**, *11*, 277. (f) Murakami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.*, **2009**, *11*, 2373. (g) Gosmini, C.; Moncomble, A. *Isr. J. Chem.* **2010**, *50*, 568. (h) Bégouin, J.-M.; Rivard, M.; Gosmini, C. *Chem. Commun* **2010**, *46*, 5972. (i) Qian, X.; Auffrant, A.; Felouat, A.; Gosmini, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10402. (j) Moncomble, A.; Le Floch, P.; Lledos, A.; Gosmini, C. *J. Org. Chem.* **2012**, *77*, 5056. (k) Nicolas, L.; Angibaud, P.; Stansfield, I.; Bonnet, P.; Meerpoel, L.;Reymond, S.; Cossy, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 11101.

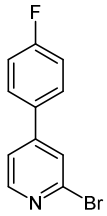
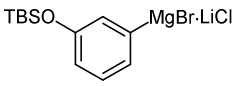
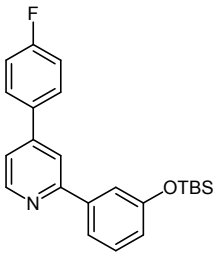
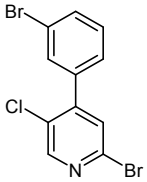
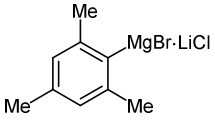
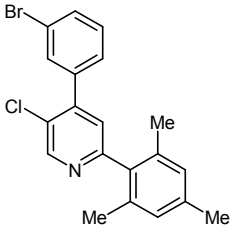
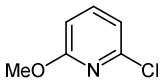
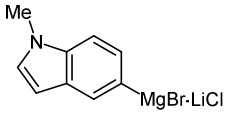
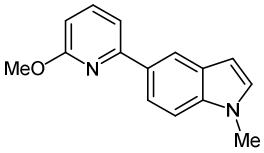
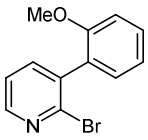
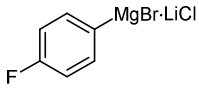
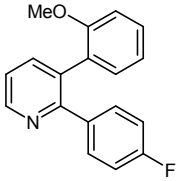
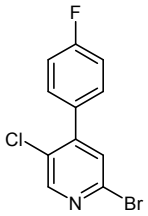
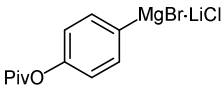
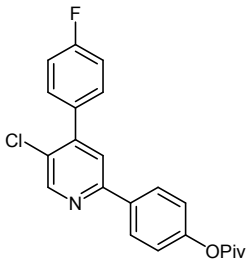
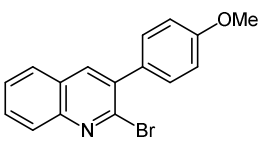
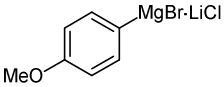
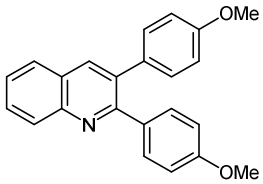
7	VCl_3	10	2
8	VCl_4	0	5
9	VCl_4	10	9
10	$MnCl_2$	0	28
11	$MnCl_2$	10	14
12	$CoCl_2$	0	46
13	**$CoCl_2$**	**10**	**90**

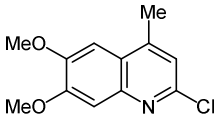
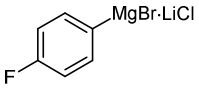
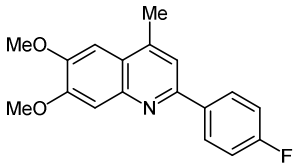
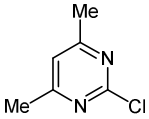
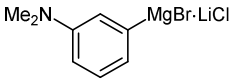
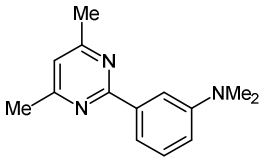
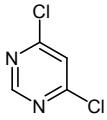
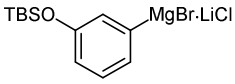
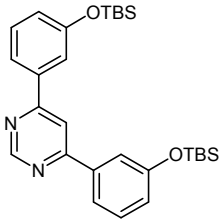
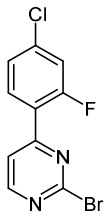
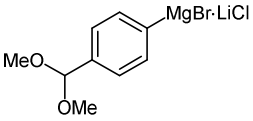
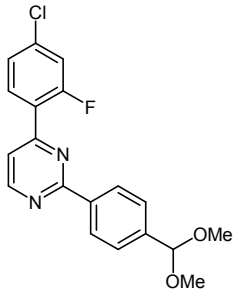
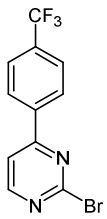
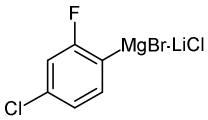
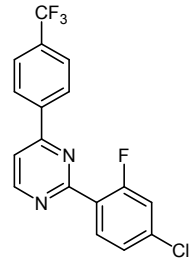
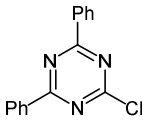
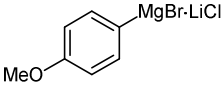
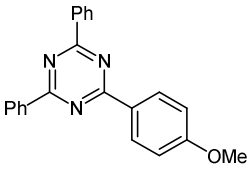
(a) Yield determined after 15 min by integration of a GC-chromatogram and comparison against undecane as a calibrated internal standard. (b) Isolated yield after purification by flash column chromatography. (c) Cu_2O was also used and gave the same results.

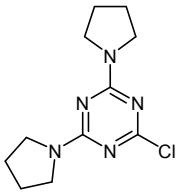
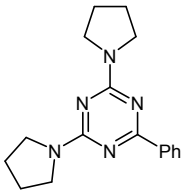
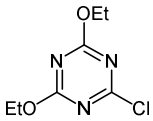
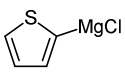
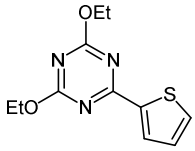
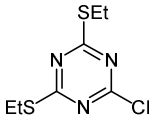
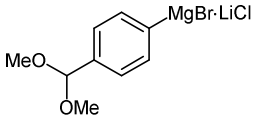
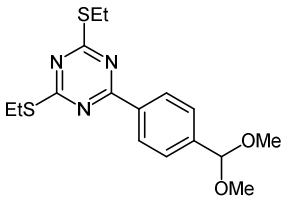
Table 12: Scope of Co- and Fe-catalyzed cross-coupling reactions utilizing isoquinoline as a ligand.



Entry	Starting material	Grignard reagent	Product[a]
1	 **35a**	 **32i**	 **34a**; Fe: 91% Co: 85%
2	 **35b**	 **32n**	 **34b**; Fe: 82% Co: 77%
3	 **35c**	 **32o**	 **34c**; Fe: 65% Co: 70%

4		**35d**		**32p**		**34d**; Fe: 71% Co: 79%
5[b]		**35e**		**32q**		**34e**; Co: 82%
6[c]		**35f**		**32r**		**34f**; Co: 65%
7		**35g**		**32g**		**34g**; Fe: 77% Co: 79%
8		**35h**		**32l**		**34h**; Fe: 65%
9		**35i**		**32i**		**34i**; Co: 78%

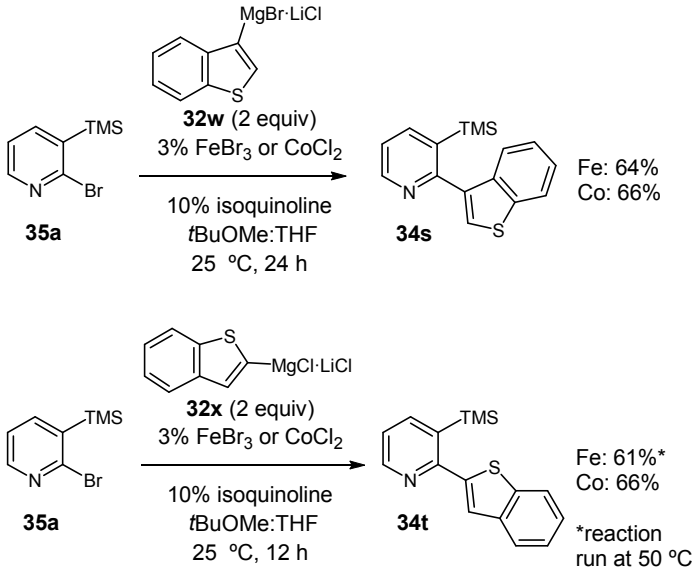
10		**35j**		**32g**		**34j**; Fe: 82% Co: 67%
11[d]		**31h**		**32s**		**34k**; Fe: 78% Co: 63%
12[e]		**35k**		**32p**		**34l**; Fe: 95%
13		**35l**		**32t**		**34m**; Co: 68%
14		**35m**		**32u**		**34n**; Fe: 61% Co: 60%
15		**35n**		**32i**		**34o**; Fe: 81%

			Co: 79%
16[f]	 **35o**	**32a**	 **34p**; Fe: 76%
17[g]	 **35p**	 **32v**	 **34q;** Fe: 84%
			Co: 79%
18	 **35q**	 **32t**	 **34r;** Fe: 61%

(a) Isolated yield after purification by flash column chromatography. (b) Reaction run at 25 °C for 5 h. (c) Reaction run at 25 °C for 1 h. (d) Reaction run at 25 °C for 30 min. (e) 4 equivalents of **32p** were used. (f) Reaction run at 50 °C for 12 h. (g) Reaction run at 25 °C for 12 h.

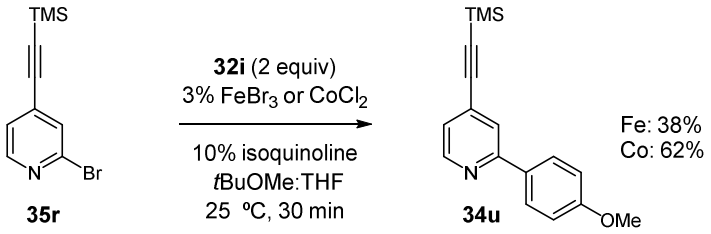
The synthesis of heteroaryl-heteroaryl coupling products is often challenging. In the case of Pd- or Ni-catalysis, deactivation of the catalyst is observed due to chelation of the product with the catalyst.[99] However, it was noted that both Fe- and Co-catalysts promoted by 10% isoquinoline allow smooth cross-couplings with either the 3-magnesiated benzothiophene **32w** or the 2-magnesiated heterocycle **32x** to afford heterobyaryls **34s** and **34t** in 61-66% isolated yield (Scheme 30).

[99] (a) Hanan, G. S.; Schubert, U. S.; Volkmer, D.; Rivière, E.; Lehn, J.-M.; Kyritsakas, N.; Fischer, J. *Can. J. Chem*. **1997**, 75, 169. (b) Kaes, C.; Katz, A.; Hosseini, M. W. *Chem. Rev.* **2000**, *100*, 3553. (c) Bedel, S.; Ulrich, G.; Picard, C.; Tisnès, P. *Synthesis* **2002**, 1564. (d) *Comprehensive Coordination Chemistry II*, Vol 1; McCleverty, J. A.; Meyer, T. J.; Eds.; Elsevier, Oxford, **2004**, 1.



Scheme 30. Heteroaryl-heteroaryl cross-coupling reactions between bromopyridine **35a** and benzothiophene.

Sensitive functional groups such as alkynes, which are prone to undergo carbometallation with Fe-catalysis,[100] gave poor yields of cross-coupling products. However, it was found that the use of 3% $CoCl_2$ and 10% isoquinoline improved the yield and allows the isolation of pyridine **34u** in 62% yield (Scheme 31).



Scheme 31. Cross-coupling reactions of acetylene-containing pyridine **35r**.

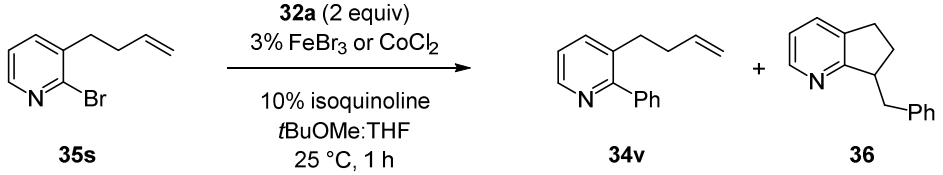
In order to probe the mechanism of Fe- and Co-catalyzed cross-coupling reactions, we have prepared radical clock **35s**.[101] Treatment of this unsaturated pyridine **35s** with PhMgCl (**32a**), using either $FeBr_3$ or $CoCl_2$, produces a 4:1 mixture of the expected cross-coupling product **34v** and the cyclized pyridine **36** indicative of radical intermediates. The addition of

[100] (a) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 621. (b) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15050. (c) Shirakawa, E.; Ikeda, D.; Masui, S.; Yoshida, M.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 272. (d) Ilies, L.; Yoshida, T.; Nakamura, E. *J. Am. Chem. Soc.* **2012**, *134*, 16951.

[101] (a) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374. (b) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886. (c) Manolikakes, G.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 205. (d) Guisán-Ceinos, M.; Tato, F.; Bunuel, E.; Calle, P.; Cárdenas, D. J. *Chem. Sci.* **2013**, *4*, 1098.

isoquinoline did not change the product ratio, but as expected, it improved the yields (compare entries 1-4 of Table 13). These results indicate that both Fe- and Co-catalyzed cross-couplings undergo the radical pathway, at least partially. Interestingly, the corresponding Pd- and Ni-catalyzed cross-couplings, using 3% $Pd(Ph_3P)_4$ or 3% $NiCl_2$(dppe) provided much less, if any, of cyclized products.

Table 13: Cyclization reactions of **35s** indicative for radicals.



35s **34v** **36**

Entry	Catalyst	34v:36	Yield (%)[a]
1	$FeBr_3$	80:20	47
2	$FeBr_3$ /isoquinoline	80:20	62
3	$CoCl_2$	80:20	72
4	$CoCl_2$ /isoquinoline	80:20	78
5[b]	$Pd(Ph_3P)_4$	100:0	64
6	$NiCl_2$(dppe)	95:5	67

(a) Isolated yield after purification by flash column chromatography. (b) Reaction was performed at 50 °C.

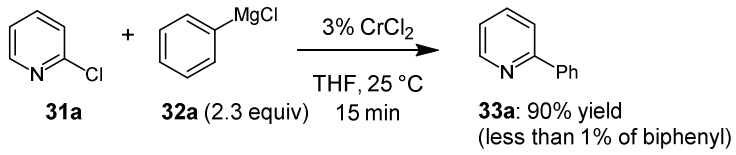
2.4. Chromium(II)-Catalyzed Cross-Coupling Reactions between Csp^2-Centers

In the search for alternative metal catalysts having an acceptable low toxicity, we have examined the potential use of chromium salts.[102] Although Cr^{VI} is highly toxic (ORL-RAT LD_{50} = 50-150 mg/kg), Cr^{II} has a much lower toxicity (ORL-RAT LD_{50} = 1870 mg/kg), also

[102] For key coupling reactions using chromium(II)-salts see: (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Okude, Y.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1977**, 3829. (c) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. (d) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (e) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. (f) Matsubara, S.; Horiuchi, M.; Takai, K.; Utimoto, K. *Chem. Lett.* **1995**, 259. (g) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349. (h) Takai, K.; Matsukawa, N.; Takahashi, A.; Fujii, T. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 152. (i) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (j) Takai, K.; Toshikawa, S.; Inoue, A.; Kokumai, R. *J. Am. Chem. Soc.* **2003**, *125*, 12990. (k) Takai, K.; Toshikawa, S.; Inoue, A.; Kokumai, R.; Hirano, M. *J. Organomet. Chem.* **2007**, *692*, 520. (l) Murakami, K.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1569. (m) Holzwarth, M. S.; Plietker, B. *ChemCatChem* **2013**, *5*, 1650.

compared to other metals: ORL-RAT $LD_{50}(NiCl_2)$ = 105 mg/kg, $(PdCl_2)$ = 2700 mg/kg, $(CoCl_2)$ = 766 mg/kg, $(MnCl_2)$ =1480 mg/kg, $(FeCl_2)$ = 450 mg/kg.[103]

Preliminary experiments showed that chromium-catalyzed cross-couplings between Csp^2-centers proceed quite smoothly and lead to significantly lower amounts of homo-coupling side-products compared to iron or cobalt. Thus, the reaction of 2-chloropyridine (**31a**, 1.0 equiv) with PhMgCl (**32a**, 2.3 equiv) in THF in the presence of 3% $CrCl_2$ (purity 99.99%) is complete within 15 min at 25 °C, affording the desired cross-coupling product **33a** in 90% yield. GC-analysis of the crude reaction mixture indicated that less than 1% of the homo-coupling product (biphenyl) is obtained (Scheme 32). Performing the same reaction with 3% $FeBr_3$ or 3% $CoCl_2$ under optimized conditions leads to about 15% of the homo-coupling product. A solvent screening (THF, *n*-hexane, toluene and *t*BuOMe) showed that THF was the optimal solvent. The optimization of the reagent stoichiometry indicated that only a small excess of Grignard reagent (1.2 equiv) was required. For all subsequent reactions standard grade $CrCl_2$ (purity 97%) was used, since no difference with $CrCl_2$ (purity 99.99%) was observed. Also, performing the cross-coupling with 5% $MnCl_2$ leads, under optimum conditions, to only 58% yield of **33a**[104] compared to 90% yield obtained with 3% $CrCl_2$.



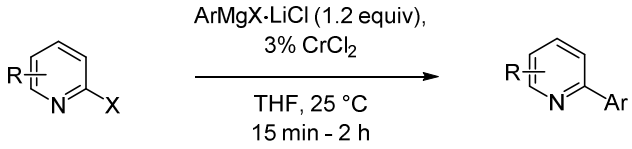
Scheme 32. Chromium-catalyzed cross-coupling between 2-chloropyridine (**31a**) and PhMgCl.

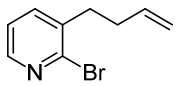
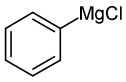
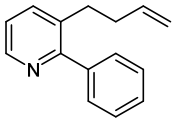
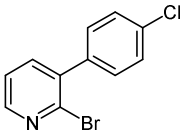
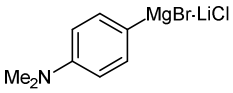
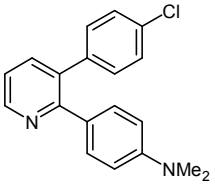
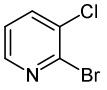
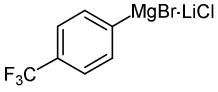
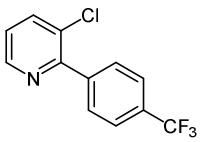
The reaction scope of this new cross-coupling proved to be quite broad. Thus, a range of *N*-heterocyclic chlorides and bromides can be readily used (Table 14). PhMgCl (**32a**) also undergoes a smooth cross-coupling with 2-bromo-3-(but-3-en-1-yl)pyridine (**35s**; 25 °C, 15 min), leading to the 2,3-disubstituted pyridine **34v** in 95% yield (entry 1 of Table 14). Interestingly, no radical cyclization product is observed in this cross-coupling (similar iron and cobalt cross-couplings produce 20% of radical cyclization product). Both electron-rich and electron-poor Grignard reagents can be used for such cross-couplings. Thus, the sterically hindered bromo-pyridine **35b** reacts with 4-*N*,*N*-dimethyl-aminophenylmagnesium bromide (**32n**) within 1.5 h at 25 °C, producing the 2,3-diarylated pyridine **34b** (80% yield; entry 2).

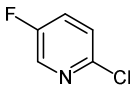
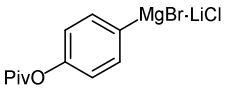
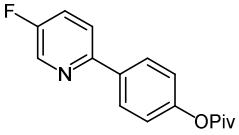
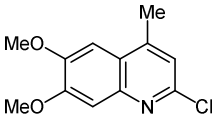
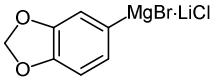
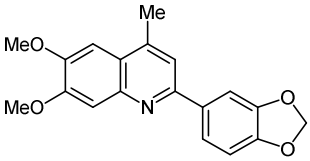
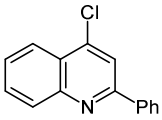
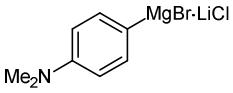
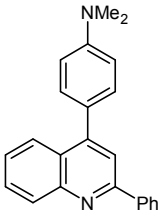
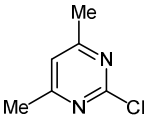
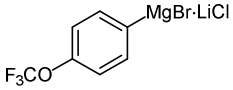
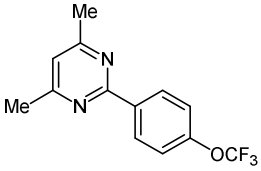
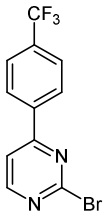
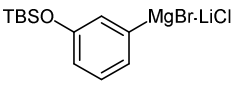
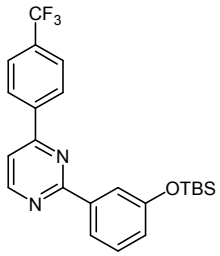
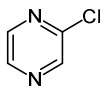
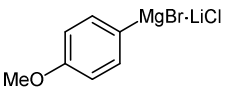
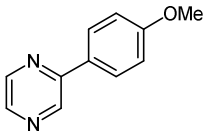
[103] according to IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung; July 2013).
[104] Rueping, M.; Ieawsuwan, W. *Synlett* **2007**, 247.

Also, the electron-poor Grignard reagent **32y** reacts with 2-bromo-3-chloropyridine (**35t**) in 15 min at 25 °C, leading to the pyridine **37a** in 76% yield (entry 3). The similar cross-coupling performed with 3% of $FeBr_3$ gives only traces of product and significant amounts of homo-coupling. 2-Chloro-5-fluoropyridine (**35u**) also undergoes the cross-coupling reaction with the sensitive ester-substituted Grignard reagent **32l** to give the pyridine **37b** in 66% yield (entry 4). Further *N*-heterocyclic halides such as the 2-chloroquinoline **35j** and the 4-chloroquinoline **35v**, react well with Grignard reagents **32k** and **32n**, affording the expected products **37c** and **37d** (74-78%; entries 5 and 6). In contrast, the corresponding iron-catalyzed cross-coupling with the 4-chloroquinoline **35v** fails, indicating that this Cr(II)-catalyzed cross-coupling may have a broader reaction scope than the corresponding Fe- and Co-catalyzed cross-couplings. Halogenated diazenes, such as the 2-chloropyrimidines **31h** and **35m** as well as the 2-chloropyrazine **31j**, rapidly react with the magnesium organometallics **32z**, **32p** and **32i** to provide the substituted diazenes **37e-g** (71-85%; entries 7-9).

Table 14: Room-temperature Cr-catalyzed cross-coupling reactions between *N*-heterocyclic halides and arylmagnesium reagents.

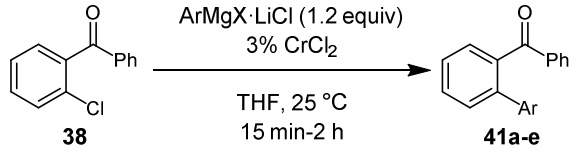


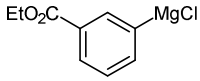
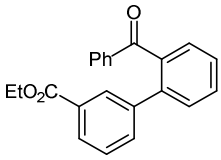
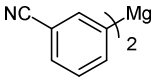
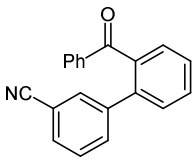
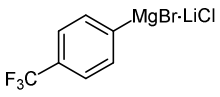
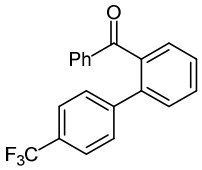
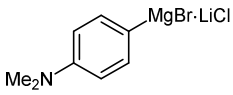
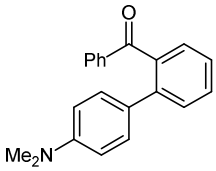
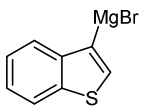
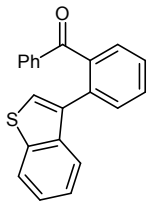
Entry	Starting material	Grignard reagent	Product[a]
1	 **35s**	 **32a**	 **34v**; 95%; 15 min
2	 **35b**	 **32n**	 **34b**; 80%; 90 min
3	 **35t**	 **32y**	 **37a**; 76%; 15 min

4	 **35u**	 **32l**	 **37b**; 66%; 15 min
5	 **35j**	 **32k**	 **37c**; 74%; 1 h
6	 **35v**	 **32n**	 **37d**; 78%; 15 min
7	 **31h**	 **32z**	 **37e**; 71%; 2 h
8	 **35m**	 **32p**	 **37f**; 85%; 15 min
9	 **31j**	 **32i**	 **37g**; 72%; 30 min

(a) Isolated yield after purification by flash column chromatography.

Table 15: Cr-catalyzed cross-coupling reactions between 2-chlorobenzophenone (**38**) and phenylmagnesium reagents.

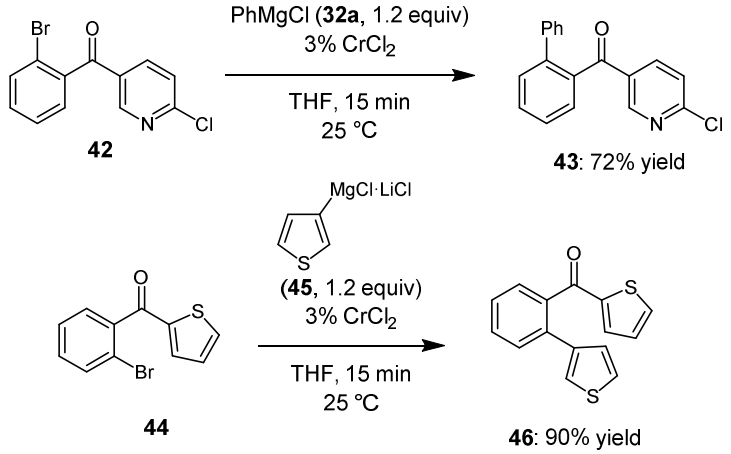


Entry	Grignard reagent	Product	Yield[a]
			
1	**39**	**41a**	79%; 15 min
			
2[b]	**40**	**41b**	71%; 2 h
			
3	**32y**	**41c**	93%; 15 min
			
4	**32n**	**41d**	94%; 15 min
			
5[c]	**32w**	**41e**	89%; 2 h

(a) Isolated yields after purification by flash column chromatography. (b) 0.7 equiv of **40** were used. (c) Reaction run at 50 °C for 2 h.

Remarkably, 2-halogenated aromatic ketones also undergo the chromium-catalyzed cross-coupling at room temperature within 15 min to 2 h (Table 15).[105] Thus, 2-chlorobenzophenone (**38**) reacts with a range of aryl- and heteroaryl-magnesium reagents (**32n**, **32w**, **32y**, **39**, **40**) yielding the corresponding polyfunctional ketones **41a-e** (71-94%; entries 1-5 of Table 15).

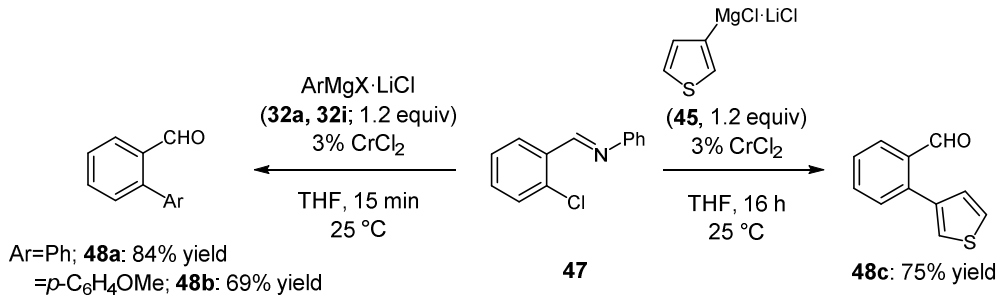
Interestingly, the (2-bromophenyl)(6-chloropyridin-3-yl)-methanone (**42**) reacts with the Grignard reagent **32a** with complete regioselectivity (no chloride-substitution occurs) and gives the pyridyl ketone **43** in 72% yield (Scheme 33). Heterocyclic ketones, such as **44**, also couple well with 3-thienylmagnesium chloride **45** affording the new ketone **46** in 90% yield (Scheme 33). These reactions show a remarkable functional group tolerance, since ester, nitriles and ketones are compatible with this Cr-catalyzed cross-coupling.



Scheme 33. Cr-catalyzed cross-coupling reactions between heteroaryl-substituted ketones and Grignard reagents.

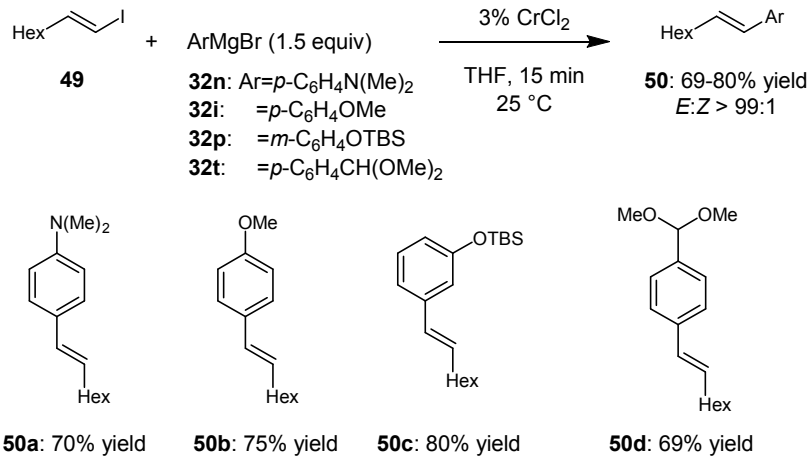
Interestingly, the imine-protected 2-chlorobenzaldehyde **47** reacts readily with various Grignard reagents (**32a**, **32i**, **45**) at 25 °C. Acidic work-up provides the aldehydes **48a-c** in 69-84% yield (Scheme 34). The presence of the sulfur-containing Grignard reagent **45** extends considerably the reaction-rate and 16 h reaction time is required to complete the cross-coupling leading to **48c**. Thus, this cross-coupling constitutes a simple way for functionalizing aromatic aldehydes in the *ortho*-position.

[105] For related Mn-catalyzed reactions see: (a) Cahiez, G.; Lepifre, F.; Ramiandrasoa, P. *Synthesis* **1999**, 2138. (b) Cahiez, G.; Luart, D.; Lecomte, F. *Org. Lett.* **2004**, *6*, 4395.



Scheme 34. Cr-catalyzed cross-coupling reactions between imine-protected aldehyde **47** and Grignard reagents.

Finally, alkenyl iodides, such as **49**, also undergo a fast stereoselective chromium-catalyzed arylation with a range of Grignard reagents (**32i, 32n, 32p, 32t**), affording in all cases the functionalized styrenes **50a-d** in 69-80% yield with an *E*:*Z* ratio better than 99:1. Remarkably, all reactions were performed at 25 °C and were completed within 15 min (Scheme 35).



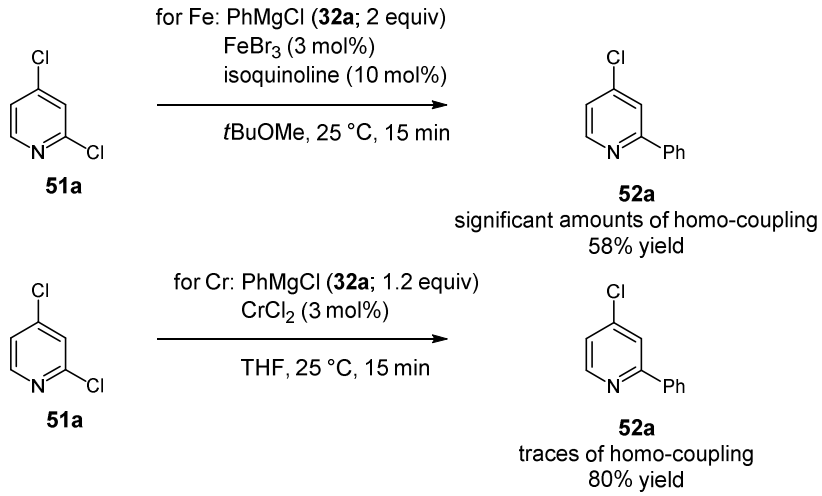
Scheme 35. Cr-catalyzed cross-coupling reactions between alkenyl iodide **49** and Grignard reagents.

2.5. Regio- and Chemoselective Chromium(II)-Catalyzed Cross-Coupling Reactions of Dihalogenated Heteroaromatics with Aromatic Grignard Reagents

After having found that unexpectedly $CrCl_2$ catalyzes very efficiently the coupling-reaction between *N*-heterocyclic chlorides and (hetero)aromatic Grignard reagents with only traces of homo-coupling by-products, we aimed to expand the scope of this cross-coupling reaction. *Malhotra* reported in 2013 an iron-catalyzed chemoselective sp^2-sp^3 cross-coupling involving

alkylmagnesium reagents.[106] As the pharmaceutical industry is searching for cheap, efficient and nonhazardous ways to form aryl-aryl bonds chemoselectively, the potential to perform regio- and chemoselective Cr(II)-catalyzed cross-couplings of dihalogenated *N*-heterocycles with aromatic Grignard reagents should be investigated.

Preliminary results showed that the coupling reaction of 2,4-dichloropyridine (**51a**) with PhMgCl (**32a**), using our optimized isoquinoline-accelerated Fe-protocol, led to an exclusive formation of the 2-arylated product **52a** in 58% isolated yield (see Scheme 36). In comparison, the related chromium(II) chloride catalyzed reaction using less equivalents of **32a** (1.2 instead of 2 equiv) furnished regioselectively the same coupling product **52a** in much higher yield (80% instead of 58% isolated yield). Also, only trace amounts of homo-coupling resulting from the Grignard reagent were detected using $CrCl_2$ as catalyst.

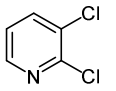
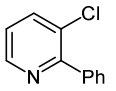
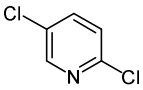
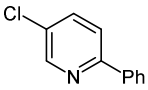
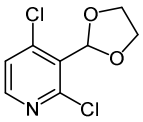
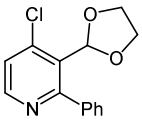
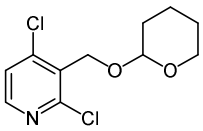
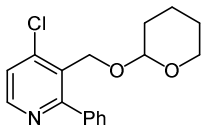


Scheme 36. Comparison of $FeBr_3$ and $CrCl_2$ in catalyzed regioselective cross-coupling reactions of 2,4-dichloropyridine (**51a**) with PhMgCl (**32a**).

The scope of this regioselective chromium-catalyzed cross-coupling was examined next. It was found, that a range of dichloro-*N*-heterocycles can be phenylated at 25 °C within 0.5 h. Thus, 2,3-dichloropyridine (**51b**) as well as 2,5-dichloropyridine (**51c**) react within minutes with **32a** to produce regioselectively the 2-arylated products **52b** (76% yield, entry 1 of Table 16) and **52c** (87% yield, entry 2). The sterically more demanding acetal-protected 2,4-dichloropyridines **51d-e** react within 30 min with **32a** to furnish the products **52d-e** in isolated yields of 67% and 76% respectively (entries 3-4).

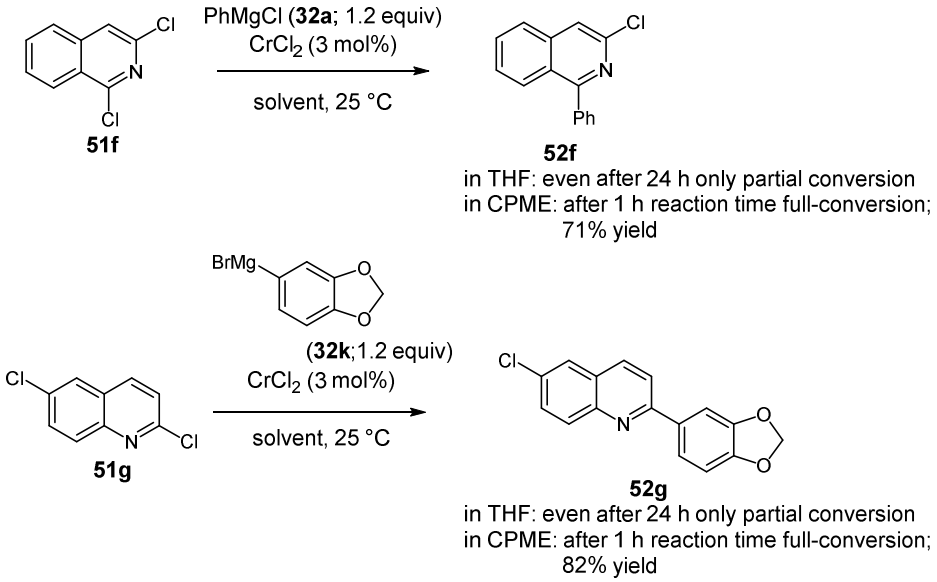
[106] Malhotra, S.; Seng, P. S.; Koenig, S. G.; Deese, A. J.; Ford, K. A. *Org. Lett.* **2013**, *15*, 3698.

Table 16: Regioselective Csp^2-Csp^2 cross-coupling reactions between dichlorinated pyridines **51b**-**e** and PhMgCl (**32a**).

Entry	Substrate	Product	Reaction time	Yield[a]
1	 **51b**	 **52b**	15 min	76%
2	 **51c**	 **52c**	15 min	87%
3	 **51d**	 **52d**	30 min	67%
4	 **51e**	 **52e**	30 min	76%

(a) Isolated yields after purification by flash column chromatography.

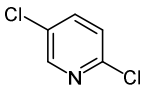
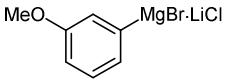
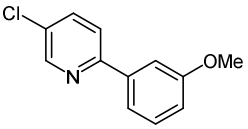
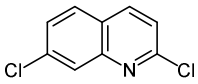
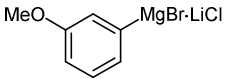
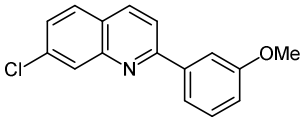
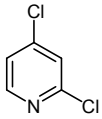
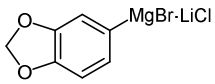
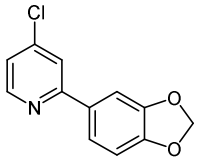
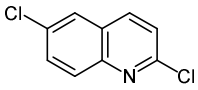
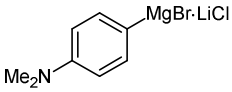
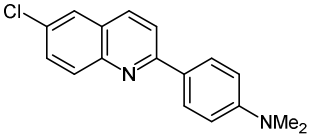
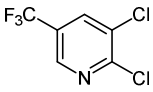
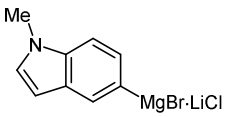
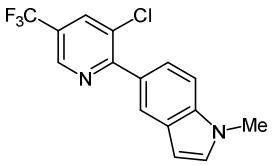
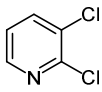
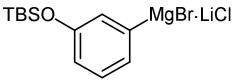
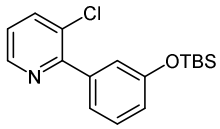
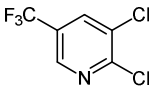
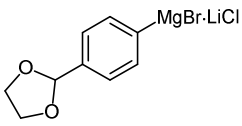
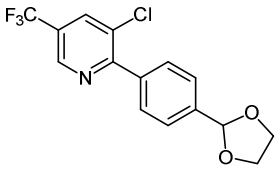
Next, $CrCl_2$-catalyzed biaryl formations on 1,3-dichloroisoquinoline **51f** and 2,6-dichloroquinoline **51g** (see Scheme 37) were investigated. Using the standard protocol in THF resulted in low conversions of starting material to desired coupling product. Thus, **51f** reacts with **32a** at position 1, but no complete conversion could be reached. A careful solvent screening revealed that CPME (cyclopentyl methyl ether) leads to much higher conversions in this $CrCl_2$-catalyzed cross-coupling reaction. The desired coupling product **52f** was obtained in 71% yield after only 1 h reaction time at room temperature, using 3 mol% of $CrCl_2$ in CPME as solvent. An analog behavior is observed in the regioselective coupling reaction between **51g** and Grignard reagent **32k**. Whereas in THF, only low conversion is observed, in CPME full-conversion is reached after 1 h at room temperature, furnishing the 2-arylated compound **52g** in 82% yield (Scheme 37).

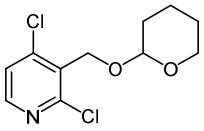
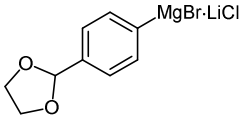
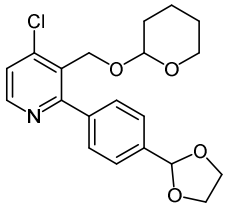
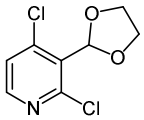
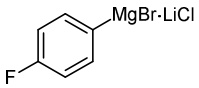
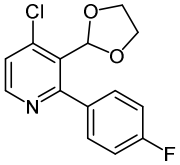
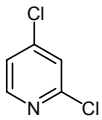
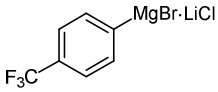
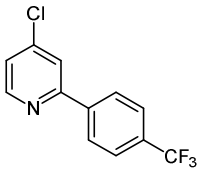
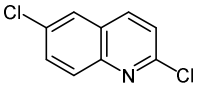
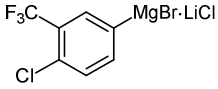
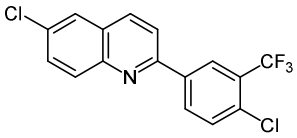
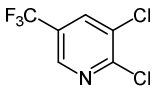
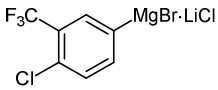
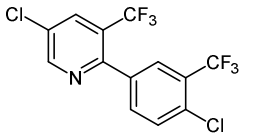
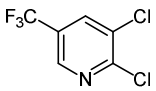
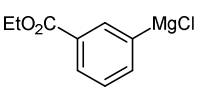
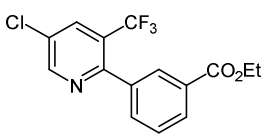


Scheme 37. Rate-acceleration in Cr(II)-catalyzed cross-couplings of isoquinoline **51f** and quinoline **51g** with aromatic Grignard reagents using CPME as solvent.

Subsequently, various aromatic Grignard reagents were prepared and used in chromium(II) chloride catalyzed chemoselective cross-coupling reactions with various dichlorinated *N*-heterocycles (see Table 17). Electron-rich Grignard reagents, like (3-methoxyphenyl)magnesium bromide (**53**), the methylenedioxy-arylmagnesium bromide **32k** or 4-(dimethylamino)phenyl magnesium bromide (**32n**) reacted smoothly with dihalogenated pyridines **51a** and **51c**, as well as with quinolines **51g** and **51h**. The coupling products **52h-k** were all obtained in good yields (71-77%, entries 1-4) in a complete regioselective manner. 5-Magnesiated indole **32r** reacts with 2,3-dichloro-5-(trifluoromethyl)pyridine (**51i**) within 1 h to furnish the 2-arylated coupling product **52l** in 56% yield (entry 5). TBS-protected 3-hydroxyphenylmagnesium bromide (**32p**) and the acetal-substituted arylmagnesium derivative **54** undergo the $CrCl_2$-catalyzed cross-coupling reaction with dichlorinated pyridines **51b**, **51e** and **51i** regioselectively in position 2 in yields from 66-82% (entries 6-8). Also electron-poor Grignard reagents reacted smootly in this cross-coupling reaction. E.g. 4-fluorophenylmagnesium bromide (**32g**) or 4-(trifluoromethyl)phenylmagnesium bromide (**32y**) undergo fast couplings with pyridines **51a** or **51d** to produce the substituted heterocycles **52p** (79% yield, entry 9) and **52q** (92% yield, entry 10). Even the electron-poor chloro-substituted Grignard reagent **55** can be coupled with quinoline **51g** and trifluoromethylated 2,3-dichloropyridine **51i** to furnish **52r** and **52s** (entries 11-12). For the first time, the sensitive ester-substituted aromatic Grignard reagent **39** can perform well in $CrCl_2$-catalyzed cross-couplings with *N*-heterocyclic halides (entry 13).

Table 17: Chemoselective Csp^2-Csp^2 cross-coupling reactions between dichlorinated heterocycles and various Grignard reagents.

Entry	Starting material	Grignard reagent	Product[a]
1	 **51c**	 **53**	 **52h**; 71%; 30 min
2	 **51h**	 **53**	 **52i**; 72%; 2 h
3	 **51a**	 **32k**	 **52j**; 77%; 15 min
4	 **51g**	 **32n**	 **52k**; 71%; 3 h
5	 **51i**	 **32r**	 **52l**; 56%; 1 h
6	 **51b**	 **32p**	 **52m**; 82%; 15 min
7	 **51i**	 **54**	 **52n**; 71%; 15 min

			
8	**51e**	**54**	**52o**; 66%; 30 min
			
9	**51d**	**32g**	**52p**; 79%; 30 min
			
10	**51a**	**32y**	**52q;** 92%; 30 min
			
11	**51g**	**55**	**52r;** 87%; 1 h
			
12	**51i**	**55**	**52s;** 66%; 30 min
			
13	**51i**	**39**	**52t;** 70%; 15 min

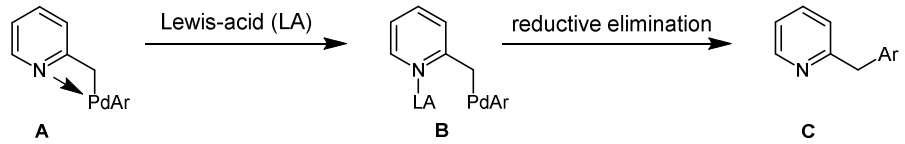
(a) Isolated yield after purification by flash column chromatography.

3. Summary and Outlook

3.1. Lewis-Acid Promoted Benzylic Cross-Couplings of Pyridines with Aryl Bromides

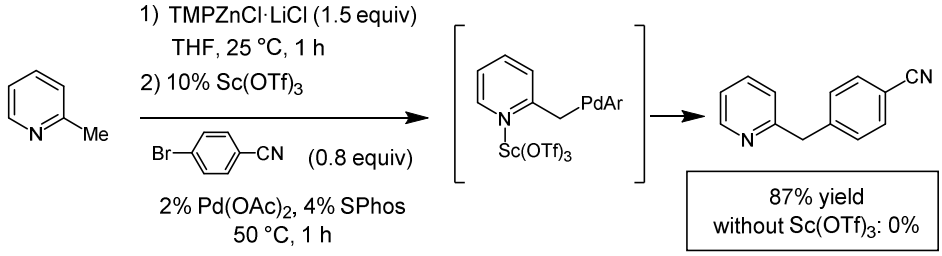
In this work, the direct benzylic metalation of various methylpyridines was developed using various TMP-bases. Subsequent cross-coupling reactions with the resulting benzylic metalated heterocycles were performed. In general, Pd-catalyzed cross-couplings with these laterally metalated methylpyridines are difficult due to the high stability of the Pd-

intermediates of type **A** which are reluctant to undergo reductive elimination due to chelate stabilization. A general solution to this problem was found by the addition of a Lewis-acid (LA) which competitively complexes the heterocyclic nitrogen leading to the tentative intermediate **B**. This facilitates the reductive elimination leading to the arylated product **C** in good yields (Scheme 38).



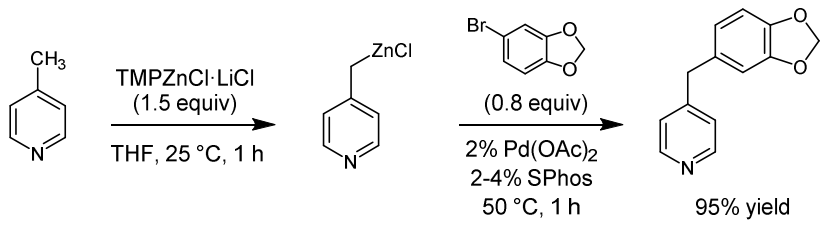
Scheme 38. Positive effect of Lewis-acids in benzylic cross-coupling reactions of methylpyridines.

Although $ZnCl_2$ is in most cases an effective Lewis-acid, for electron-deficient aryl bromides, the use of catalytic amounts of $Sc(OTf)_3$ (10 mol%) leads by far to the best results. Under these Lewis-acid assisted conditions, a general method for the arylation of various methyl-substituted pyridines and related heterocycles was established (Scheme 39).



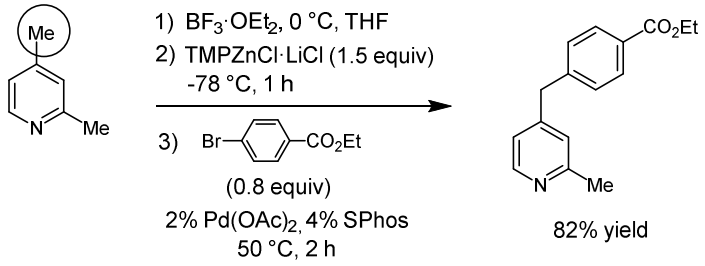
Scheme 39. Efficient arylation of 2-picoline promoted by $Sc(OTf)_3$.

Furthermore, it was shown for the first time, that 4-picoline can be metalated efficiently with TMPZnCl·LiCl in benzylic position. Subsequent *Negishi* cross-coupling reactions furnish several benzylic arylated 4-picoline derivatives (Scheme 40).



Scheme 40. First arylation of 4-picoline.

It was also found that a Lewis-acid such as $BF_3 \cdot OEt_2$ promotes highly regioselective metalations in the case of 2,4-lutidine (Scheme 41).

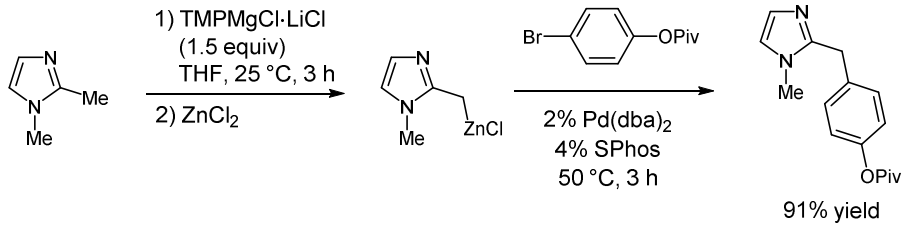


Scheme 41. $BF_3 \cdot OEt_2$ promoted regioselective zincation of 2,4-lutidine.

3.2. Benzylic Arylation of 2-Methyl-5-Membered Heterocycles using TMP-Bases

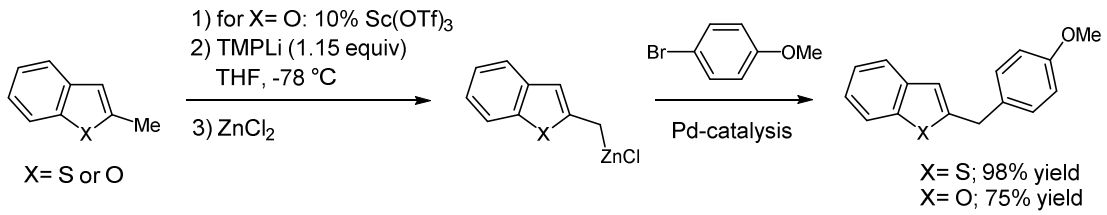
So far, the arylation of methyl-substituted 5-membered heterocycles has been an unsolved problem. For example, no benzylic C-H activation followed by cross-coupling has been reported for 1,2-dimethylimidazole and only alkylation reactions have been performed successfully after initial deprotonation with *n*-butyllithium. Furthermore, no benzylic metalation and subsequent arylation of 2-methylbenzothiophenes and 2-methylbenzofurans has been described. In this work, it was shown that such a direct benzylic arylation can be performed on various methyl-substituted 5-membered heterocycles using TMP-bases and subsequent *Negishi* cross-coupling reactions.

Thus, 1,2-dimethylimidazole can be metalated selectively at the 2-methyl position using the mild magnesium base TMPMgCl·LiCl. Subsequent transmetalation with $ZnCl_2$ and palladium catalyzed cross-coupling reaction with various aryl bromides yields 2-benzylated imidazoles in high yields (Scheme 42).



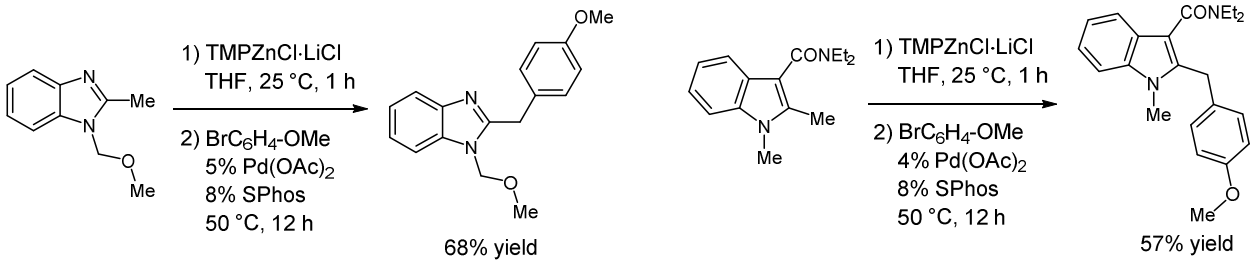
Scheme 42. Efficient arylation of 1,2-dimethylimidazole.

Efforts were made to extend this method to even less acidic methyl-substituted 5-membered heterocycles. It was found that 2-methylbenzothiophene and 2-methylbenzofuran is readily metalated with TMPLi. After treatment with $ZnCl_2$, the resulting heterocyclic benzylic reagent was smoothly arylated with aryl bromides under palladium catalysis (Scheme 43).



Scheme 43. Benzylic arylation of 2-methylbenzothiophene and 2-methylbenzofuran.

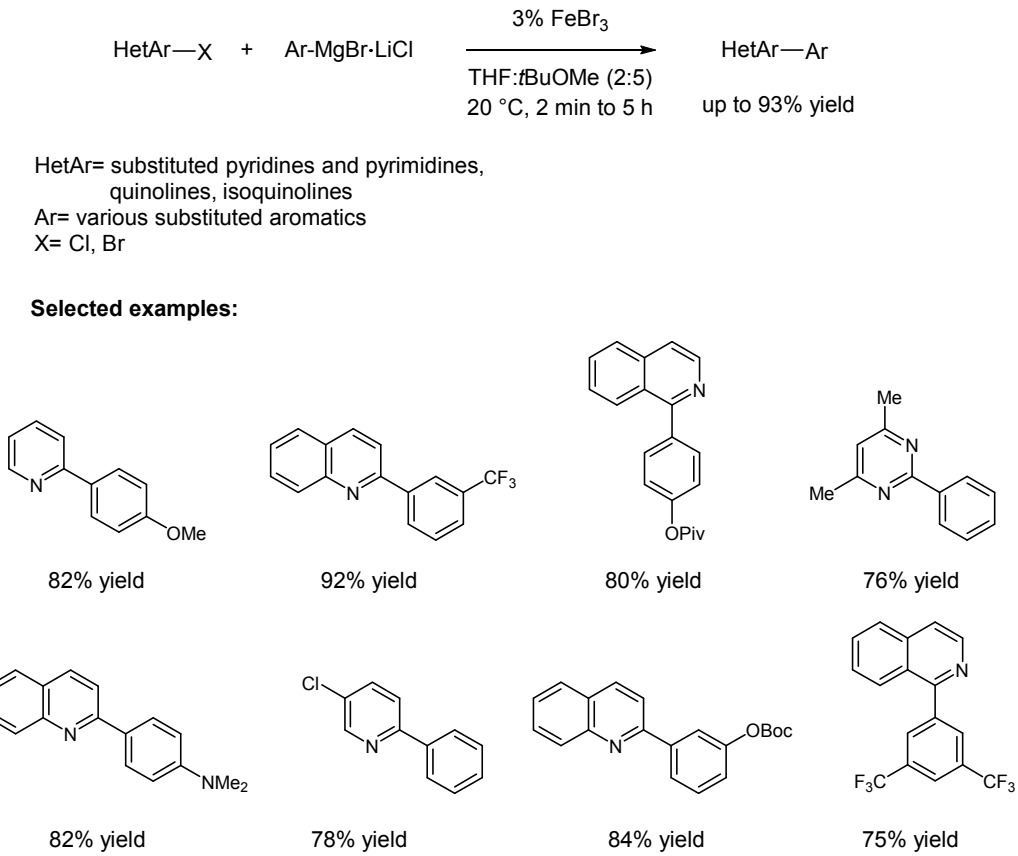
The generality of this approach is demonstrated by performing the arylation of other related 5-membered heterocycles such as 2-methyl-indole and 2-methylbenzimidazole. In these cases, the mild and selective zinc base TMPZnCl·LiCl was sufficient for benzylic zincation (Scheme 44).



Scheme 44. Benzylic cross-coupling of protected 2-methylbenzimidazole and a 2-methylindole.

3.3. Iron-Catalyzed Cross-Coupling of *N*-Heterocyclic Chlorides and Bromides with Arylmagnesium Reagents Using *t*BuOMe as Solvent

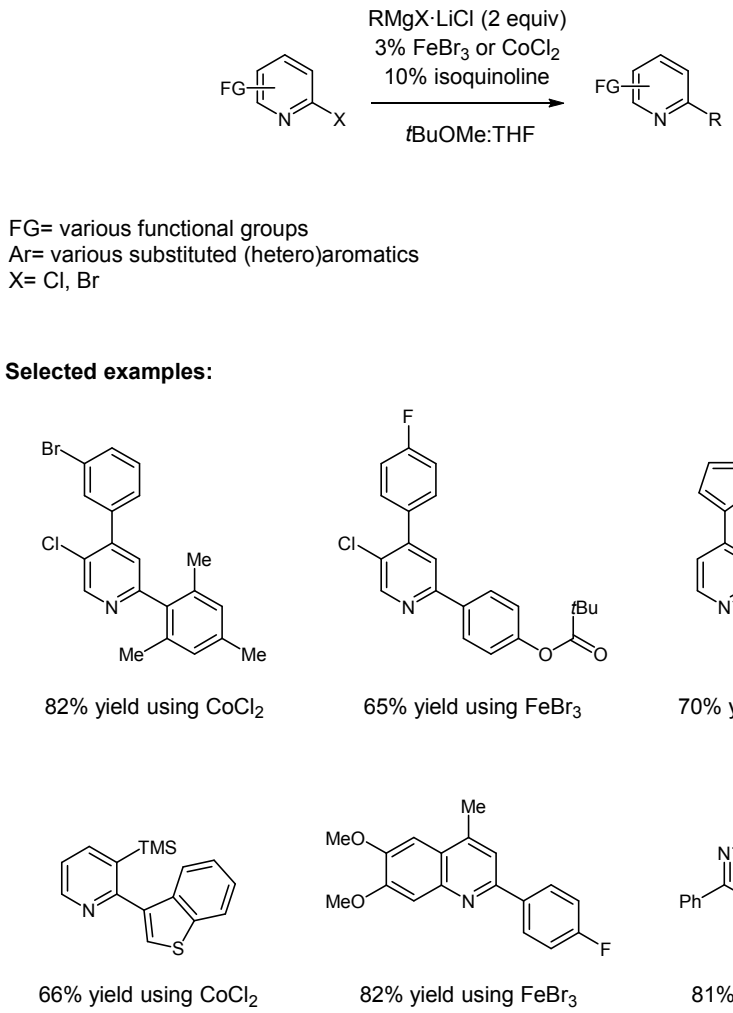
An extension to previously described iron-catalyzed cross-coupling reactions between aromatic halides and aromatic Grignard reagents has been achieved. It was found that apolar ethereal solvents like *t*BuOMe suppress significantly the undesired formation of homo-coupling by-products that result from the Grignard reagent. A wide range of functionalized Grignard reagents was prepared using direct magnesium insertion into the aromatic C-Br bond, and was cross-coupled with various *N*-heterocyclic halides in the presence of 3% $FeBr_3$ in a THF/*t*BuOMe solvent mixture (Scheme 45).



Scheme 45. Fe-catalyzed Csp^2-Csp^2 coupling reactions in *t*BuOMe as solvent.

3.4. Ligand-Accelerated Fe- and Co-Catalyzed Cross-Coupling Reactions between *N*-Heterocyclic Halides and Arylmagnesium Reagents

Iron- as well as cobalt-catalyzed cross-coupling reactions between *N*-heterocyclic halides and aromatic Grignard reagents were optimized by the addition of isoquinoline as practical ligand. It was found that isoquinoline can accelerate significantly these cross-coupling reactions and is able to suppress the formation of homo-coupling side-products. Furthermore, the scope of such coupling reactions was extended to heterocyclic Grignard reagents that reacted previously in lower efficiency (Scheme 46).



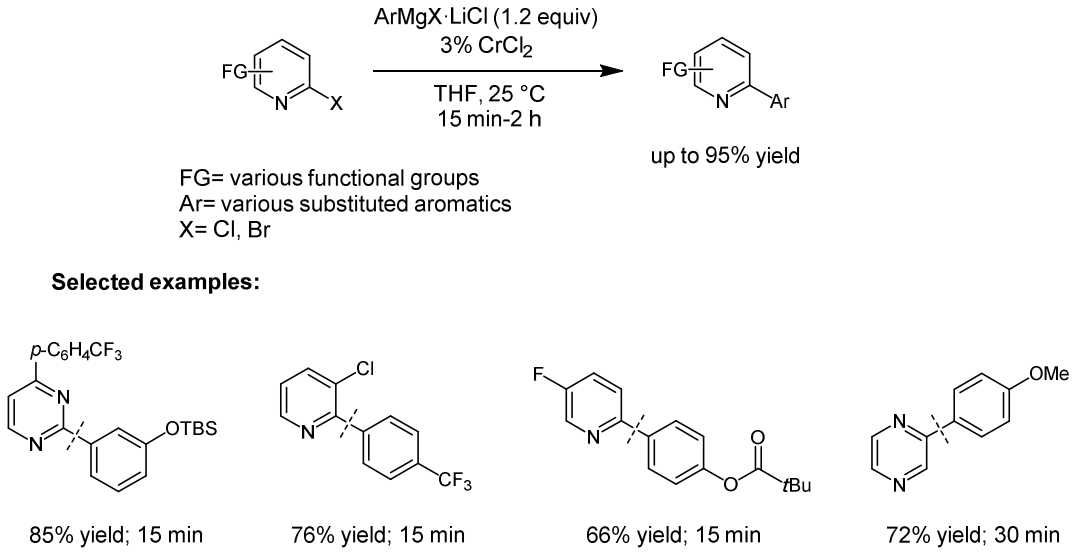
Scheme 46. Ligand-accelerated Fe- and Co-catalyzed cross-coupling reactions.

Future work could focus on optimizing this ligand system. Preliminary results indicate that more electron-rich quinolines and isoquinolines lead to even faster reactions between *N*-heterocyclic halides and (hetero)aromatic Grignard reagents. Future extensions could involve coupling reactions with non-activated aromatic halides instead of *N*-heterocyclic halides.

3.5. Chromium(II)-Catalyzed Cross-Coupling Reactions between Csp^2-Centers

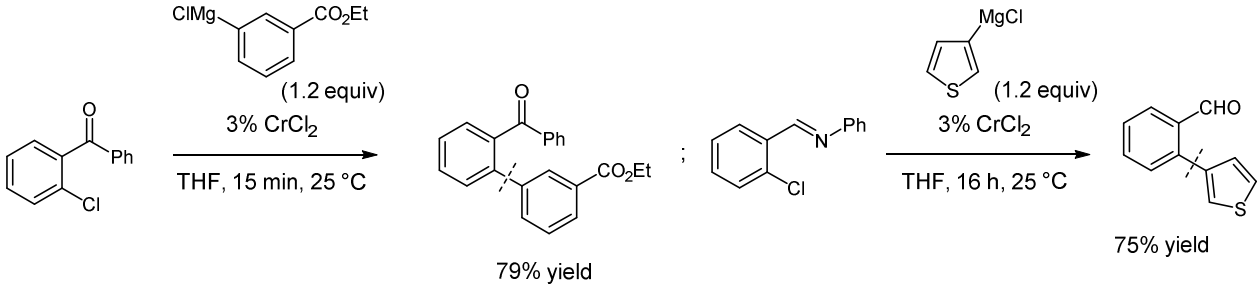
Against common wisdom, toxicological data indicate that $CrCl_2$ is a chromium-salt of low toxicity, compared to other commonly used salts like $PdCl_2$, $NiCl_2$ or even $CoCl_2$. Therefore $CrCl_2$ is sold as a low-toxic chemical by major international suppliers. In this work it was shown, that unexpectedly $CrCl_2$ can undergo very efficiently aryl-aryl cross-coupling reactions between a range of aromatic halides and aromatic Grignard reagents, using a very simple procedure. No ligand or additive is required for coupling reactions to proceed at room temperature in the presence of $CrCl_2$ with THF as solvent. Using this novel methodology,

various unsymmetrical biaryls are formed from *N*-heterocyclic halides and aromatic Grignard reagents (Scheme 47).



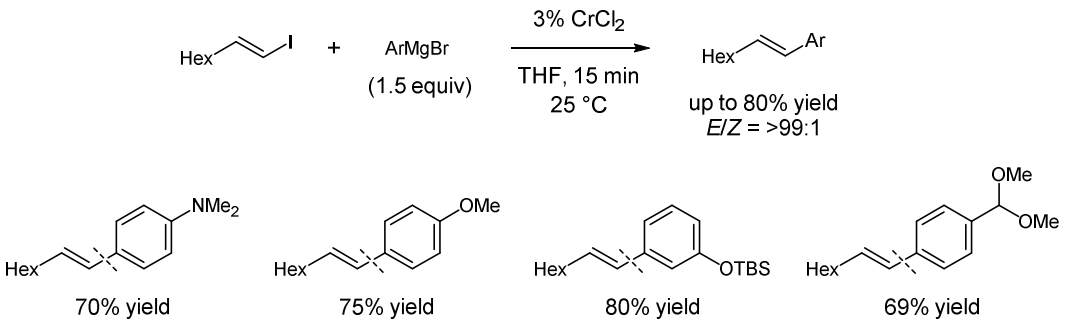
Scheme 47. $CrCl_2$-catalyzed cross-coupling reactions between *N*-heterocyclic halides and aromatic Grignard reagents.

It was found that also aromatic chloro-and bromo-ketones as well as chloro-imines react smoothly under these $CrCl_2$-catalyzed conditions (Scheme 48).



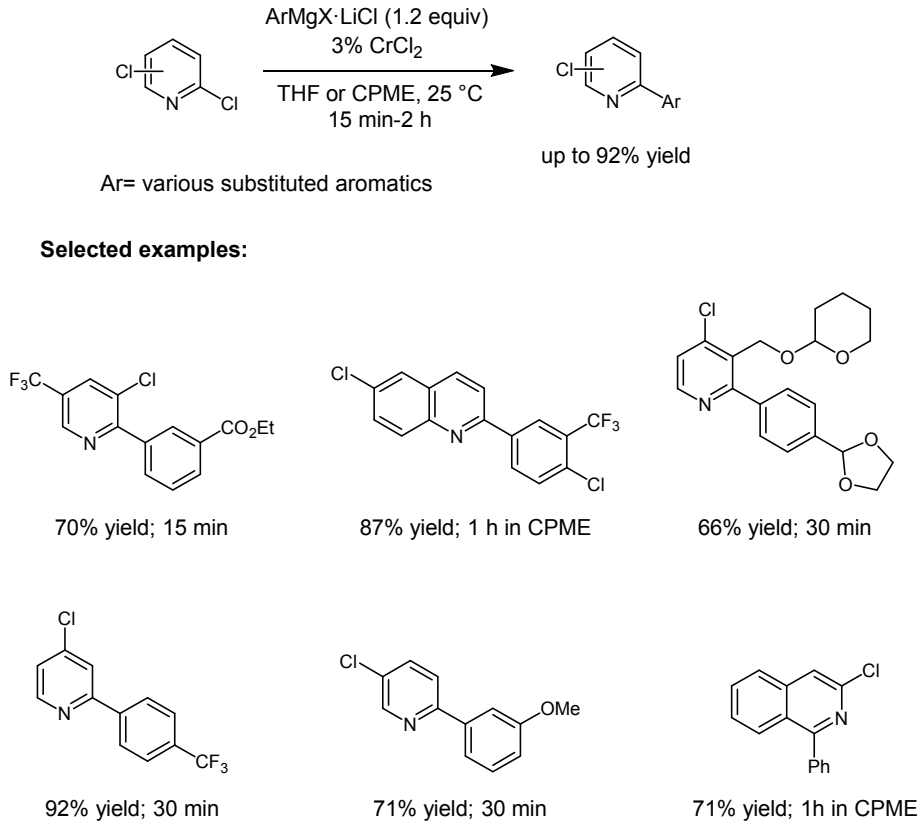
Scheme 48. $CrCl_2$-catalyzed coupling reactions of aromatic chloro-ketones and chloro-imines.

Furthermore, also alkenyliodides are able to undergo $CrCl_2$-catalyzed coupling reactions with aromatic Grignard reagents in a stereoselective manner (Scheme 49).



Scheme 49. *E*-Alkenyl iodides undergo stereoselective Cr(II)-catalyzed cross-couplings.

This chromium-catalysis protocol was also applied to regio- and chemoselective cross-coupling reactions of dihalogenated heteroaromatics with aromatic Grignard reagents. Similar coupling reactions of more electron-rich dihalogenated quinolines or isoquinolines proceed much faster in CPME than in THF (Scheme 50).



Scheme 50. Regio- and chemoselective $CrCl_2$-catalyzed Csp^2-Csp^2 coupling reactions.

After having made the unexpected discovery that $CrCl_2$ can serve as a catalyst in cross-coupling reactions, future work could focus on extending the scope of chromium-catalysis to other potential reactions like aminations, C-H activations and carbometalation reactions.

C. Experimental Section

1. General Considerations

All reactions were carried out with magnetic stirring and, if the reagents were air or moisture sensitive, in flame-dried glassware under argon. Syringes which were used to transfer reagents and solvents were purged with argon prior to use.

1.1. Solvents

Solvents were dried according to standard procedures by distillation over drying agents and stored under argon.

***t*BuOMe** was predried over $CaCl_2$ and distilled from CaH_2.

CPME was predried over $CaCl_2$ and distilled from CaH_2.

Et_2O was predried over calcium hydride and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

Hexane was predried over $CaCl_2$ and distilled from CaH_2.

NEP was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

NMP was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Toluene was predried over $CaCl_2$ and distilled from CaH_2.

Solvents for column chromatography were distilled prior to use.

1.2. Reagents

All reagents were obtained from commercial sources and used without further purification unless otherwise stated. Following compounds were prepared according to literature procedures: compound **27**,[91] compound **44**,[107] compound **47**[108] and compound **49**.[109]

$BF_3 \cdot OEt_2$ was distilled under Ar prior to use.

***n*BuLi** solution in hexane was purchased from Rockwood Lithium GmbH.

***i*PrMgCl·LiCl** solution in THF was purchased from Rockwood Lithium GmbH.

PhMgCl solution in THF was purchased from Rockwood Lithium GmbH.

TMPH was distilled under Ar prior to use.

TMPLi was prepared in the following way:

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[107] Sui, Y.-Z.; Zhang, X.-C.; Wu, J.-W.; Li, S.; Zhou, J.-N.; Li, M.; Fang, W.; Chan, A. S. C.; Wu, J. *Chem. Eur. J.* **2012**, *18*, 7486.
[108] da Silva-Filho, L. C.; Lacerda Júnior, V.; Gomes Constantino, M.; da Silva, G. V. J. *Synthesis* **2008**, 2527.
[109] Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004**, *6*, 4215.

A dry and argon flushed 250 mL *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with freshly distilled TMPH (10.2 mL, 60 mmol) dissolved in THF (60 mL). This solution was cooled to -40 °C and *n*BuLi (2.4 M in hexane, 25 mL, 60 mmol) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm up slowly to -10 °C for 1 h. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved. The freshly prepared TMPLi solution was titrated prior to use at -10 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of ca. 1.0 M in THF was obtained. TMPLi is stored at -78 °C under an argon atmosphere.

TMPMgCl·LiCl was prepared in the following way:

A dry and argon flushed 250 mL flask, equipped with a magnetic stirrer and a septum, was charged with freshly titrated *i*PrMgCl·LiCl (100 mL, 1.2 M in THF, 120 mmol). TMPH (19.8 g, 126 mmol, 1.05 equiv) was added dropwise at room temperature. The reaction mixture was stirred at r.t. until gas evolution was completed (ca. 48 h). The freshly prepared TMPMgCl·LiCl solution was titrated prior to use at 25 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of ca. 1.1 M in THF was obtained.

TMPZnCl·LiCl was prepared in the following way:

A dry and argon flushed 250 mL *Schlenk*-flask, equipped with a magnetic stirrer and a septum, was charged with freshly distilled TMPH (10.2 mL, 60 mmol) dissolved in THF (60 mL). This solution was cooled to -40 °C and *n*BuLi (2.4 M in hexane, 25 mL, 60 mmol) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm up slowly to -10 °C for 1 h. $ZnCl_2$ (1.0 M in THF, 66 mL, 66 mmol) was added dropwise and the resulting solution was stirred for 30 min at -10 °C and then for 30 min at 25 °C. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved. The freshly prepared TMPZnCl·LiCl solution was titrated prior to use at 25 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of about 1.3 M in THF was obtained.

$ZnCl_2$ solution (1.0 M) was prepared by drying $ZnCl_2$ (100 mmol, 13,6 g) in a *Schlenk*-flask under vacuum at 140 °C for 5 h. After cooling, 100 mL dry THF were added and stirring was continued until the salt was dissolved.

1.3. Content Determination of Organometallic Reagents

Organzinc and organomagnesium reagents were titrated against I_2 in THF.

Organolithium reagents were titrated against menthol using 1,10-phenanthroline as indicator in THF.

TMPLi, **TMPMgCl·LiCl** and **TMPZnCl·LiCl** were titrated against benzoic acid using 4-(phenylazo)diphenylamine as indicator in THF.

1.4. Chromatography

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from Merck.

Thin layer chromatography was performed using SiO_2 pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined under UV light at 254 nm and/or by staining of the TLC plate with one of the solutions given below followed by heating with a heat gun:

- $KMnO_4$ (3.0 g), 5 drops of conc. H_2SO_4 in water (300 mL).
- Phosphomolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12 mL) in water (230 mL).

1.5. Analytical Data

NMR spectra were recorded on VARIAN Mercury 200, BRUKER AXR 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to the residual solvent peak of $CHCl_3$ (δ_H: 7.25, δ_C: 77.0). For the characterization of the observed signal multiplicities the following appreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet) as well as br (broad).

Mass spectroscopy: High resolution (HRMS) and low resolution (MS) spectra were recorded on a FINNIGAN MAT 95Q instrument. Electron impact ionization (EI) was conducted with an electron energy of 70 eV.

For the combination of gas chromatography with mass spectroscopic detection, a GC/MS from Hewlett-Packard HP 6890 / MSD 5973 was used.

Infrared spectra (IR) were recorded from 4500 cm^{-1} to 650 cm^{-1} on a PERKIN ELMER Spectrum BX-59343 instrument. For detection a SMITHS DETECTION DuraSampl*IR* II Diamond ATR sensor was used. The absorption bands are reported in wavenumbers (cm^{-1})

Melting points (M.p.) were determined on a BÜCHI B-540 apparatus and are uncorrected.

2. Typical Procedures (TP)

2.1. Typical Procedure for the Metalation of Methylpyridines and Related *N*-Heterocycles with TMPZnCl·LiCl (7) (TP1).

In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, the respective methylpyridine (1.00 equiv) was dissolved in dry THF (2 mL). Then, TMPZnCl·LiCl (**7**; 1.5 equiv) was added dropwise and the reaction mixture was stirred at the desired temperature for 10 min. The completion of the zincation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

2.2. Typical Procedure for Fe-Catalyzed Cross-Coupling Reactions of *N*-Heterocyclic Chlorides and Bromides with Arylmagnesium Reagents Using tBuOMe as Solvent (TP2).

In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, the appropriate halogenated *N*-heterocycle (1.0 mmol, 1.0 equiv.) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL). Then, the appropriate Grignard reagent (2.3 mmol, 2.3 equiv) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture. When the conversion was complete it was quenched with brine or with a mixture of aqueous saturated solution of NH_4Cl and ammonia (10:1) and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained after purification by flash chromatography.

2.3. Typical Procedure for Fe- or Co-Catalyzed Cross-Coupling Reactions with Isoquinoline (TP3).

A solution of the appropriate Grignard reagent (concentration in THF varying depending on the identity of the Grignard reagent, 1.0 mmol, 2.0 equiv) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and the aryl halide (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for the indicated time before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to yield the crude compound, which was purified by column chromatography to yield the final compound as an analytically pure substance.

2.4. Typical Procedure for Cr-Catalyzed Cross-Coupling Reactions between Aryl Halides and Aromatic Grignard Reagents (TP4).

A solution of the appropriate Grignard reagent (concentration in THF varying depending on the nature of the Grignard reagent, 1.2 mmol, 1.2 equiv) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv.; 97% purity) and the aryl halide (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for the indicated time before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield the final compound as an analytically pure substance.

2.5. Typical Procedure for Cr-Catalyzed Cross-Coupling Reactions with Imine 47 (TP5).

A solution of the appropriate Grignard reagent (concentration in THF varying depending on the nature of the Grignard reagent, 1.2 mmol, 1.2 equiv) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and imine **47** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for the indicated time before being quenched with an aq. solution of HCl (2M) and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield the final compound as an analytically pure substance.

2.6. Typical Procedure for Cr-Catalyzed Cross-Coupling Reactions with Alkenyl Iodide 49 (TP6).

A solution of the appropriate Grignard reagent (concentration in THF varying depending on the nature of the Grignard reagent, 1.5 mmol, 1.5 equiv) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and alkenyl iodide **49** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for the indicated time before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield the final compound as an analytically pure substance.

2.7. Typical Procedure for Cr-Catalyzed Regio- and Chemoselective Cross-Coupling Reactions in THF as Solvent (TP7).

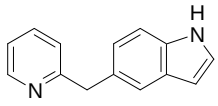
A solution of the appropriate Grignard reagent (concentration in THF varying depending on the nature of the Grignard reagent, 1.2 mmol, 1.2 equiv) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and the dihalogenated halide (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for the indicated time before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield the final compound as an analytically pure substance.

2.8. Typical Procedure for Cr-Catalyzed Regio- and Chemoselective Cross-Coupling Reactions in CPME as Solvent (TP8).

A solution of the appropriate Grignard reagent (concentration in THF varying depending on the nature of the Grignard reagent, 1.2 mmol, 1.2 equiv) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and the dihalogenated halide (1 mmol, 1.0 equiv) in CPME (5 mL) at 25 °C. The suspension was stirred at 25 °C for the indicated time before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield the final compound as an analytically pure substance.

3. Benzylic Cross-Coupling of Pyridines with Aryl Bromides

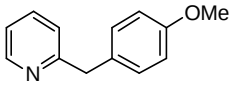
Synthesis of 5-(pyridine-2-ylmethyl)-1*H*-indole (6a):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 2.00 mL, 2.60 mmol) was added to a solution of 2-methylpyridine (**1a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 5-bromoindole (**9a**: 196 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 7 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 3:2) furnished 5-(pyridine-2-ylmethyl)-1*H*-indole (**6a**: 180 mg, 86%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.58 (d, *J* = 4.89 Hz, 1H), 8.22 (s, 1H), 7.57 (dt, *J* = 7.62, 1.88 Hz, 1H), 7.57-7.56 (m, 1H), 7.35 (d, *J* = 8.69 Hz, 1H), 7.21 (t, *J* = 2.96 Hz, 1H), 7.16-7.09 (m, 3H), 6.53-6.51 (m, 1H), 4.29 (s, 2H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 162.1, 149.1, 136.5, 134.7, 130.8, 128.2, 124.4, 123.5, 123.1, 121.0, 120.9, 111.1, 102.5, 44.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3114, 3097, 3028, 2852, 2361, 1739, 1592, 1474, 1344, 1218, 1138, 1093, 998, 889, 793, 755, 736, 655.
MS (EI, 70 eV): *m/z* (%) = 208 (M^+, 70), 207 (100), 130 (48), 127 (18), 44 (62).
HRMS for $C_{14}H_{12}N_2$: calc.: 208.1000; found: 208.0933 (M^+).

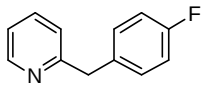
Synthesis of 2-(4-methoxybenzyl)pyridine (6b):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylpyridine (**1a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**9b**: 187 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 7:3) furnished 2-(4-methoxybenzyl)pyridine (**6b**: 190 mg, 95%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.52 (dd, *J* = 5.80, 1.92 Hz, 1H), 7.54 (dt, *J* = 7.49, 2.02 Hz, 1H), 7.16 (d, *J* = 8.76 Hz, 2H), 7.07 (d, *J* = 7.49 Hz, 2H), 6.83 (d, *J* = 8.76 Hz, 2H), 4.08 (s, 2H), 3.76 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 161.4, 158.2, 149.3, 136.5, 131.6, 130.1, 123.0, 121.1, 114.0, 55.2, 43.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3004, 2951, 2931, 2833, 1737, 1609, 1587, 1508, 1470, 1433, 1300, 1243, 1175, 1032, 993, 850, 841, 805, 781, 748, 725.
MS (EI, 70 eV): *m/z* (%) = 199 (M^+, 57), 198 (100), 184 (52), 167 (12), 156 (15), 121 (15).
HRMS for $C_{13}H_{13}NO$: calc.: 199.0997; found: 199.0975 (M^+).

Synthesis of 2-(4-fluorobenzyl)pyridine (6c):

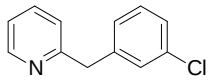


TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylpyridine (**1a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-4-fluorobenzene (**9c**: 175 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 6 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by

flash-chromatography (*i*-hexane/ether, 4:1) furnished 2-(4-fluorobenzyl)pyridine (**6c**: 147 mg, 78%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.55 (dd, *J* = 4.63, 1.92 Hz, 1H), 7.58 (dt, *J* = 7.82, 2.02 Hz, 1H), 7.22 (dd, *J* = 8.68, 5.57 Hz, 2H), 7.13-7.09 (m, 2H), 6.98 (d, *J* = 8.68, 5.57 Hz, 2H), 4.12 (s, 2H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 161.5 ($^1J_{C-F}$ = 253.4 Hz), 160.8, 149.4, 136.6, 135.2, 130.4 ($^3J_{C-F}$ = 7.9 Hz), 123.0, 121.3, 115.3 ($^2J_{C-F}$ = 21.4 Hz), 43.8.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 3008, 2924, 2362, 1892, 1738, 1600, 1588, 1570, 1506, 1472, 1434, 1298, 1098, 994, 846, 790, 748, 628.
MS (EI, 70 eV): *m/z* (%) = 187 (M^+, 22), 186 (100), 109 (8), 93 (10), 83 (8).
HRMS for $C_{12}H_{10}FN$: calc.: 187.0797; found: 187.0742 (M^+).

Synthesis of 2-(3-chlorobenzyl)pyridine (6d):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylpyridine (**1a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-3-chlorobenzene (**9d**: 191 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 6 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 7:3) furnished 2-(3-chlorobenzyl)pyridine (**6d**: 134 mg, 66%) as a slightly yellow oil.

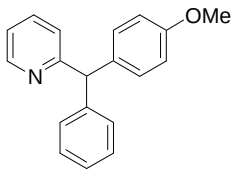
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.58 (ddd, *J* = 4.88, 1.86, 0.91 Hz, 1H), 7.61 (dt, *J* = 7.39, 2.02 Hz, 1H), 7.28-7.12 (m, 6H), 4.14 (s, 2H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 160.1, 149.5, 141.5, 136.6, 134.3, 129.8, 129.2, 127.3, 126.6, 123.1, 121.5, 44.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 2924, 1737, 1668, 1588, 1568, 1471, 1428, 1303, 1077, 994, 865, 775, 769, 694, 681.

MS (EI, 70 eV): *m/z* (%) = 203 (M^+, 22), 202 (100), 167 (71), 139 (4), 84 (11).

HRMS for $C_{12}H_{10}ClN$: calc.: 203.0502; found: 203.0471 (M^+).

Synthesis of 2-((4-methoxyphenyl)(phenyl)methyl)pyridine (6e):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-(benzyl)pyridine (**1b**: 220 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**9b**: 187 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 20 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 7:3) furnished 2-((4-methoxyphenyl)(phenyl)methyl)-pyridine (**6e**: 272 mg, 99%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.62 (ddd, *J* = 4.88, 1.86, 0.95 Hz, 1H), 7.62 (dt, *J* = 7.76, 1.97 Hz, 1H), 7.34-7.05 (m, 9H), 6.86 (dt, *J* = 8.78, 2.98 Hz, 2H), 5.67 (s, 1H), 3.80 (s, 3H).

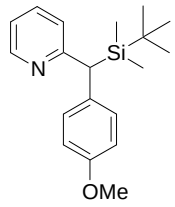
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 163.6, 158.2, 149.5, 143.1, 136.4, 135.0, 130.3, 129.3, 128.6, 126.4, 123.7, 121.3, 113.8, 58.6, 55.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3004, 2951, 2931, 2876 1737, 1609, 1587, 1504, 1465, 1427, 1300, 1241, 1177, 1032, 993, 850, 841, 805, 781, 748, 725.

MS (EI, 70 eV): *m/z* (%) = 275 (M^+, 100), 260 (31), 243 (8), 230 (12), 197 (32), 167 (23), 153 (23).

HRMS for $C_{19}H_{17}NO$: calc.: 275.1310; found: 275.1305 (M^+).

Synthesis of 2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)methyl)pyridine (6f):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-(*tert*-butyldimethylsilyl)pyridine (**1c**: 269 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**9b**: 187 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 11 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 95:5) furnished 2-((*tert*-butyldimethylsilyl)(4-methoxyphenyl)methyl)pyridine (**6f**: 288 mg, 92%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.55 (ddd, *J* = 4.89, 1.92, 0.91 Hz, 1H), 7.47 (dt, *J* = 7.58, 2.03 Hz, 1H), 7.42 (dt, *J* = 8.66, 2.15 Hz, 2H), 7.16 (dt, *J* = 7.76, 2.07 Hz, 1H), 6.98 (ddd, *J* = 7.52, 4.85, 1.18 Hz, 1H), 6.80 (dt, *J* = 8.66, 2.15 Hz, 2H), 3.78 (s, 4H), 0.72 (s, 9H), 0.05 (s, 6H).

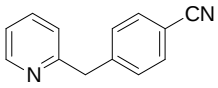
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 163.6, 157.4, 148.9, 135.9, 134.2, 129.9, 123.2, 120.0, 113.5, 55.2, 45.0, 27.0, 17.8, -6.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2948, 2927, 2852, 1583, 1504, 1465, 1427, 1240, 1181, 1031, 869, 857, 824, 807, 778, 692.

MS (EI, 70 eV): *m/z* (%) = 313 (M^+, 14), 298 (9), 256 (100), 242 (10), 225 (23), 212 (11), 198 (10), 182 (11), 167 (13), 154 (8), 120 (3), 73 (42).

HRMS for $C_{19}H_{27}NOSi$: calc.: 313.1862; found: 313.1855 (M^+).

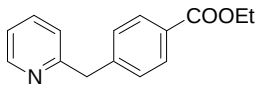
Synthesis of 4-(pyridin-2-ylmethyl)benzonitrile (6g):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylpyridine (**1a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Sc(OTf)_3$ (64 mg, 0.13 mmol, 0.10 equiv) was added at 25 °C. After being stirred for 15 min, $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromobenzonitrile (**9j**: 183 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 4-(pyridin-2-ylmethyl)benzonitrile (**6g**: 170 mg, 87%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.58 (ddd, *J* = 4.84, 1.86, 0.81 Hz, 1H), 7.65 (dt, *J* = 7.77, 1.77 Hz, 1H), 7.60 (dt, *J* = 8.55, 2.06 Hz, 2H), 7.39 (dt, *J* = 8.55, 2.06 Hz, 2H), 7.21-7.14 (m, 2H), 4.22 (s, 2H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 159.2, 149.6, 145.0, 136.9, 132.3, 129.8, 123.3, 121.8, 118.9, 110.4, 44.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3061, 3044, 3005, 2932, 2226, 1737, 1670, 1585, 1504, 1470, 1433, 1310, 1153, 1048, 994, 865, 809, 774, 749, 691.
MS (EI, 70 eV): *m/z* (%) = 194 (M^+, 23), 193 (100), 166 (4), 140 (2), 89 (3).
HRMS (ESI) for $C_{13}H_{10}N_2$: calc.: 195.0922; found: 195.0916 ($[M+H]^+$).

Synthesis of ethyl 4-(pyridin-2-ylmethyl)benzoate (6h):

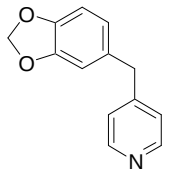


TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-methylpyridine (**1a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Sc(OTf)_3$ (64 mg, 0.13 mmol, 0.10 equiv) was added at 25 °C. After being stirred for 15 min, $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and ethyl 4-bromobenzoate (**9k**: 227 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at

50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished ethyl 4-(pyridin-2-ylmethyl)benzoate (**6h**: 206 mg, 85%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.57 (d, *J* = 5.13 Hz, 1H), 8.00 (d, *J* = 8.62 Hz, 2H), 7.61 (dt, *J* = 7.71, 1.94 Hz, 1H), 7.35 (d, *J* = 8.62 Hz, 2H), 7.18-7.11 (m, 2H), 4.38 (q, *J* = 7.10 Hz, 2H), 4.23 (s, 2H), 1.39 (t, *J* = 7.10 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 166.5, 160.0, 149.5, 144.7, 136.7, 129.9, 129.1, 128.7, 123.2, 121.5, 60.8, 44.6, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2904, 1710, 1709, 1585, 1472, 1434, 1415, 1366, 1270, 1176, 1100, 1020, 752, 702.
MS (EI, 70 eV): *m/z* (%) = 241 (M^+, 32), 240 (100), 212 (26), 196 (15), 167 (41).
HRMS (ESI) for $C_{15}H_{15}NO_2$: calc.: 242.1181; found: 242.1175 ($[M+H]^+$).

Synthesis of 4-(benzo[*d*][1,3]dioxol-5-ylmethyl)pyridine (10a):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**2a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 5-bromobenzo[1,3]dioxol (**9e**: 199 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (CH_2Cl_2/MeOH, 99:1) furnished 4-(benzo[*d*][1,3]dioxol-5-ylmethyl)pyridine (**10a**: 203 mg, 95%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.51 (d, *J* = 6.06 Hz, 2H), 7.11 (d, *J* = 6.06 Hz, 2H), 6.78 (d, *J* = 8.45 Hz, 1H), 6.68-6.65 (m, 2H), 5.95 (s, 2H), 3.89 (s, 2H).

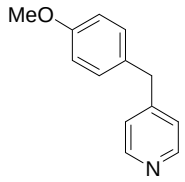
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 150.1, 149.9, 147.9, 146.3, 132.6, 124.0, 122.0, 109.4, 108.4, 101.0, 40.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 3024, 2982, 2854, 1596, 1485, 1440, 1413, 1244, 1186, 1109, 1033, 925, 868, 814, 799, 767, 728, 713.

MS (EI, 70 eV): *m/z* (%) = 213 (M^+, 100), 183 (17), 154 (22), 135 (36), 127 (10), 77 (11).

HRMS for $C_{13}H_{11}NO_2$: calc.: 213.0790; found: 213.0784 (M^+).

Synthesis of 4-(4-methoxybenzyl)pyridine (10b):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**2a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OCOCF_3)_2$ (12 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**9b**: 187 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 4-(4-methoxybenzyl)pyridine (**10b**: 195 mg, 98%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.50 (d, *J* = 5.53 Hz, 2H), 7.13-7.08 (m, 4H), 6.88 (dt, *J* = 8.71, 3.05 Hz, 2H), 3.98 (s, 2H), 3.81 (s, 3H).

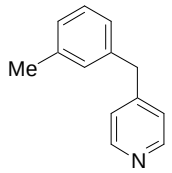
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 158.4, 150.5, 149.8, 130.9, 130.0, 124.1, 114.1, 55.3, 40.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3065, 3027, 2954, 2907, 2834, 1737, 1598, 1509, 1413, 1245, 1176, 1152, 1107, 1030, 993, 796, 759.

MS (EI, 70 eV): *m/z* (%) = 199 (M^+, 100), 184 (23), 168 (17), 154 (11), 121 (54).

HRMS for $C_{13}H_{13}NO$: calc.: 199.0997; found: 199.0977 (M^+).

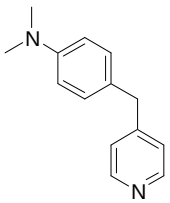
Synthesis of 4-(3-methylbenzyl)pyridine (10c):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**2a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-3-methylbenzene (**9f**: 169 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1 then 2:3) furnished 4-(3-methylbenzyl)pyridine (**10c**: 150 mg, 82%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.52 (d, *J* = 5.53 Hz, 2H), 7.25-6.97 (m, 6H), 3.95 (s, 2H), 2.35 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 150.1, 149.8, 138.8, 138.4, 129.8, 128.6, 127.4, 126.0, 124.2, 41.2, 21.4.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3023, 2920, 2854, 1737, 1720, 1597, 1558, 1490, 1413, 1284, 1247, 1217, 1110, 993, 800, 778, 750, 698.
MS (EI, 70 eV): *m/z* (%) = 183 (M^+, 100), 168 (58), 152 (4), 141 (5), 128 (4), 115 (5), 105 (6), 91 (7).
HRMS for $C_{13}H_{13}N$: calc.: 183.1048; found: 183.1047 (M^+).

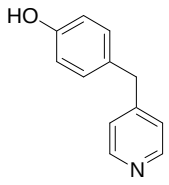
Synthesis of *N*,*N*-dimethyl-4-(pyridine-4-ylmethyl)aniline (10d):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**2a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromo-*N*,*N*-dimethylaniline (**9g**: 199 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1 then 2:3) furnished *N*,*N*-dimethyl-4-(pyridine-4-ylmethyl)aniline (**10d**: 149 mg, 70%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.49 (dd, *J* = 4.63, 1.54 Hz, 2H), 7.12 (d, *J* = 6.03 Hz, 2H), 7.06 (dt, *J* = 9.25, 2.41 Hz, 2H), 6.71 (dt, *J* = 9.25, 2.41 Hz, 2H), 3.89 (s, 2H), 2.95 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 151.1, 149.7, 149.4, 129.7, 126.7, 124.1, 112.9, 40.7, 40.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3020, 2894, 2808, 2338, 2360, 1739, 1611, 1597, 1518, 1484, 1445, 1420, 1410, 1346, 1230, 1170, 111, 1065, 945, 914, 827, 787, 720.
MS (EI, 70 eV): *m/z* (%) = 212 (M^+, 100), 195 (4), 167 (14), 134 (60), 118 (14).
HRMS for $C_{14}H_{16}N_2$: calc.: 212.1313; found: 212.1323 (M^+).

Synthesis of 4-(pyridin-4-ylmethyl)phenol (10e):

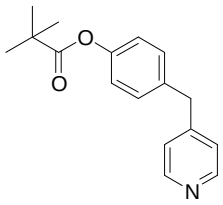


TMPZnCl·LiCl (**7**: 1.30 M in THF, 2.00 mL, 2.60 mmol) was added to a solution of 4-methylpyridine (**2a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OCOCF_3)_2$ (12 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromo-phenol (**9h**: 172 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-

chromatography (CH_2Cl_2/MeOH, 97:3) furnished 4-(pyridin-4-ylmethyl)phenol (**10e**: 155 mg, 84%) as a colorless oil.

^{1}H-NMR (300 MHz, DMSO): δ / ppm = 9.24 (s, 1H), 8.43 (dd, *J* = 4.49, 1.56 Hz, 2H), 7.19 (dd, *J* = 4.33, 1.66 Hz, 2H), 7.03 (d, *J* = 8.46 Hz, 2H), 6.69 (d, *J* = 8.46 Hz, 2H), 3.83 (s, 2H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 156.2, 151.1, 149.9, 130.2, 130.0, 124.3, 115.7, 39.7.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2997, 2925, 2883, 2794, 2673, 2594, 2360, 2339, 1602, 1513, 1455, 1420, 1430, 1380, 1245, 1217, 1205, 1007, 919, 845, 804.
MS (EI, 70 eV): *m/z* (%) = 185 (M^+, 100), 167 (8), 156 (9), 128 (7), 107 (43), 77 (14).
HRMS for $C_{12}H_{11}NO$: calc.: 185.0841; found: 185.0840 (M^+).

Synthesis of 4-(pyridin-4-ylmethyl)phenyl pivalate (10f):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**2a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OCOCF_3)_2$ (12 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromophenyl pivalate (**9i**: 256 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 2:3) furnished 4-(pyridin-4-ylmethyl)phenyl pivalate (**10f**: 218 mg, 81%) as a colorless oil.

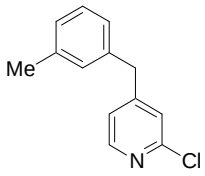
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.52 (dd, *J* = 5.75, 1.61 Hz, 2H), 7.18 (d, *J* = 8.63 Hz, 2H), 7.11 (d, *J* = 5.75 Hz, 2H), 7.03 (d, *J* = 8.63 Hz, 2H), 3.98 (s, 2H), 1.36 (s, 9H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 177.1, 149.9, 149.8, 149.7, 135.1, 129.9, 124.1, 121.7, 40.6, 39.1, 27.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3069, 3033, 3017, 2933, 2973, 2872, 1741, 1595, 1505, 1477, 1411, 1277, 1294, 1112, 1030, 899, 806, 760.

MS (EI, 70 eV): *m/z* (%) = 269 (M^+, 26), 226 (4), 185 (100), 156 (12), 128 (10), 107 (11), 85 (8), 57 (50).

HRMS for $C_{17}H_{19}NO_2$: calc.: 269.1416; found: 269.1425 (M^+).

Synthesis of 2-chloro-4-(3-methylbenzyl)pyridine (10g):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-chloro-4-methylpyridine (**2b**: 165 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), PCy_3 (12 mg, 4 mol%) and 1-bromo-3-methylbenzene (**9f**: 169 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 4:1) furnished 2-chloro-4-(3-methylbenzyl)pyridine (**10g**: 150 mg, 69%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.26 (d, *J* = 5.05 Hz, 1H), 7.22 (t, *J* = 7.22, 1H), 7.14 (dd, *J* = 1.47, 0.72 Hz, 1H), 7.08 (d, *J* = 7.61 Hz, 1H), 7.03 (d, *J* = 5.05 Hz, 1H), 6.98-6.95 (m, 2H), 3.91 (s, 2H), 2.33 (s, 3H).

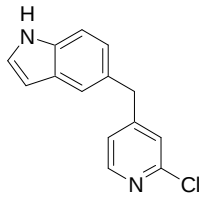
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 153.6, 151.7, 149.5, 138.6, 137.9, 129.8, 128.8, 127.7, 126.0, 124.4, 123.0, 40.9, 21.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3052, 2920, 2863, 1740, 1720, 1589, 1558, 1490, 1413, 1381, 1284, 1247, 1217, 1110, 1084, 993, 800, 745, 750, 715, 698.

MS (EI, 70 eV): *m/z* (%) = 217 (M^+, 100), 202 (42), 182 (32), 166 (35), 152 (9), 139 (10).

HRMS (ESI) for $C_{13}H_{13}ClN$: calc.: 218.0737; found: 218.0732 ($[M+H]^+$).

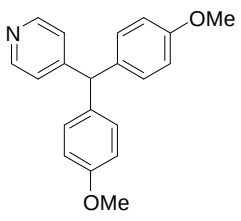
Synthesis of 5-((2-chloropyridine-4-yl)methyl)-1*H*-indole (10h):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2-chloro-4-methylpyridine (**2b**: 165 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 5-bromoindole (**9a**: 195 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 3:2) furnished 5-((2-chloropyridine-4-yl)methyl)-1*H*-indole (**10h**: 167 mg, 69%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.23 (d, *J* = 5.26 Hz, 1H), 8.16 (s, 1H), 7.42 (s, 1H), 7.34 (dd, *J* = 8.36 Hz, 1H), 7.23-7.14 (m, 2H), 7.06 (d, *J* = 5.12 Hz, 1H), 6.96 (d, *J* = 8.36 Hz, 1H), 6.51-6.49 (m, 1H), 4.04 (s, 2H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 155.2, 151.4, 149.1, 134.8, 129.2, 128.3, 124.8, 125.6, 123.2, 123.1, 121.0, 111.5, 102.5, 41.1.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3052, 3022, 2920, 2863, 1740, 1589, 1545, 1464, 1381, 1216, 1119, 1084, 989, 835, 785, 745, 715, 697.
MS (EI, 70 eV): *m/z* (%) = 242 (M^+, 100), 205 (21), 178 (10), 151 (8), 130 (79).
HRMS (ESI) for $C_{14}H_{12}ClN_2$: calc.: 243.0689; found: 243.0683 ($[M+H]^+$).

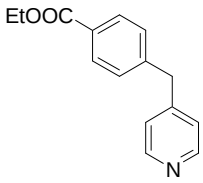
Synthesis of 4-(bis(4-methoxyphenyl)methyl)pyridine (10i):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-(4-methoxybenzyl)pyridine (**10b**: 259 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**9b**: 187 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 7:3) furnished 4-(bis(4-methoxyphenyl)methyl)-pyridine (**10i**: 283 mg, 93%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.52 (dd, *J* = 4.44, 1.60 Hz, 2H), 7.06-6.99 (m, 6H), 6.89-6.83 (m, 4H), 5.42 (s, 1H), 3.81 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 158.4, 153.4, 149.8, 134.6, 130.2, 124.3, 113.9, 55.3, 54.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066, 3032, 2995, 2833, 1608, 1594, 1581, 1506, 1491, 1457, 1441, 1412, 1303, 1240, 1177, 1111, 1030, 819.
MS (EI, 70 eV): *m/z* (%) = 305 (M^+, 61), 274 (23), 227 (100), 212 (6), 198 (7), 169 (7), 154 (14).
HRMS for $C_{20}H_{19}NO_2$: calc.: 305.1416; found: 305.1411 (M^+).

Synthesis of ethyl 4-(pyridin-4-ylmethyl)benzoate of (10j):

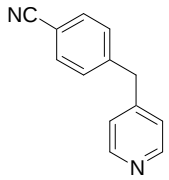


TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**2a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Sc(OTf)_3$ (64 mg, 0.13 mmol, 0.10 equiv) was added at 25 °C. After being stirred for 15 min, $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and ethyl 4-bromobenzoate (**9k**: 227 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl

and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished ethyl 4-(pyridin-4-ylmethyl)benzoate (**10j**: 188 mg, 78%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.49 (dd, *J* = 4.45, 1.68 Hz, 2H), 7.97 (dt, *J* = 8.37, 1.93 Hz, 2H), 7.26-7.05 (m, 4H), 4.35 (q, *J* = 7.08 Hz, 2H), 4.01 (s, 2H), 1.36 (t, *J* = 7.08 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 166.3, 149.7, 149.5, 143.8, 130.0, 130.0, 129.0, 124.2, 60.9, 41.2, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3028, 2981, 2931, 1710, 1597, 1413, 1365, 1270, 1177, 1100, 1020, 994, 870, 786, 754, 704.
MS (EI, 70 eV): *m/z* (%) = 241 (M^+, 31), 213 (32), 196 (100), 167 (43), 139 (10), 115 (8).
HRMS (ESI) for $C_{15}H_{16}NO_2$: calc.: 242.1181; found: 242.1173 ($[M+H]^+$).

Synthesis of 4-(pyridin-4-ylmethyl)benzonitrile of (10k):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**2a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Sc(OTf)_3$ (64 mg, 0.13 mmol, 0.10 equiv) was added at 25 °C. After being stirred for 15 min, $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromobenzonitrile (**9j**: 183 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 4-(pyridin-4-ylmethyl)benzonitrile (**10k**: 146 mg, 75%) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.53 (dd, *J* = 4.55, 2.00 Hz, 2H), 7.60 (dt, *J* = 8.30, 1.93 Hz, 2H), 7.30-7.23 (m, 2H), 7.12 (d, *J* = 6.05 Hz, 2H), 4.05 (s, 2H).

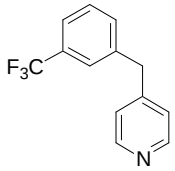
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 149.8, 148.5, 144.2, 132.5, 129.8, 124.2, 119.6, 110.9, 41.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3064, 3016, 226, 1739, 1597, 1554, 1506, 1496, 1414, 1426, 1223, 993, 927, 865, 840, 783, 722.

MS (EI, 70 eV): *m/z* (%) = 194 (M^+, 100), 166 (9), 140 (9), 116 (10), 89 (7), 63 (5).

HRMS (ESI) for $C_{13}H_{10}N_2$: calc.: 195.0922; found: 195.0916 ($[M+H]^+$).

Synthesis of 4-(3-(trifluoromethyl)benzyl)pyridine (10l):



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 4-methylpyridine (**2a**: 121 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h according to **TP1**. $Sc(OTf)_3$ (64 mg, 0.13 mmol, 0.10 equiv) was added at 25 °C. After being stirred for 15 min, $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-3-(trifluoromethyl)benzene (**9l**: 224 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 1 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 2:3) furnished 4-(3-(trifluoromethyl)benzyl)pyridine (**10l**: 185 mg, 78%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.55 (dd, *J* = 6.23, 1.72 Hz, 2H), 7.55-7.36 (m, 4H), 7.11 (d, *J* = 6.23, 2H), 4.05 (s, 2H).

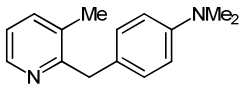
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 150.1, 148.8, 139.8, 132.4, 131.1 ($^2J_{C-F}$ = 32.2 Hz), 129.2, 125.7 ($^3J_{C-F}$ = 3.8 Hz), 124.1, 124.0 ($^1J_{C-F}$ = 272.2 Hz), 123.6 ($^3J_{C-F}$ = 3.8 Hz), 40.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3070, 3028, 2992, 1737, 1673, 1598, 1449, 1414, 1327, 1160, 117, 1071, 919, 880, 791, 701, 663.

MS (EI, 70 eV): *m/z* (%) = 237 (M^+, 100), 218 (6), 167 (18), 159 (7), 139 (3).

HRMS for $C_{13}H_{10}F_3N$: calc.: 237.0765; found: 237.0760 (M^+).

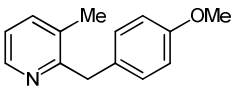
Synthesis of *N*,*N*-dimethyl-4-((3-methylpyridin-2-yl)methyl)aniline (13a)



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2,3-lutidine (**12a**: 139 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 15 min according to **TP1**. NEP (0.2 mL), $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromo-*N*,*N*-dimethylaniline (**9g**: 199 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/EtOAc, 1:1) furnished *N*,*N*-dimethyl-4-((3-methylpyridin-2-yl)methyl)aniline (**13a**: 192 mg, 85%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.43 (d, *J* = 4.13 Hz, 1H), 7.40 (d, *J* = 7.27 Hz, 1H), 7.01-7.15 (m, 3H), 6.67 (d, *J* = 8.75 Hz, 2H), 4.11 (s, 2H), 2.90 (s, 6H), 2.26 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.5, 149.0, 146.5, 137.9, 131.6, 129.2, 126.9, 121.4, 112.8, 41.2, 40.7, 18.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2917, 2874, 2797, 1613, 1517, 1442, 1342, 1212, 1161, 946, 804, 781.
MS (EI, 70 eV): m/z (%) = 226 (M^+, 100), 225 (39), 211 (18), 209 (11), 181 (22), 134 (77), 120 (20), 112 (17), 104 (13).
HRMS for $C_{15}H_{18}N_2$: calc. 226.1470; found: 226.1452 (M^+).

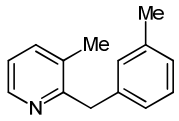
Synthesis of 2-(4-methoxybenzyl)-3-methylpyridine (13b)



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2,3-lutidine (**12a**: 139 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 15 min according to **TP1**. NEP (0.2 mL), $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**9b**: 187 mg, 1.00 mmol, 0.80 equiv.) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 2-(4-methoxybenzyl)-3-methylpyridine (**13b**: 192 mg, 90%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.42 (d, *J* = 3.81 Hz, 1H), 7.41 (d, *J* = 7.34 Hz, 1H), 7.03-7.17 (m, 3H), 6.81 (d, *J* = 8.66 Hz, 2H), 4.14 (s, 2H), 3.76 (s, 3H), 2.25 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.0, 157.9, 146.6, 138.0, 131.6, 131.0, 129.5, 121.6, 113.8, 55.1, 41.2, 18.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2952, 2931, 2833, 1610, 1573, 1508, 1440, 1301, 1244, 1175, 1110, 1033, 816, 785.
MS (EI, 70 eV): m/z (%) = 213 (M^+, 57), 212 (100), 198 (78), 196 (11), 170 (16), 168 (15), 121 (14), 78 (12), 44 (10).
HRMS for $C_{14}H_{15}NO$: calc. 213.1154; found: 213.1129 (M^+).

Synthesis of 3-methyl-2-(3-methylbenzyl)pyridine (13c)

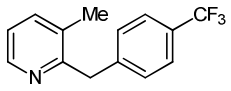


TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2,3-lutidine (**12a**: 139 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 15 min according to **TP1**. NEP (0.2 mL), $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-3-methylbenzene (**9f**: 171 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced

pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 3-methyl-2-(3-methylbenzyl)pyridine (**13c**: 179 mg, 91%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.45 (d, *J* = 3.96 Hz, 1H), 7.43 (d, *J* = 7.43Hz, 1H), 6.98-7.19 (m, 5H), 4.18 (s, 2H), 2.30 (s, 3H), 2.27 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.8, 146.6, 138.8, 138.0, 137.9, 131.7, 129.4, 128.2, 126.8, 125.7, 121.6, 42.1, 21.4, 18.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2971, 2921, 2862, 1606, 1584, 1573, 1447, 1438, 1422, 1104, 786, 765, 715, 694.
MS (EI, 70 eV): m/z (%) = 197 (M^+, 30), 196 (100), 194 (10), 182 (15), 181 (25), 180 (12), 167 (6), 98 (6), 84(6), 77 (7).
HRMS for $C_{14}H_{15}N$: calc. 197.1204; found: 197.1187 (M^+).

Synthesis of 3-methyl-2-(4-(trifluoromethyl)benzyl)pyridine (13d)



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 2,3-lutidine (**12a**: 139 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 15 min according to **TP1**. NEP (0.2 mL), $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-bromo-4-(trifluoromethyl)benzene (**9m**: 225 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 3-methyl-2-(4-(trifluoromethyl)benzyl)pyridine (**13d**: 221 mg, 88%) as a slightly yellow oil.

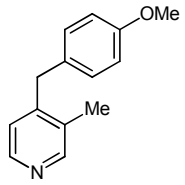
^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.44 (d, *J* = 3.96 Hz, 1H), 7.52 (m, *J* = 8.09 Hz, 2H), 7.45 (d, *J* = 7.27 Hz, 1H), 7.31 (m, *J* = 7.93 Hz, 2H), 7.11 (dd, *J* = 7.60, 4.95 Hz, 1H), 4.25 (s, 2H), 2.25 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.8, 146.9, 143.1, 138.2, 131.7, 129.0, 128.5 ($^2J_{C\text{-}F}$ = 32.3 Hz), 125.3 ($^3J_{C\text{-}F}$ = 3.9 Hz), 124.3 ($^1J_{C\text{-}F}$ = 271.8 Hz), 122.0, 41.8, 18.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 1618, 1574, 1444, 1415, 1321, 1160, 1109, 1065, 1018, 818, 788, 715.

MS (EI, 70 eV): m/z (%) = 251 (M^+, 100), 250 (39), 248 (21), 236 (22), 235 (15), 181 (39), 167 (12), 65 (8).

HRMS for $C_{14}H_{12}F_3N$: calc. 251.0922; found: 251.0911 (M^+).

Synthesis of 4-(4-methoxybenzyl)-3-methylpyridine (14)



TMPZnCl·LiCl (**7**: 1.30 M in THF, 1.50 mL, 1.95 mmol) was added to a solution of 3,4-lutidine (**12b**: 139 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 15 min according to **TP1**. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**9b**: 187 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 4-(4-methoxybenzyl)-3-methylpyridine (**14**: 196 mg, 92%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.31-8.38 (m, 2H), 7.02 (m, *J* = 8.66 Hz, 2H), 6.95 (d, *J* = 4.99 Hz, 1H), 6.83 (m, *J* = 8.66 Hz, 2H), 3.88 (s, 2H), 3.77 (s, 3H), 2.23 (s, 3H).

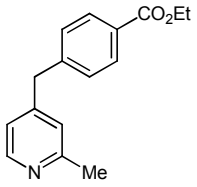
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.1, 150.5, 148.3, 147.5, 131.9, 130.0, 129.7, 124.1, 114.0, 55.1, 37.7, 16.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2953, 2931, 2834, 1610, 1593, 1510, 1453, 1441, 1301, 1245, 1176, 1032, 814, 775, 758.

MS (EI, 70 eV): m/z (%) = 213 (M^+, 100), 198 (15), 182 (13), 167 (8), 121 (73), 115 (9), 108 (43), 105 (79), 78 (25), 77 (13).

HRMS for $C_{14}H_{15}NO$: calc. 213.1154; found: 213.1158 (M^+).

Synthesis of ethyl 4-((2-methylpyridin-4-yl)methyl)benzoate (15a)



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2,4-lutidine (**12c**: 139 mg, 1.30 mmol, 1.00 equiv) was dissolved in dry THF (5 mL). $BF_3{\cdot}OEt_2$ (163 mg, 1.43 mmol, 1.10 equiv) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 15 min. Then, TMPZnCl·LiCl (**7**: 1.50 mL, 1.30 M in THF, 1.95 mmol, 1.50 equiv.) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature for 1 h. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and ethyl 4-bromobenzoate (**9k**: 227 mg, 1.00 mmol, 0.80 equiv) were added and the reaction mixture was warmed slowly to 50 °C and was stirred at that temperature for 2 h. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/EtOAc, 1:1) furnished ethyl 4-((2-methylpyridin-4-yl)methyl)benzoate (**15a**: 209 mg, 82%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.38 (d, *J* = 5.14 Hz, 1H), 7.98 (m, *J* = 8.25 Hz, 2H), 7.23 (m, *J* = 8.07 Hz, 2H), 6.94 (s, 1H), 6.89 (d, *J* = 5.14 Hz, 1H), 4.36 (q, *J* = 7.15 Hz, 2H), 3.96 (s, 2H), 2.50 (s, 3H), 1.37 (t, *J* = 7.15 Hz, 3H).

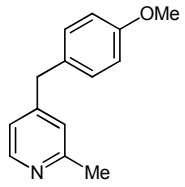
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.3, 158.5, 149.3, 149.1, 144.1, 129.9, 129.2, 128.9, 123.6, 121.2, 60.9, 41.1, 24.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2979, 1711, 1600, 1415, 1366, 1271, 1177, 1099, 1020, 749, 705.

MS (EI, 70 eV): m/z (%) = 255 (M^+, 40), 227 (36), 211 (18), 210 (100), 182 (30), 181 (22), 167 (15), 115 (7), 90 (6).

HRMS for $C_{16}H_{17}NO_2$: calc. 255.1259; found: 255.1247 (M^+).

Synthesis of 4-(4-methoxybenzyl)-2-methylpyridine (15b)



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2,4-lutidine (**12c**: 139 mg, 1.25 mmol, 1.00 equiv) was dissolved in dry THF (5 mL). $BF_3 \cdot OEt_2$ (163 mg, 1.43 mmol, 1.10 equiv) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 15 min. Then, TMPZnCl·LiCl (**7**: 1.50 mL, 1.30 M in THF, 1.95 mmol, 1.50 equiv) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature for 1 h. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromoanisole (**9b**: 187 mg, 1.00 mmol, 0.80 equiv) were added and the reaction mixture was warmed slowly to 50 °C and was stirred at that temperature for 2 h. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 4-(4-methoxybenzyl)-2-methylpyridine (**15b**: 196 mg, 92%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.36 (d, *J* = 5.01 Hz, 1H), 7.08 (d, *J* = 8.61 Hz, 2H), 6.80-6.99 (m, 4H), 3.86 (s, 2H), 3.78 (s, 3H), 2.50 (s, 3H).

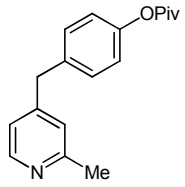
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.2, 150.7, 148.9, 131.0, 129.9, 123.5, 121.2, 114.0, 55.2, 40.2, 24.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2931, 2834, 1601, 1510, 1463, 1440, 1300, 1245, 1176, 1033, 928, 815, 769.

MS (EI, 70 eV): m/z (%) = 213 (M^+, 100), 212 (20), 198 (29), 182 (9), 170 (6), 128 (6), 121 (62), 77 (7).

HRMS for $C_{14}H_{15}NO$: calc. 213.1154; found: 213.1157 (M^+).

Synthesis of 4-((2-methylpyridin-4-yl)methyl)phenyl pivalate (15c)



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2,4-lutidine (**12c**: 139 mg, 1.30 mmol, 1.00 equiv) was dissolved in dry THF (5 mL). $BF_3{\cdot}OEt_2$ (163 mg, 1.43 mmol, 1.10 equiv) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 15 min. Then, TMPZnCl·LiCl (**7**: 1.50 mL, 1.30 M in THF, 1.95 mmol, 1.50 equiv) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature for 1 h. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromophenyl pivalate (**9i**: 257 mg, 1.00 mmol, 0.80 equiv) were added and the reaction mixture was warmed slowly to 50 °C and was stirred at that temperature for 2 h. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 4-((2-methylpyridin-4-yl)methyl)phenyl pivalate (**15c**: 232 mg, 82%) as a slightly yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.37 (d, *J* = 4.95 Hz, 1H), 7.15 (d, *J* = 8.44 Hz, 2H), 6.86 - 7.04 (m, 4H), 3.90 (s, 2H), 2.50 (s, 3H), 1.34 (s, 9H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 177.0, 158.3, 150.0, 149.7, 149.0, 136.2, 129.8, 123.6, 121.6, 121.2, 40.4, 38.9, 27.0, 24.2.

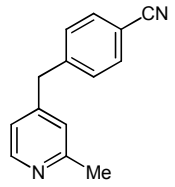
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2976, 2963, 1743, 1602, 1505, 1276, 1196, 1162, 1115, 1016, 894, 818, 759, 731.

MS (EI, 70 eV): m/z (%) = 283 (M^+, 4), 199 (34), 198 (8), 107 (12), 85 (31), 77 (6), 57 (100), 41 (13).

HRMS for $C_{18}H_{21}NO_2$: calc. 283.1572; found: 283.1570 (M^+).

M.p. (°C): 72.0-73.4 °C.

Synthesis of 4-((2-methylpyridin-4-yl)methyl)benzonitrile (15d)



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2,4-lutidine (**12c**: 139 mg, 1.30 mmol, 1.00 equiv) was dissolved in dry THF (5 mL). $BF_3{\cdot}OEt_2$ (163 mg, 1.43 mmol, 1.10 equiv) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 15 min. Then, TMPZnCl·LiCl (**7**: 1.50 mL, 1.30 M in THF, 1.95 mmol, 1.50 equiv) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature for 1 h. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-bromobenzonitrile (**9j**: 182 mg, 1.00 mmol, 0.80 equiv) were added and the reaction mixture was warmed slowly to 50 °C and was stirred at that temperature for 2 h. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/EtOAc, 1:1) furnished 4-((2-methylpyridin-4-yl)methyl)benzonitrile (**15d**: 160 mg, 77%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.42 (d, *J* = 4.95 Hz, 1H), 7.61 (d, *J* = 8.25 Hz, 2H), 7.24 - 7.32 (m, 2H), 6.95 (s, 1H), 6.90 (d, *J* = 5.14 Hz, 1H), 3.99 (s, 2H), 2.53 (s, 3H).

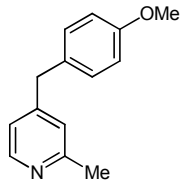
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.8, 149.3, 148.4, 144.5, 132.4, 129.7, 123.6, 121.2, 118.6, 110.7, 41.1, 24.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2227, 1677, 1599, 1560, 1504, 1407, 1287, 1177, 1021, 858, 816, 770.

MS (EI, 70 eV): m/z (%) = 208 (M^+, 100), 207 (26), 193 (9), 192 (9), 166 (7), 140 (7), 116 (4), 89 (3).

HRMS for $C_{14}H_{12}N_2$: calc. 208.1000; found: 208.0994 (M^+).

Synthesis of 4-(4-methoxybenzyl)-2-methylpyridine (15b)



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2,4-lutidine (**12c**: 139 mg, 1.30 mmol, 1.00 equiv) was dissolved in dry THF (5 mL). $BF_3{\cdot}OEt_2$ (163 mg, 1.43 mmol, 1.10 equiv) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 15 min. Then, TMPZnCl·LiCl (**7**: 1.50 mL, 1.30 M in THF, 1.95 mmol, 1.50 equiv) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature for 1 h. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 4-methoxyphenyl trifluoromethanesulfonate (**9n**: 256 mg, 1.00 mmol, 0.80 equiv) were added and the reaction mixture was warmed slowly to 50 °C and was stirred at that temperature for 2 h. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 4-(4-methoxybenzyl)-2-methylpyridine (**15b**: 209 mg, 98%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.35 (d, *J* = 4.95 Hz, 1H), 7.02 - 7.14 (m, 2H), 6.79 - 7.00 (m, 4H), 3.85 (s, 2H), 3.77 (s, 3H), 2.50 (s, 3H).

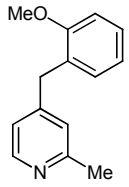
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.3, 158.2, 150.9, 148.8, 131.0, 129.9, 123.6, 121.2, 114.0, 55.2, 40.3, 24.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2931, 2834, 1601, 1510, 1440, 1300, 1245, 1176, 1106, 1033, 815, 769, 760.

MS (EI, 70 eV): m/z (%) = 213 (M^+, 100), 212 (20), 198 (34), 182 (13), 168 (9), 128 (9), 121 (76), 77 (16).

HRMS for $C_{14}H_{15}NO$: calc. 213.1154; found: 213.1150 (M^+).

Synthesis of 4-(2-methoxybenzyl)-2-methylpyridine (15e)



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2,4-lutidine (**12c**: 139 mg, 1.30 mmol, 1.00 equiv) was dissolved in dry THF (5 mL). $BF_3{\cdot}OEt_2$ (163 mg, 1.43 mmol, 1.10 equiv) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 15 min. Then, TMPZnCl·LiCl (**7**: 1.50 mL, 1.30 M in THF, 1.95 mmol, 1.50 equiv) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature for 1 h. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 2-bromoanisole (**9o:** 187 mg, 1.00 mmol, 0.80 equiv) were added and the reaction mixture was warmed slowly to 50 °C and was stirred at that temperature for 2 h. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 4-(2-methoxybenzyl)-2-methylpyridine (**15e**: 196 mg, 92%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.36 (d, *J* = 5.14 Hz, 1H), 7.25 (td, *J* = 7.89, 1.83 Hz, 1H), 7.10 (dd, *J* = 7.34, 1.28 Hz, 1H), 6.99 (s, 1H), 6.85-6.96 (m, 3H), 3.92 (s, 2H), 3.80 (s, 3H), 2.51 (s, 3H).

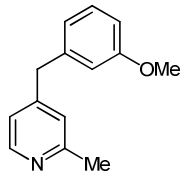
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.9, 157.2, 150.4, 148.7, 130.4, 127.9, 127.5, 123.5, 121.2, 120.5, 110.4, 55.2, 35.3, 24.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2956, 2923, 2835, 1601, 1492, 1462, 1438, 1291, 1242, 1178, 1106, 1027, 816, 751.

MS (EI, 70 eV): m/z (%) = 213 (M^+, 100), 198 (26), 182 (17), 180 (9), 121 (15), 107 (16), 91 (12).

HRMS for $C_{14}H_{15}NO$: calc. 213.1154; found: 213.1157 (M^+).

Synthesis of 4-(3-methoxybenzyl)-2-methylpyridine (15f)



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2,4-lutidine (**12c**: 139 mg, 1.30 mmol, 1.00 equiv) was dissolved in dry THF (5 mL). $BF_3{\cdot}OEt_2$ (163 mg, 1.43 mmol, 1.10 equiv) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 15 min. Then, TMPZnCl·LiCl (**7**: 1.50 mL, 1.30 M in THF, 1.95 mmol, 1.50 equiv) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature for 1 h. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 3-chloroanisole (**9p**: 143 mg, 1.00 mmol, 0.80 equiv) were added and the reaction mixture was warmed slowly to 50 °C and was stirred at that temperature for 2 h. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 4-(3-methoxybenzyl)-2-methylpyridine (**15f**: 183 mg, 86%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.37 (d, *J* = 5.14 Hz, 1H), 7.23 (t, *J* = 7.89 Hz, 1H), 6.97 (s, 1H), 6.92 (d, *J* = 5.14 Hz, 1H), 6.73-6.81 (m, 2H), 6.71 (s, 1H), 3.88 (s, 2H), 3.77 (s, 3H), 2.51 (s, 3H).

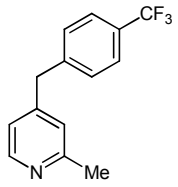
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 159.8, 158.2, 150.2, 148.8, 140.4, 129.6, 123.7, 121.3, 121.3, 114.9, 111.6, 55.1, 41.1, 24.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 2921, 2834, 1596, 1584, 1488, 1453, 1435, 1258, 1147, 1048, 1041, 763, 746, 695.

MS (EI, 70 eV): m/z (%) = 213 (M^+, 100), 212 (17), 182 (11), 170 (8), 128 (6), 121 (17), 91 (5), 77 (5).

HRMS for $C_{14}H_{15}NO$: calc. 213.1154; found: 213.1144 (M^+).

Synthesis of 2-methyl-4-(4-(trifluoromethyl)benzyl)pyridine (15g)

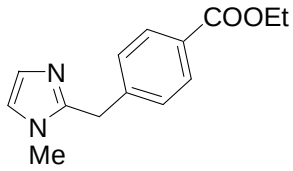


In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2,4-lutidine (**12c**: 139 mg, 1.30 mmol, 1.00 equiv) was dissolved in dry THF (5 mL). $BF_3{\cdot}OEt_2$ (163 mg, 1.43 mmol, 1.10 equiv) was added dropwise at 0 °C and the mixture was stirred at 0 °C for 15 min. Then, TMPZnCl·LiCl (**7**: 1.50 mL, 1.30 M in THF, 1.95 mmol, 1.50 equiv) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature for 1 h. $Pd(OAc)_2$ (5 mg, 2 mol%), SPhos (16 mg, 4 mol%) and 1-chloro-4-(trifluoromethyl)benzene (**9q**: 181 mg, 1.00 mmol, 0.80 equiv) were added and the reaction mixture was warmed slowly to 50 °C and was stirred at that temperature for 2 h. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/ether, 1:1) furnished 2-methyl-4-(4-(trifluoromethyl)benzyl)pyridine (**15g**: 221 mg, 88%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.41 (d, *J* = 5.14 Hz, 1H), 7.57 (m, *J* = 8.07 Hz, 2H), 7.29 (m, *J* = 7.89 Hz, 2H), 6.97 (s, 1H), 6.91 (d, *J* = 5.14 Hz, 1H), 3.98 (s, 2H), 2.53 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 158.6, 149.1, 143.1, 143.0, 129.3, 129.0 ($^2J_{C\text{-}F}$ = 32.5 Hz), 125.6 ($^3J_{C\text{-}F}$ = 3.9 Hz), 124.1 ($^1J_{C\text{-}F}$ = 272.1 Hz), 123.7, 121.2, 40.9, 24.2.
IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}) = 1602, 1561, 1418, 1321, 1161, 1119, 1105, 1065, 1018, 857, 815, 773.
MS (EI, 70 eV): m/z (%) = 251 (M^+, 100), 250 (15), 236 (4), 182 (15), 181 (9), 167 (7), 159 (3), 141 (3).
HRMS for $C_{14}H_{12}F_3N$: calc. 251.0922; found: 251.0911 (M^+).

4. Benzylic Arylation of 2-Methyl-5-Membered Heterocycles Using TMP-Bases

Synthesis of ethyl 4-((1-methyl-1*H*-imidazol-2-yl)methyl)benzoate (19a):



TMPMgCl·LiCl (**17**: 1.15 M in THF, 1.70 mL, 1.95 mmol) was added to a solution of 1,2-dimethylimidazole (**16**: 125 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 3 h. $Pd(dba)_2$ (15 mg, 2 mol%), SPhos (21 mg, 4 mol%) and ethyl 4-bromobenzoate (**9k**: 229 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (DCM/MeOH, 99:1) furnished ethyl 4((1methyl-1*H*-imidazol-2-yl)methyl)benzoate (**19a**: 208 mg, 85%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.98 (dt, *J* = 8.36, 1.91 Hz, 2H), 7.25 (d, *J* = 8.36 Hz, 2H), 7.00 (d, *J* = 1.36 Hz, 1H), 6.84 (d, *J* = 1.36 Hz, 1H), 4.37 (q, *J* = 7.08 Hz, 2H), 4.18 (s, 2H), 3.45 (s, 3H), 1.38 (t, *J* = 7.08 Hz, 2H).

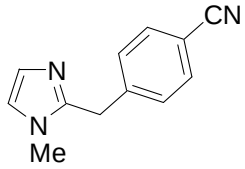
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 166.4, 145.9, 142.3, 130.0, 129.1, 128.3, 127.3, 121.2, 60.9, 33.5, 32.9, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3060 (vw), 3030 (vw), 3028 (vw), 2978 (s), 2930 (vw), 2853 (vw), 1710 (s), 1609 (m), 1587 (m), 1471 (vw), 1449 (w), 1417 (w), 1392 (w), 1366 (m), 1273 (s), 1179 (m), 1104 (s), 1021 (m), 1010 (m), 937 (vw), 851 (w), 746 (s), 697 (S).

MS (EI, 70 eV): *m/z* (%) = 244 (M^+, 100), 229 (11), 215 (53), 199 (27), 171 (26), 156 (17), 81 (40).

HRMS ($C_{14}H_{16}N_2O_2$): calc.: 244.1212; found: 244.1220 (M^+).

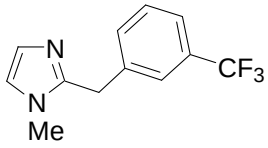
Synthesis of 4-((1-methyl-1*H*-imidazol-2-yl)methyl)benzonitrile (19b):



TMPMgCl·LiCl (**17**: 1.15 M in THF, 1.70 mL, 1.95 mmol) was added to a solution of 1,2-dimethylimidazole (**16**: 125 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 3 h. $Pd(dba)_2$ (15 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 4-bromobenzonitrile (**9j**: 182 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (DCM/MeOH, 99:1) furnished 4-((1-methyl-1*H*-imidazol-2-yl)methyl)benzonitrile (**19b**: 141 mg, 71%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.61 (d, *J* = 8.02 Hz, 2H), 7.31 (d, *J* = 8.02 Hz, 2H), 7.00 (d, *J* = 1.25 Hz, 1H), 6.86 (d, *J* = 1.25 Hz, 1H), 4.18 (s, 2H), 3.49 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 145.2, 142.6, 132.5, 129.2, 127.6, 121.3, 118.7, 110.8, 33.4, 32.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3359 (w), 3143 (w), 3112 (w), 2947 (w), 2852 (vw), 2226 (s), 1607 (s), 1496 (s), 1470 (m), 1416 (s), 1281 (s), 1170 (m), 1126 (s), 1084 (w), 1021 (w), 934 (w), 854 (m), 823 (m), 781 (s), 735 (s), 704 (m).
MS (EI, 70 eV): *m/z* (%) = 208 (M^+, 70), 207 (100), 130 (48), 127 (18), 44 (62).
HRMS ($C_{12}H_{11}N_3$): calc.: 197.0953; found: 197.0928 (M^+).

Synthesis of 1-methyl-2-(3-(trifluoromethyl)benzyl)-1*H*-imidazole (19c):

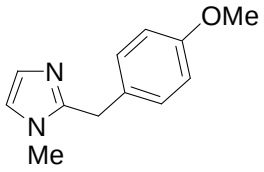


TMPMgCl·LiCl (**17**: 1.15 M in THF, 1.70 mL, 1.95 mmol) was added to a solution of 1,2-dimethylimidazole (**16**: 125 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 3 h. $Pd(dba)_2$ (15 mg, 2 mol%),

SPhos (21 mg, 4 mol%) and 1-bromo-3-trifluoromethylbenzene (**9l**: 225 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (DCM/MeOH, 99:1) furnished 1-methyl-2-(3-(trifluoromethyl)benzyl)-1*H*-imidazole (**19c**: 186 mg, 77%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.53-7.32 (m, 4H), 6.98 (d, *J* = 1.33 Hz, 1H), 6.83 (d, *J* = 1.33 Hz, 1H), 4.16 (s, 2H), 3.47 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 145.7, 138.1, 134 ($^2J_{C-F}$ = 32.2 Hz), 131.8, 129.2, 127.4, 125.0 ($^3J_{C-F}$ = 3.8 Hz), 124.0 ($^1J_{C-F}$ = 274.5 Hz), 123.6 ($^3J_{C-F}$ = 3.8 Hz), 121.2, 32.2, 32.9.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3357 (vw), 3110 (vw), 2931 (vw), 1711 (vw), 1677 (vw), 1615 (vw), 1496 (m), 1448 (w), 1330 (s), 1282 (m), 1160 (s), 1116 (s), 1074 (s), 917 (w), 972 (w), 775 (m), 734 (m), 700 (s), 663 (w).
MS (EI, 70 eV): *m/z* (%) = 239 (M^+, 100), 225 (27), 205 (16), 171 (16), 81 (49).
HRMS ($C_{12}H_{11}F_3N_2$): calc.: 240.0874; found: 240.0901 (M^+).

Synthesis of 2-(4-methoxybenzyl)-1-methyl-1*H*-imidazole (19d):



TMPMgCl·LiCl (**17**: 1.15 M in THF, 1.70 mL, 1.95 mmol) was added to a solution of 1,2-dimethylimidazole (**16**: 125 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 3 h. $Pd(dba)_2$ (15 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 4-bromoanisole (**9b**: 187 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (DCM/MeOH, 98:2) furnished 2-(4-methoxybenzyl)-1-methyl-1*H*-imidazole (**19d**: 150 mg, 74%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.09 (d, *J* = 8.84 Hz, 2H), 6.97 (s, 1H), 6.85-6.79 (m, 3H), 4.07 (s, 2H), 3.77 (s, 3H), 3.45 (s, 3H).

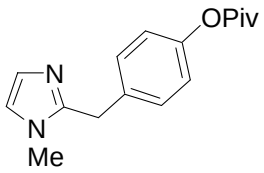
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 158.3, 147.0, 129.3, 128.8, 126.6, 121.0, 114.1, 55.2, 33.0, 32.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3362 (vw), 3110 (vw), 3001 (vw), 2934 (w), 2836 (vw), 1609 (m), 1584 (m), 1510 (s), 1498 (m), 1463 (m), 1442 (m), 1410 (w), 1302 (w), 1281 (m), 1244 (s), 1176 (m), 1123 (m), 1108 (m), 1084 (w), 1029 (s), 932 (w), 835 (m), 821 (m), 782 (s), 736 (s), 705 (w), 661 (vw).

MS (EI, 70 eV): *m/z* (%) = 202 (M^+, 65), 187 (58), 170 (5), 159 (9), 121 (100).

HRMS ($C_{12}H_{14}N_2O$): calc.: 202.1106; found: 202.1093 (M^+).

Synthesis of 4-((1-methyl-1*H*-imidazol-2-yl)methyl)phenyl pivalate (19e):



TMPMgCl·LiCl (**17**: 1.15 M in THF, 1.70 mL, 1.95 mmol) was added to a solution of 1,2-dimethylimidazole (**16**: 125 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 3 h. $Pd(dba)_2$ (15 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 4-bromophenylpivalate (**9i**: 258 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (DCM/MeOH, 9:1) furnished 4-((1-methyl-1*H*-imidazol-2-yl)methyl)phenyl pivalate (**19e**: 249 mg, 91%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.16-7.01 (m, 3H), 6.95 (d, *J* = 8.17 Hz, 2H), 6.82 (d, *J* = 1.36 Hz, 1H), 4.18 (s, 2H), 3.43 (s, 3H), 1.35 (s, 9H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 177.1, 149.9, 146.8, 133.7, 129.1, 126.7, 121.7, 121.3, 57.1, 39.0, 35.2, 33.2, 27.6, 27.1.

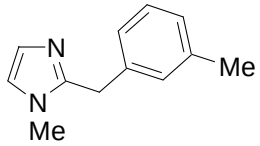
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3117 (vw), 3037 (vw), 2973 (w), 2935 (w), 2873 (vw), 1744 (s), 1605 (w), 1594 (w), 1546 (vw), 1505 (m), 1478 (m), 1461 (m), 1420 (w),

1396 (w), 1366 (vw), 1278 (m), 1250 (vw), 1199 (m), 1166 (m), 1113 (s), 1029 (w), 1017 (w), 894 (w), 773 (m), 758 (m), 737 (m), 703 (w).

MS (EI, 70 eV): *m/z* (%) = 272 (M^+, 100), 187 (73), 173 (17), 159 (14), 107 (29), 82 (65), 57 (71).

HRMS ($C_{16}H_{20}N_2O_2$): calc.: 272.1525; found: 272.1516 (M^+).

Synthesis of 1-methyl-2-(3-methylbenzyl)-1*H*-imidazole (19f):



TMPMgCl·LiCl (**17**: 1.15 M in THF, 1.70 mL, 1.95 mmol) was added to a solution of 1,2-dimethylimidazole (**16**: 125 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 3 h. $Pd(dba)_2$ (15 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 3-bromotoluene (**9f**: 172 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (DCM/MeOH, 99:1 (500 mL) then 98:2) furnished 1-methyl-2-(3-methylbenzyl)-1*H*-imidazole (**19f**: 155 mg, 83%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.16 (t, *J* = 7.53, 1H), 7.04-6.93 (m, 4H), 6.79 (d, *J* = 1.55 Hz, 1H), 4.06 (s, 2H), 3.44 (s, 3H), 2.29 (s, 3H).

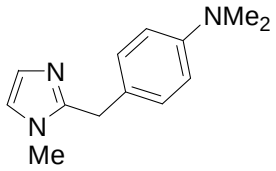
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 146.8, 138.3, 137.0, 129.0, 128.5, 127.4, 127.1, 125.3, 121.0, 33.4, 32.9, 21.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3363 (vw), 3137 (vw), 3108 (vw), 2947 (w), 2921 (w), 1644 (w), 1606 (m), 1590 (w), 1494 (s), 1461 (m), 1431 (m), 1410 (m), 1379 (vw), 1281 (s), 1219 (vw), 1168 (vw), 1122 (s), 1089 (w), 1039 (w), 998 (w), 936 (w), 886 (vw), 760 (s), 693 (s), 656 (w).

MS (EI, 70 eV): *m/z* (%) = 185 (M^+, 100), 171 (30), 156 (10), 105 (21), 81 (18).

HRMS ($C_{12}H_{14}N_2$): calc.: 186.1157; found: 186.1142 (M^+).

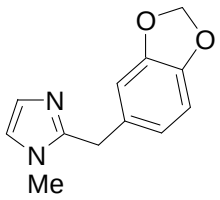
Synthesis of *N*,*N*-dimethyl-4-((1-methyl-1*H*-imidazol-2-yl)methyl)aniline (19g):



TMPMgCl·LiCl (**17**: 1.15 M in THF, 1.70 mL, 1.95 mmol) was added to a solution of 1,2-dimethylimidazole (**16**: 125 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 3 h. $Pd(dba)_2$ (15 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 4-bromo-*N*,*N*-dimethylaniline (**9g**: 200 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (DCM/MeOH, 98:2) furnished *N*,*N*-dimethyl-4-((1-methyl-1*H*-imidazol-2-yl)methyl)aniline (**19g**: 171 mg, 79%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.13-6.96 (m, 3H), 6.80 (d, *J* = 1.55 Hz, 1H), 6.68 (m, 2H), 4.06 (s, 2H), 3.44 (s, 3H), 2.92 (s, 6H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 149.4, 147.8, 129.0, 126.8, 124.8, 120.9, 112.9, 40.7, 33.0, 32.5.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3279 (w), 3135 (w), 3009 (w), 2889 (w), 2811 (w), 1696 (w), 1619 (s), 1527 (s), 1491 (s), 1447 (s), 1411 (m), 1363 (m), 1281 (m), 1236 (w), 1187 (w), 1174 (w), 1123 (m), 1006 (m), 1087 (w), 1070 (w), 951 (m), 933 (m), 848 (w), 827 (w), 808 (m), 775 (s), 749 (s), 705 (m), 656 (w).
MS (EI, 70 eV): *m/z* (%) = 215 (M^+, 100), 200 (47), 184 (6), 170 (17), 156 (16), 134 (65), 118 (16).
HRMS ($C_{13}H_{17}N_3$): calc.: 215.1422; found: 215.1416 (M^+).

Synthesis of 2-benzo[*d*][1,3]dioxol-5-ylmethyl)-1-methyl-1*H*-imidazole (19h):



TMPMgCl·LiCl (**17**: 1.15 M in THF, 1.70 mL, 1.95 mmol) was added to a solution of 1,2-dimethylimidazole (**16**: 125 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 3 h. $Pd(dba)_2$ (15 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 5-bromo-benzo[1,3]dioxole (**9e**: 201 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (DCM/MeOH, 99:1) furnished 2-benzo[*d*][1,3]dioxol-5-ylmethyl)-1-methyl-1*H*-imidazole (**19h**: 154 mg, 71%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 6.98 (d, *J* = 1.36 Hz, 1H), 6.84-6.59 (m, 4H), 5.93 (s, 2H), 4.04 (s, 2H), 3.48 (s, 3H).

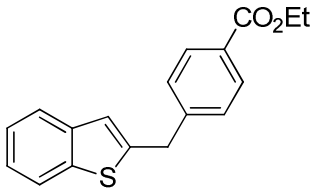
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 147.9, 146.7, 146.3, 130.8, 127.1, 121.2, 121.0, 108.8, 108.3, 101.0, 33.2, 32.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3269 (w), 3142 (vw), 3069 (vw), 2905 (w), 2788 (vw), 1697 (w), 1605 (w), 1500 (s), 1490 (s), 1447 (m), 1413 (w), 1349 (w), 1282 (m), 1255 (s), 1214 (m), 1188 (w), 1113 (s), 1038 (s), 946 (m), 923 (s), 856 (m), 863 (m), 781 (s), 753 (m), 700 (m), 661 (m).

MS (EI, 70 eV): *m/z* (%) = 216 (M^+, 100), 201 (16), 187 (11), 157 (30), 135 (76).

HRMS ($C_{12}H_{12}N_2O_2$): calc.: 216.0899; found: 216.0887 (M^+).

Synthesis of ethyl 4-(benzo[*b*]thiophen-2-ylmethyl)benzoate (23a):



TMPLi (**21**: 1.25 M in THF, 1.20 mL, 1.15 equiv) was added to a solution of 2-methylbenzo[*b*]thiophene (**20a**: 193 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at -78 °C and the reaction mixture was then stirred at this temperature for 15 min. A solution of $ZnCl_2$ (1 M in THF, 1.56 mL, 1.20 equiv) was added and the mixture was allowed to warm up to 25 °C. $Pd(OAc)_2$ (6 mg, 2 mol%), SPhos (21 mg, 4 mol%) and ethyl 4-bromobenzoate (**9k**: 229 mg, 1.00 mmol, 0.8 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous

NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O, 20:1) furnished 4-(benzo[*b*]thiophen-2-ylmethyl)benzoate (**23a**: 255 mg, 86%) as a white powder.

Melting point (°C): 91.3 – 92.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 8.02 (m, *J* = 8.22 Hz, 2H), 7.74 (d, *J* = 7.92 Hz, 1H), 7.67 (d, *J* = 7.78 Hz, 1H), 7.37 (m, *J* = 8.22 Hz, 2H), 7.30 - 7.33 (m, 1H), 7.25 - 7.28 (m, 1H), 7.01 (s, 1H), 4.38 (q, *J* = 7.04 Hz, 2H), 4.28 (s, 2H), 1.40 (t, *J* = 7.12 Hz, 3H).

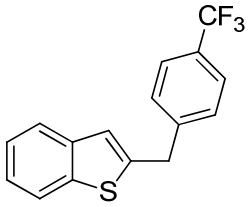
^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 166.4, 144.6, 143.8, 139.9, 139.8, 129.9, 129.1, 128.7, 124.2, 123.8, 123.0, 122.1, 122.0, 60.9, 36.9, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2971, 2360, 2340, 1737, 1714, 1366, 1277, 1252, 1230, 1217, 1205, 1108, 1102, 834, 744, 726, 712.

MS (EI, 70 eV): *m/z* (%) = 296 (M^+, 100), 295 (17), 251 (24), 223 (44), 147 (52), 126 (12).

HRMS ($C_{18}H_{16}O_2S$): calc.: 296.0871; found: 296.0866 (M^+).

Synthesis of 2-(4-(trifluoromethyl)benzyl)benzo[*b*]thiophene (23b):



TMPLi (**21**: 1.25 M in THF, 1.20 mL, 1.15 equiv) was added to a solution of 2-methylbenzo[*b*]thiophene (**20a**: 193 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at -78 °C and the reaction mixture was then stirred at this temperature for 15 min. A solution of $ZnCl_2$ (1 M in THF, 1.56 mL, 1.20 equiv) was added and the mixture was allowed to warm up to 25 °C. $Pd(OAc)_2$ (6 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 1-bromo-4-(trifluoromethyl)benzene (**9m**: 225 mg, 1.00 mmol, 0.8 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane) furnished 2-(4-(trifluoromethyl)benzyl)benzo[*b*]thiophene (**23b**: 263 mg, 90%) as a white powder.

Melting point (°C): 83.7 – 85.3.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.78 (d, *J* = 7.99 Hz, 1H), 7.71 (d, *J* = 7.87 Hz, 1H), 7.61 (m, *J* = 8.11 Hz, 2H), 7.42 (m, *J* = 8.11 Hz, 2H), 7.33 - 7.37 (m, 1H), 7.28 - 7.32 (m, 1H), 7.05 (s, 1H), 4.29 (s, 2H).

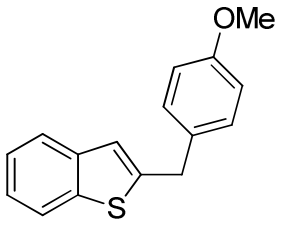
^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 143.5, 143.5 (d, *J* = 1.4 Hz), 139.9, 139.8, 129.1 (q, *J* = 32.5 Hz), 129.0, 125.5 (q, *J* = 3.9 Hz), 124.3, 124.2 (q, *J* = 272.1 Hz), 123.9, 123.1, 122.2, 122.2, 36.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2359, 2340, 1739, 1719, 1700, 1418, 1372, 1366, 1320, 1229, 1217, 1207, 1123, 1114, 1102, 1067, 1018, 854, 836, 749, 727.

MS (EI, 70 eV): *m/z* (%) = 292 (M^+, 100), 291 (51), 223 (17), 221 (21), 147 (57).

HRMS ($C_{16}H_{11}F_3S$): calc.: 292.0534; found: 292.0525 (M^+).

Synthesis of 2-(4-methoxybenzyl)benzo[*b*]thiophene (23c):



TMPLi (**21**: 1.25 M in THF, 1.20 mL, 1.15 equiv) was added to a solution of 2-methylbenzo[*b*]thiophene (**20a**: 193 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at -78 °C and the reaction mixture was then stirred at this temperature for 15 min. A solution of $ZnCl_2$ (1 M in THF, 1.56 mL, 1.20 equiv) was added and the mixture was allowed to warm up to 25 °C. $Pd(OAc)_2$ (6 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 1-bromo-4-methoxybenzene (**9b**: 187 mg, 1.00 mmol, 0.8 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O, 20:1) furnished 2-(4-methoxybenzyl)benzo[*b*]thiophene (**23c**: 249 mg, 98%) as a white powder.

Melting point (°C): 117.6 – 118.6.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.75 (d, *J* = 7.70 Hz, 1H), 7.67 (d, *J* = 7.52 Hz, 1H), 7.23 - 7.35 (m, 4H), 7.01 (s, 1H), 6.90 (d, *J* = 8.62 Hz, 2H), 4.19 (s, 2H), 3.83 (s, 3H).

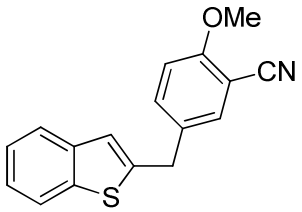
^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 158.4, 145.8, 140.1, 139.8, 131.7, 129.8, 124.1, 123.6, 122.9, 122.1, 121.3, 114.0, 55.3, 36.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2359, 2341, 1739, 1719, 1700, 1610, 1508, 1490, 1472, 1463, 1456, 1436, 1420, 1374, 1366, 1300, 1237, 1231, 1218, 1206, 1181, 1174, 1162, 1150, 1103, 1034, 1010, 838, 823, 813, 757, 743, 726.

MS (EI, 70 eV): *m/z* (%) = 254 (M^+, 39), 253 (26), 223 (11), 147 (15), 74 (76), 59 (100).

HRMS ($C_{16}H_{14}OS$): calc.: 254.0765; found: 254.0762 (M^+).

Synthesis of 5-(benzo[*b*]thiophen-2-ylmethyl)-2-methoxybenzonitrile (23d):



TMPLi (**21**: 1.25 M in THF, 1.20 mL, 1.15 equiv) was added to a solution of 2-methylbenzo[*b*]thiophene (**20a**: 193 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at -78 °C and the reaction mixture was then stirred at this temperature for 15 min. A solution of $ZnCl_2$ (1 M in THF, 1.56 mL, 1.20 equiv) was added and the mixture was allowed to warm up to 25 °C. $Pd(OAc)_2$ (6 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 5-bromo-2-methoxybenzonitrile (**9r**: 212 mg, 1.00 mmol, 0.8 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O, 5:1) furnished 5-(benzo[*b*]thiophen-2-ylmethyl)-2-methoxybenzonitrile (**23d**: 218 mg, 78%) as a slightly yellow powder.

Melting point (°C): 93.9 – 95.2.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.74 (d, *J* = 7.80 Hz, 1H), 7.68 (d, *J* = 7.60 Hz, 1H), 7.42 - 7.48 (m, 2H), 7.25 - 7.36 (m, 2H), 7.00 (s, 1H), 6.91 (d, *J* = 8.38 Hz, 1H), 4.15 (s, 2H), 3.90 (s, 3H).

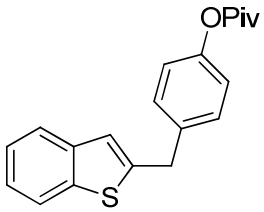
^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 160.0, 143.7, 139.8, 139.7, 134.6, 133.5, 132.1, 124.3, 123.9, 123.0, 122.1, 121.9, 116.3, 111.4, 101.7, 56.0, 35.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2361, 2341, 2224, 1739, 1701, 1608, 1580, 1496, 1471, 1457, 1435, 1417, 1366, 1292, 1280, 1265, 1230, 1217, 1182, 1152, 1134, 1123, 1108, 1092, 1064, 1017, 941, 899, 870, 832, 819, 760, 751, 737, 728, 720.

MS (EI, 70 eV): *m/z* (%) = 279 (M^+, 100), 278 (45), 264 (8), 248 (10), 147 (27).

HRMS ($C_{17}H_{13}NOS$): calc.: 279.0718; found: 279.0712 (M^+).

Synthesis of 4-(benzo[*b*]thiophen-2-ylmethyl)phenyl pivalate (23e):



TMPLi (**21**: 1.25 M in THF, 1.20 mL, 1.15 equiv) was added to a solution of 2-methylbenzo[*b*]thiophene (**20a**: 193 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at -78 °C and the reaction mixture was then stirred at this temperature for 15 min. A solution of $ZnCl_2$ (1 M in THF, 1.56 mL, 1.20 equiv) was added and the mixture was allowed to warm up to 25 °C. $Pd(OAc)_2$ (6 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 4-bromophenyl pivalate (**9i**: 257 mg, 1.00 mmol, 0.8 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O, 20:1) furnished 4-(benzo[*b*]thiophen-2-ylmethyl)phenyl pivalate (**23e**: 315 mg, 97%) as a white powder.

Melting point (°C): 100.0 – 101.1.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.75 (d, *J* = 7.96 Hz, 1H), 7.67 (d, *J* = 7.96 Hz, 1H), 7.29 - 7.33 (m, 3H), 7.25 - 7.28 (m, 1H), 7.04 (d, *J* = 8.51 Hz, 2H), 7.00 (s, 1H), 4.23 (s, 2H), 1.37 (s, 9H).

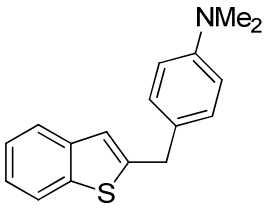
^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 177.1, 149.8, 144.8, 140.0, 139.8, 136.7, 129.7, 124.1, 123.7, 122.9, 122.1, 121.8, 121.6, 39.0, 36.3, 27.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2971, 2360, 2340, 1739, 1507, 1489, 1475, 1457, 1444, 1433, 1420, 1394, 1366, 1279, 1229, 1217, 1203, 1164, 1128, 1105, 1062, 1034, 1016, 938, 901, 868, 854, 820, 796, 764, 745, 727, 676.

MS (EI, 70 eV): *m/z* (%) = 324 (M^+, 100), 241 (22), 240 (30), 239 (61), 221 (9), 147 (20).

HRMS ($C_{20}H_{20}O_2S$): calc.: 324.1184; found: 324.1179 (M^+).

Synthesis of 4-(benzo[*b*]thiophen-2-ylmethyl)-*N*,*N*-dimethylaniline (23f):



TMPLi (**21**: 1.25 M in THF, 1.20 mL, 1.15 equiv) was added to a solution of 2-methylbenzo[*b*]thiophene (**20a**: 193 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at -78 °C and the reaction mixture was then stirred at this temperature for 15 min. A solution of $ZnCl_2$ (1 M in THF, 1.56 mL, 1.20 equiv) was added and the mixture was allowed to warm up to 25 °C. $Pd(OAc)_2$ (6 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 4-bromo-*N*,*N*-dimethylaniline (**9g**: 200 mg, 1.00 mmol, 0.8 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O, 20:1) furnished 4-(benzo[*b*]thiophen-2-ylmethyl)-*N*,*N*-dimethylaniline (**23f**: 249 mg, 93%) as a white powder.

Melting point (°C): 91.1 – 92.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.77 (d, *J* = 7.96 Hz, 1H), 7.69 (d, *J* = 7.96 Hz, 1H), 7.30 - 7.36 (m, 1H), 7.25 - 7.30 (m, 1H), 7.22 (m, *J* = 8.78 Hz, 2H), 7.03 (s, 1H), 6.78 (m, *J* = 8.51 Hz, 2H), 4.18 (s, 2H), 2.97 (s, 6H).

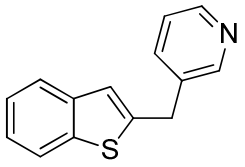
^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 149.3, 146.6, 140.1, 139.8, 129.4, 127.7, 124.0, 123.4, 122.8, 122.1, 121.0, 112.9, 40.7, 36.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2359, 2340, 1739, 1719, 1700, 1615, 1519, 1508, 1498, 1489, 1474, 1464, 1456, 1447, 1436, 1419, 1366, 1352, 1338, 1311, 1228, 1217, 1206, 1192, 1160, 1149, 1127, 1062, 820, 805, 746, 726.

MS (EI, 70 eV): *m/z* (%) = 267 (M^+, 100), 266 (51), 223 (15), 221 (11), 147 (6), 133 (6).

HRMS ($C_{17}H_{17}NS$): calc.: 267.1082; found: 267.1078 (M^+).

Synthesis of 3-(benzo[*b*]thiophen-2-ylmethyl)pyridine (23g):



TMPLi (**21**: 1.25 M in THF, 1.20 mL, 1.15 equiv) was added to a solution of 2-methylbenzo[*b*]thiophene (**20a**: 193 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at -78 °C and the reaction mixture was then stirred at this temperature for 15 min. A solution of $ZnCl_2$ (1 M in THF, 1.56 mL, 1.20 equiv) was added and the mixture was allowed to warm up to 25 °C. $Pd(OAc)_2$ (6 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 3-bromopyridine (**9s**: 158 mg, 1.00 mmol, 0.8 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O, 1:1) furnished 3-(benzo[*b*]thiophen-2-ylmethyl)pyridine (**23g**: 153 mg, 68%) as a slightly yellow powder.

Melting point (°C): 71.9 – 73.8.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 8.62 (d, *J* = 1.66 Hz, 1H), 8.54 (d, *J* = 3.59 Hz, 1H), 7.59 - 7.85 (m, 3H), 7.24 - 7.38 (m, 3H), 7.04 (s, 1H), 4.26 (s, 2H).

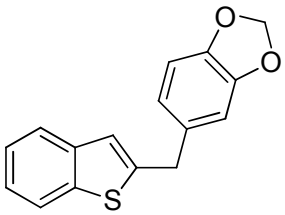
^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 149.5, 147.8, 143.2, 139.9, 139.8, 136.6, 135.2, 124.3, 124.0, 123.6, 123.1, 122.2, 122.2, 34.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2360, 2340, 1572, 1478, 1454, 1428, 1420, 1299, 1235, 1182, 1147, 1130, 1122, 1104, 1092, 1064, 1024, 1012, 940, 909, 860, 841, 813, 787, 748, 728, 714, 699, 676, 668.

MS (EI, 70 eV): *m/z* (%) = 225 (M^+, 100), 224 (54), 223 (11), 148 (6), 147 (49), 112 (6).

HRMS ($C_{14}H_{11}NS$): calc.: 225.0612; found: 225.0603 (M^+).

Synthesis of 5-(benzo[*b*]thiophen-2-ylmethyl)benzo[*d*][1,3]dioxole (23h):



TMPLi (**21**: 1.25 M in THF, 1.20 mL, 1.15 equiv) was added to a solution of 2-methylbenzo[*b*]thiophene (**20a**: 193 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at -78 °C and the reaction mixture was then stirred at this temperature for 15 min. A solution of $ZnCl_2$ (1 M in THF, 1.56 mL, 1.20 equiv) was added and the mixture was allowed to warm up to 25 °C. $Pd(OAc)_2$ (6 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 5-bromobenzo[d][1,3]dioxole (**9e**: 201 mg, 1.00 mmol, 0.8 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane) furnished 5-(benzo[*b*]thiophen-2-ylmethyl)benzo[*d*][1,3]dioxole (**23h**: 233 mg, 87%) as a slightly orange powder.

Melting point (°C): 93.8 – 95.6.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.74 (d, *J* = 7.96 Hz, 1H), 7.67 (d, *J* = 7.96 Hz, 1H), 7.31 (t, *J* = 7.14 Hz, 1H), 7.24 - 7.27 (m, 1H), 7.01 (s, 1H), 6.78 (s, 3H), 5.94 (s, 2H), 4.14 (s, 2H).

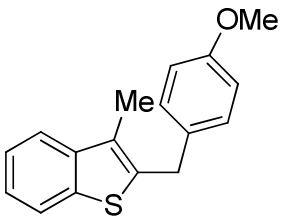
^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 147.8, 146.3, 145.4, 140.0, 139.8, 133.3, 124.1, 123.6, 122.9, 122.1, 121.7, 121.5, 109.2, 108.3, 100.9, 36.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2360, 2340, 1737, 1719, 1498, 1485, 1456, 1436, 1419, 1398, 1373, 1362, 1235, 1218, 1205, 1188, 1154, 1112, 1096, 1036, 1014, 943, 924, 865, 828, 814, 806, 773, 746, 726, 720, 662.

MS (EI, 70 eV): *m/z* (%) = 268 (M^+, 100), 267 (54), 238 (17), 210 (11), 208 (24), 165 (10), 147 (40), 104 (13).

HRMS ($C_{16}H_{12}O_2S$): calc.: 268.0558; found: 268.0549 (M^+).

Synthesis of 2-(4-methoxybenzyl)-3-methylbenzo[*b*]thiophene (23i):

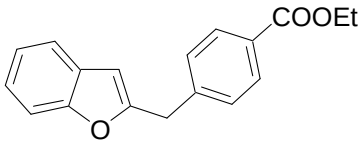


TMPLi (**21**: 1.25 M in THF, 1.20 mL, 1.15 equiv) was added to a solution of 2,3-dimethylbenzo[*b*]thiophene (**20b**: 211 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at -78 °C and the reaction mixture was then stirred at this temperature for 15 min. A solution of $ZnCl_2$

(1 M in THF, 1.56 mL, 1.20 equiv) was added and the mixture was allowed to warm up to 25 °C. $Pd(OAc)_2$ (6 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 1-bromo-4-methoxybenzene (**9b**: 187 mg, 1.00 mmol, 0.8 equiv) were added to the reaction mixture. The resulting mixture was stirred for 2 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O, 20:1) furnished 2-(4-methoxybenzyl)-3-methylbenzo[*b*]thiophene (**23i**: 231 mg, 86%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.80 (d, *J* = 7.70 Hz, 1H), 7.71 (d, *J* = 7.89 Hz, 1H), 7.40 - 7.46 (m, 1H), 7.31 - 7.37 (m, 1H), 7.24 (m, *J* = 8.62 Hz, 2H), 6.92 (m, *J* = 8.62 Hz, 2H), 4.22 (s, 2H), 3.84 (s, 3H), 2.45 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 158.2, 140.9, 138.6, 138.4, 131.8, 129.4, 127.2, 123.8, 123.6, 122.1, 121.4, 113.9, 55.2, 33.5, 11.6.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3058, 2997, 2970, 2912, 2833, 1739, 1719, 1610, 1584, 1509, 1460, 1436, 1379, 1366, 1317, 1301, 1273, 1243, 1175, 1152, 1127, 1108, 1073, 1033, 1016, 933, 820, 784, 752, 728, 708, 674, 668.
MS (EI, 70 eV): *m/z* (%) = 268 (M^+, 85), 253 (100), 237 (8), 221 (9), 161 (26), 160 (11).
HRMS ($C_{17}H_{16}OS$): calc.: 268.0922; found: 268.0915 (M^+).

Synthesis of ethyl 4-(benzofuran-2-ylmethyl)benzoate (26a):

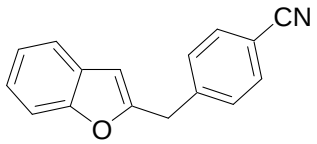


TMPLi (**21**: 1.30 M in THF, 1.50 mL, 1.5 equiv) was added to a solution of 2-methylbenzofuran (**24**: 172 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at -78 °C and the reaction mixture was then stirred at this temperature for 1 h. A solution of $ZnCl_2$ (1 M in THF, 1.95 mL, 1.5 equiv) was added and the mixture was allowed to warm up to 25 °C. $Pd(OAc)_2$ (6 mg, 2 mol%), Xantphos (15 mg, 2 mol%) and ethyl 4-bromobenzoate (**9k**: 229 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced

pressure. Purification by flash-chromatography (*i*-hexane/Et_2O, 10:1) furnished ethyl 4-(benzofuran-2-ylmethyl)benzoate (**26a**: 179 mg, 64%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 8.03 (dt, *J* = 8.46 Hz, 2H), 7.50 (dd, *J* = 6.42, 1.72 Hz, 1H), 7.46-7.34 (m, 3H), 7.27-7.16 (m, 2H), 6.42 (s, 1H), 4.39 (q, *J* = 7.10 Hz, 2H), 4.18 (s, 2H), 1.41 (t, *J* = 7.10 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 166.4, 156.6, 155.0, 142.4, 129.9, 129.1, 128.9, 128.6, 123.6, 122.6, 120.4, 110.9, 103.7, 60.9, 35.0, 14.3.
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063 (vw), 3037 (vw), 2981 (w), 2934 (w), 1711 (s), 1611 (m), 1586 (m), 1474 (m), 1453 (s), 1416 (m), 1366 (m), 1271 (s), 1250 (s), 1176 (m), 1101 (s), 1021 (m), 1010 (m), 951 (m), 924 (w), 854 (m), 826 (m), 794 (m), 749 (s), 720 (s), 686 (w).
MS (EI, 70 eV): *m/z* (%) = 280 (M^+, 100), 251 (26), 235 (35), 207 (89), 178 (45), 131 (53).
HRMS ($C_{18}H_{16}O_3$): calc.: 280.1099; found: 280.1081 (M^+).

Synthesis of 4-(benzofuran-2-ylmethyl)benzonitrile (26b):



$Sc(OTf)_3$ (49 mg, 0.10 mmol) was added to a solution of 2-methylbenzofuran (**24**: 172 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 15 min then cooled to -78 °C. TMPLi (**21**: 1.30 M in THF, 1.50 mL, 1.5 equiv) was added to the solution. After 1 h at -78 °C, a solution of $ZnCl_2$ (1 M in THF, 1.95 mL, 1.5 equiv) was added and the mixture was allowed to warm up to 25 °C. After 30 min at 25 °C, $Pd(OAc)_2$ (6 mg, 2 mol%), Xantphos (15 mg, 2 mol%) and 4-bromobenzonitrile (**9j**: 183 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O, 10:1) furnished 4-(benzofuran-2-ylmethyl)benzonitrile (**26b**: 121 mg, 52%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.64 (dt, *J* = 8.39, 1.87 Hz, 2H), 7.52 (dd, *J* = 6.42, 2.14 Hz, 1H), 7.46-7.40 (m, 3H), 7.27-7.19 (m, 2H), 6.47 (s, 1H), 4.19 (s, 2H).

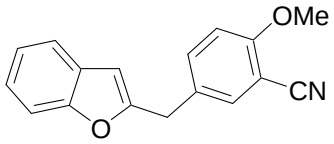
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 155.6, 155.0, 142?8, 132.4, 129.6, 128.5, 123.9, 122.8, 120.6, 118.8, 111.0, 110.8, 104.1, 35.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3062 (w), 3037 (w), 2918 (vw), 2229 (s), 1600 (m), 1583 (m), 1482 (m), 1453 (s), 1432 (m), 1315 (vw), 1289 (vw), 1251 (s), 1191 (m), 1164 (m), 1145 (m), 1104 (w), 1007 (w), 955 (s), 932 (m), 891 (w), 864 (vw), 797 (s), 738 (s), 707 (w), 682 (s).

MS (EI, 70 eV): *m/z* (%) = 233 (M^+, 100), 214 (7), 204 (15), 190 (4), 176 (8), 131 (53).

HRMS ($C_{16}H_{11}NO$): calc.: 233.0841; found: 233.0815 (M^+).

Synthesis of 5-(benzofuran-2-ylmethyl)-2-methoxybenzonitrile (26c):



$Sc(OTf)_3$ (49 mg, 0.10 mmol) was added to a solution of 2-methylbenzofuran (**24**: 172 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 15 min then cooled to -78 °C. TMPLi (**21**: 1.30 M in THF, 1.50 mL, 1.5 equiv) was added to the solution. After 1 h at -78 °C, a solution of $ZnCl_2$ (1 M in THF, 1.95 mL, 1.5 equiv) was added and the mixture was allowed to warm up to 25 °C. After 30 min at 25 °C, $Pd(dba)_2$ (15 mg, 2 mol%), SPhos (21 mg, 4 mol%) and 2-methoxy-5-bromobenzonitrile (**9r**: 212 mg, 1.00 mmol, 0.80 equiv) were added to the reaction mixture. The resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O, 10:1) furnished 5-(benzofuran-2-ylmethyl)-2-methoxybenzonitrile (**26c**: 197 mg, 75%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.53-7.37 (m, 4H), 7.24-7.15 (m, 2H), 6.92 (d, *J* = 8.46 Hz, 1H), 6.40 (d, *J* = 1.02 Hz, 1H), 4.05 (s, 2H), 3.92 (s, 3H).

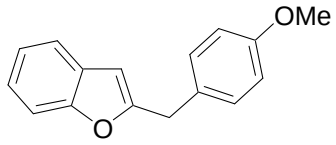
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 160.2, 156.4, 155.0, 134.8, 133.8, 129.9, 128.5, 123.7, 122.7, 116.3, 111.5, 110.9, 103.7, 101.9, 56.1, 33.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3057 (vw), 3036 (vw), 2947 (w), 2929 (w), 2225 (m), 1711 (w), 1609 (m), 1584 (m), 1501 (s), 1453 (s), 1287 (s), 1266 (s), 1251 (s), 1181 (m), 1158 (m), 1121 (m), 1019 (m), 952 (m), 894 (w), 813 (s), 742 (s).

MS (EI, 70 eV): *m/z* (%) = 263 (M^+, 100), 248 (21), 232 (16), 220 (11), 190 (16), 165 (14), 131 (29).

HRMS ($C_{17}H_{13}NO_2$): calc.: 263.0946; found: 263.0947 (M^+).

Synthesis of 2-(4-methoxybenzyl)benzofuran (26d):



TMPLi (**21**: 1.30 M in THF, 1.50 mL, 1.5 equiv) was added to a solution of 2-methylbenzofuran (**24**: 172 mg, 1.30 mmol, 1.00 equiv) in THF (2 mL) at -78 °C and the reaction mixture was then stirred at this temperature for 1 h. A solution of $ZnCl_2$ (1 M in THF, 1.95 mL, 1.5 equiv) was added and the mixture was allowed to warm up to 25 °C. $Pd(dba)_2$ (15 mg, 2 mol%), Xantphos (15 mg, 2 mol%) and 1-bromo-4-methoxybenzene (**9b**: 187 mg, 1.00 mmol, 0.8 equiv) were added to the reaction mixture. The resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/Et_2O, 50:1) furnished 2-(4-methoxybenzyl)benzofuran (**26d**: 178 mg, 75 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.52-7.38 (m, 2H), 7.29-7.15 (m, 4H), 6.90 (dt, *J* = 8.79, 2.39 Hz, 2H), 6.39-6.37 (m, 1H), 4.08 (s, 2H), 3.82 (s, 3H).

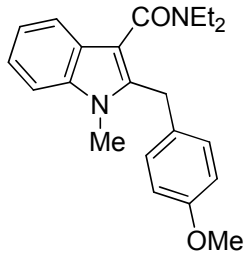
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 158.5, 158.3, 155.0, 129.9, 129.3, 128.9, 123.3, 122.5, 120.4, 114.0, 110.9, 103.1, 55.4, 55.3, 34.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3063 (vw), 3037 (vw), 2981 (w), 1711 (s), 1611 (m), 1586 (w), 1453 (m), 1416 (w), 1271 (s), 1250 (m), 1176 (m), 1101 (s), 1021 (m), 951 (m), 854 (w), 826 (w), 794 (m), 749 (s), 720 (s), 686 (w).

MS (EI, 70 eV): *m/z* (%) = 238 (M^+, 100), 223 (17), 207 (29), 194 (8), 178 (7), 165 (16), 131 (13).

HRMS ($C_{16}H_{11}NO$): calc.: 238.0994; found: 238.0967 (M^+).

Synthesis of *N*,*N*-diethyl-2-(4-methoxybenzyl)-1-methyl-1*H*-indole-3-carboxamide (29):



TMPZnCl·LiCl (**7**: 1.37 M in THF, 0.55 mL, 1.50 equiv) was added to a solution of *N*,*N*-diethyl-1,2-dimethyl-1*H*-indole-3-carboxamide (**27**: 122 mg, 0.5 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h. $Pd(OAc)_2$ (5 mg, 4 mol%), SPhos (16 mg, 8 mol%) and 1-bromo-4-methoxybenzene (**9b**: 94 mg, 0.5 mmol, 1.0 equiv) were added to the reaction mixture. The resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/EtOAc, 3:2) furnished *N*,*N*-diethyl-2-(4-methoxybenzyl)-1-methyl-1*H*-indole-3-carboxamide (**29**: 100 mg, 57%) as an orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.49 (d, *J* = 7.25 Hz, 1H), 7.11 - 7.32 (m, 5H), 6.81 (d, *J* = 8.58 Hz, 2H), 4.26 (s, 2H), 3.77 (s, 3H), 3.36 - 3.70 (m, 7H), 1.16 (s, 6H).

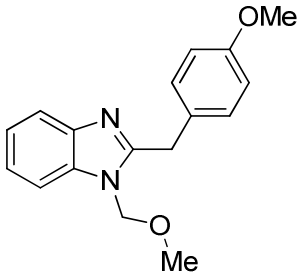
^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 167.6, 158.1, 139.4, 136.3, 130.3, 129.3, 125.2, 121.5, 120.2, 119.1, 113.9, 110.7, 109.2, 55.2, 41.0, 30.4, 29.9, 13.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2970, 2933, 2360, 2341, 1740, 1735, 1609, 1585, 1570, 1558, 1541, 1510, 1465, 1457, 1436, 1424, 1399, 1377, 1366, 1328, 1302, 1275, 1242, 1218, 1176, 1152, 1129, 1121, 1099, 1068, 1032, 1015, 858, 846, 816, 779, 741, 720.

MS (EI, 70 eV): *m/z* (%) = 350 (M^+, 18), 279 (13), 277 (100), 262 (30), 247 (26), 234 (24), 218 (15), 206 (11).

HRMS ($C_{22}H_{26}N_2O_2$): calc.: 350.1994; found: 350.1990 (M^+).

Synthesis of 2-(4-methoxybenzyl)-1-(methoxymethyl)-1*H*-benzo[*d*]imidazole (30):



TMPZnCl·LiCl (**7**: 1.37 M in THF, 1.10 mL, 1.50 equiv) was added to a solution of 1-(methoxymethyl)-2-methyl-1*H*-benzo[*d*]imidazole (**28**: 176 mg, 1.0 mmol, 1.00 equiv) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for 1 h. $Pd(OAc)_2$ (11 mg, 5 mol%), SPhos (33 mg, 8 mol%) and 1-bromo-4-methoxybenzene (**9b**: 168 mg, 0.9 mmol, 0.9 equiv) were added to the reaction mixture. The resulting mixture was stirred for 12 h at 50 °C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 2 mL), extracted with ethyl acetate (3 x 5 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by flash-chromatography (*i*-hexane/EtOAc, 1:1) furnished 2-(4-methoxybenzyl)-1-(methoxymethyl)-1*H*-benzo[*d*]imidazole (**30**: 173 mg, 68%) as a slightly yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm: 7.74 - 7.80 (m, 1H), 7.36 - 7.43 (m, 1H), 7.23 - 7.29 (m, 2H), 7.20 (m, *J* = 8.57 Hz, 2H), 6.82 (m, *J* = 8.85 Hz, 2H), 5.31 (s, 2H), 4.31 (s, 2H), 3.75 (s, 3H), 3.16 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 158.6, 153.8, 142.3, 135.5, 129.5, 128.0, 122.8, 122.4, 119.5, 114.2, 109.4, 74.3, 56.1, 55.2, 33.5.

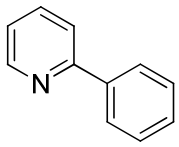
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2998, 2933, 2835, 2360, 2340, 1735, 1718, 1652, 1612, 1585, 1510, 1456, 1425, 1410, 1387, 1364, 1328, 1302, 1279, 1244, 1203, 1176, 1153, 1118, 1094, 1062, 1031, 1009, 966, 917, 846, 830, 815, 775, 741, 725, 704.

MS (EI, 70 eV): *m/z* (%) = 282 (M^+, 71), 268 (12), 251 (36), 239 (100), 237 (38), 221 (11), 219 (27), 131 (58), 121 (88).

HRMS ($C_{17}H_{18}N_2O_2$): calc.: 282.1368; found: 282.1366 (M^+).

5. Iron-Catalyzed Cross-Coupling of *N*-Heterocylic Chlorides and Bromides with Arylmagnesium Reagents Using *t*BuOMe as Solvent

Synthesis of 2-phenylpyridine (33a):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloro- or 2-bromo-pyridine (**31a** or **31b**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, phenylmagnesium chloride (**32a**; 2.3 equiv, 1.7 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 1.5 h (for 2-chloropyridine) or 70 min (for 2-bromopyridine). The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 82% yield (for 2-chloropyridine) or in 83% yield (for 2-bromopyridine) as a colorless oil after purification by flash chromatography (silica gel, 6:1 *i*-hexane/ethyl acetate + 0.5% triethylamine)

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.23 (m, 1 H), 7.45 (m, 3 H), 7.75 (m, 2 H), 8.01 (m, 2 H), 8.70 (d, *J*=4.7 Hz, 1 H).

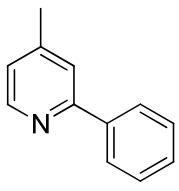
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.60 (s, 1 C), 122.10 (s, 1 C), 126.92 (s, 1 C), 128.74 (s, 1 C), 128.99 (s, 1 C), 136.84 (s, 1 C), 139.24 (s, 1 C), 149.53 (s, 1 C), 157.39 (s, 1 C).

MS (70 eV, EI) m/z (%): 155 (100) $[M]^+$, 154 (60), 128 (10), 127 (10), 77 (9), 59 (10), 43 (7).

IR ATR ν (cm^{-1}): 3062, 3036, 3008, 2927, 1586, 1580, 1564, 1468, 1449, 1424, 1293, 1152, 1074, 1020, 988, 800, 737, 692.

HRMS (EI) for **$C_{11}H_9N$** (155.1735) $[M]^+$: 155.1731.

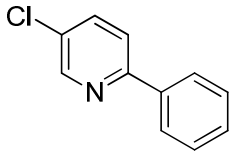
Synthesis of 4-methyl-2-phenylpyridine (33b):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloro-4-methylpyridine (**31c**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, phenylmagnesium chloride (**32a**; 2.3 equiv, 1.7 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 2 h. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 84% yield as a colorless oil after purification by flash chromatography (silica gel, 6:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.41 (s, 3 H), 7.06 (d, *J*=4.1 Hz, 1 H), 7.44 (m, 3 H), 7.55 (s, 1 H), 7.98 (d, *J*=7.2 Hz, 2 H), 8.55 (d, *J*=4.7 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 21.24 (s, 1 C), 121.59 (s, 1 C), 123.14 (s, 1 C), 126.94 (s, 1 C), 128.68 (s, 1 C), 128.88 (s, 1 C), 139.26 (s, 1 C), 147.99 (s, 1 C), 149.18 (s, 1 C), 157.21 (s, 1 C).
MS (70 eV, EI) m/z (%): 169 (100) $[M]^+$, 168 (38), 128 (10), 167 (18), 154 (27), 115 (6), 77 (3).
IR ATR ν (cm^{-1}): 3058, 2921, 1601, 1582, 1557, 1472, 1446, 1400, 1386, 1377, 1073, 1030, 989, 866, 826, 774, 734, 692.
HRMS (EI) for **$C_{12}H_{11}N$** (169.0891) $[M]^+$: 169.0884.

Synthesis of 5-chloro-2-phenylpyridine (33c):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-bromo-5-chloropyridine (**31d**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, phenylmagnesium chloride (**32a**; 2.3 equiv, 1.7 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 70 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 78% yield as a white solid after purification by flash chromatography (silica gel, 30:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 65.1 – 66.8 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.47 (m, 3 H), 7.71 (m, 2 H), 7.95 (s, 1 H), 7.98 (d, *J*=1.4 Hz, 1 H), 8.65 (d, *J*=1.9 Hz, 1 H).

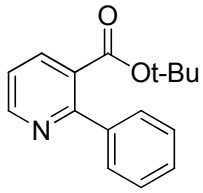
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 121.17 (s, 1 C), 126.82 (s, 1 C), 128.85 (s, 1 C), 129.33 (s, 1 C), 130.63 (s, 1 C), 136.60 (s, 1 C), 138.00 (s, 1 C), 148.34 (s, 1 C), 155.48 (s, 1 C).

MS (70 eV, EI) m/z (%): 189 (100) $[M]^+$, 188 (18), 154 (37), 153 (8), 127 (13), 126 (7), 77 (8).

IR ATR ν (cm^{-1}): 3059, 3033, 2921, 1573, 1554, 1459, 1442, 1365, 1290, 1136, 1111, 1074, 1006, 920, 835, 774, 730, 691.

HRMS (EI) for **$C_{11}H_8ClN$** (189.0345) $[M]^+$: 189.0339.

Synthesis of *tert*-butyl 2-phenylnicotinate (33d):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, *tert*-butyl 2-chloronicotinate (**31e**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, phenylmagnesium chloride (**32a**; 2.3 equiv, 1.7 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 5 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 60% yield as a white solid after purification by flash chromatography (silica gel, 8:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 70.2 – 72.2 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.29 (s, 9 H), 7.31 (dd, *J*=7.7, 4.7 Hz, 1 H), 7.42 (m, 3 H), 7.52 (m, 2 H), 8.07 (dd, *J*=7.7, 1.7 Hz, 1 H), 8.73 (dd, *J*=5.0, 1.7 Hz, 1 H).

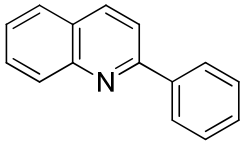
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.51 (s, 1 C), 82.17 (s, 1 C), 121.54 (s, 1 C), 128.03 (s, 1 C), 128.38 (s, 1 C), 128.67 (s, 1 C), 128.93 (s, 1 C), 137.73 (s, 1 C), 140.64 (s, 1 C), 150.68 (s, 1 C), 158.75 (s, 1 C), 167.20 (s, 1 C).

MS (70 eV, EI) m/z (%): 255 (19) $[M]^+$, 200 (23), 199 (100), 198 (40), 182 (28), 155 (62), 154 (26), 127 (16), 57 (10).

IR ATR ν (cm^{-1}): 2977, 2362, 2349, 1701, 1580, 1560, 1428, 1369, 1311, 1293, 1255, 1168, 1128, 1077, 1056, 850, 792, 755, 732, 701.

HRMS (EI) for **$C_{16}H_{17}NO_2$** (255.1259) $[M]^+$: 255.1247.

Synthesis of 2-phenylquinoline (33e):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**31f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, phenylmagnesium chloride (**32a**; 2.3 equiv, 1.7 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 5 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 88% yield as a beige solid after purification by flash chromatography (silica gel, 10:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 81.9 – 83.6 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.50 (m, 4 H), 7.75 (m, 1 H), 7.86 (m, 2 H), 8.22 (m, 4 H).

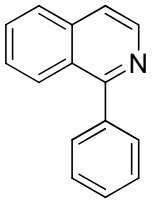
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 119.04 (s, 1 C), 126.38 (s, 1 C), 127.18 (s, 1 C), 127.45 (s, 1 C), 127.65 (s, 1 C), 128.85 (s, 1 C), 129.44 (s, 1 C), 129.52 (s, 1 C), 129.81 (s, 1 C), 137.03 (s, 1 C), 139.35 (s, 1 C), 147.98 (s, 1 C), 157.27 (s, 1 C).

MS (70 eV, EI) m/z (%): 206 (20), 205 (100) $[M]^+$, 204 (70), 203 (13), 175 (12), 169 (15), 102 (9), 84 (8), 44 (27).

IR ATR ν (cm^{-1}): 2923, 2853, 2362, 1740, 1596, 1490, 1446, 1318, 1240, 1213, 1186, 1126, 1050, 1024, 923, 829, 770, 747, 690, 676.

HRMS (EI) for **$C_{15}H_{11}N$** (205.0891) $[M]^+$: 205.0884.

Synthesis of 1-phenylisoquinoline (33f):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**31g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, phenylmagnesium chloride (**32a**; 2.3 equiv, 1.7 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 5 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 90% yield as a white solid after purification by flash chromatography (silica gel, 10:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 97.6 – 99.5 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.53 (m, 4 H), 7.69 (m, 4 H), 7.89 (d, *J*=8.3 Hz, 1 H), 8.12 (d, *J*=8.6 Hz, 1 H), 8.62 (d, *J*=5.5 Hz, 1 H).

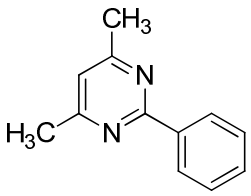
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.01 (s, 1 C), 126.68 (s, 1 C), 126.99 (s, 1 C), 127.26 (s, 1 C), 127.64 (s, 1 C), 128.36 (s, 1 C), 128.69 (s, 1 C), 129.93 (s, 1 C), 130.16 (s, 1 C), 136.93 (s, 1 C), 139.23 (s, 1 C), 141.86 (s, 1 C), 160.60 (s, 1 C).

MS (70 eV, EI) m/z (%): 206 (7), 205 (46) $[M]^+$, 204 (100), 203 (13), 176 (7), 102 (8).

IR ATR ν (cm^{-1}): 3053, 2921, 2364, 2337, 1618, 1582, 1552, 1500, 1440, 1380, 1352, 1319, 1304, 1167, 1020, 973, 954, 875, 823, 803, 798, 767, 754, 706, 699, 675.

HRMS (EI) for **$C_{15}H_{11}N$** (205.0891) $[M]^+$: 205.0864.

Synthesis of 4,6-dimethyl-2-phenylpyrimidine (33g):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloro-4,6-dimethylpyrimidine (**31h**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, phenylmagnesium chloride (**32a**; 2.3 equiv, 1.7 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 2 h. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 76% yield as a white solid after purification by flash chromatography (silica gel, 10:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 82.8 – 84.0 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.54 (s, 6 H), 6.92 (s, 1 H), 7.47 (m, 3 H), 8.43 (d, *J*=1.9 Hz, 1 H), 8.45 (d, *J*=4.4 Hz, 1 H).

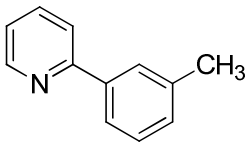
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 24.11 (s, 1 C), 117.97 (s, 1 C), 128.24 (s, 1 C), 128.42 (s, 1 C), 130.31 (s, 1 C), 137.94 (s, 1 C), 164.06 (s, 1 C), 166.77 (s, 1 C).

MS (70 eV, EI) m/z (%): 185 (16), 184 (100) $[M]^+$, 169 (20), 104 (19), 103 (27), 77 (6).

IR ATR ν (cm^{-1}): 3068, 2924, 2853, 2361, 1595, 1574, 1550, 1534, 1442, 1434, 1379, 1364, 1342, 1173, 1025, 932, 854, 749, 693, 662.

HRMS (EI) for **$C_{12}H_{12}N2$** (184.1000) $[M]^+$: 184.0995.

Synthesis of 2-(*m*-tolyl)pyridine (33j):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-bromopyridine (**31b**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, *m*-tolyl-magnesium bromide (**32b**; 2.3 equiv, 1.1 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 1.5 h. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 80% yield as a yellow oil after purification by flash chromatography (silica gel, 5:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.44 (s, 3 H), 7.22 (m, 2 H), 7.37 (t, *J*=7.6 Hz, 1 H), 7.73 (m, 3 H), 7.85 (s, 1 H), 8.69 (d, *J*=4.7 Hz, 1 H).

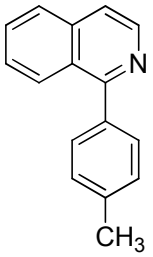
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 21.51 (s, 1 C), 120.61 (s, 1 C), 121.61 (s, 1 C), 123.99 (s, 1 C), 127.64 (s, 1 C), 128.62 (s, 1 C), 129.70 (s, 1 C), 136.67 (s, 1 C), 138.39 (s, 1 C), 139.35 (s, 1 C), 149.58 (s, 1 C), 157.63 (s, 1 C).

MS (70 eV, EI) m/z (%): 170 (14), 168 (52), 167 (23), 154 (10), 115 (5).

IR ATR ν (cm^{-1}): 3049, 3008, 2918, 2860, 1584, 1565, 1473, 1460, 1431, 1302, 1293, 1152, 1087, 1043, 991, 883, 804, 762, 742, 724, 694.

HRMS (EI) for **$C_{12}H_{11}N$** (169.0891) $[M+H]^+$: 169.0886.

Synthesis of 1-(*p*-tolyl)isoquinoline (33k):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**31g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, *p*-tolyl-magnesium bromide (**32b**; 2.3 equiv, 1.2 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 2 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 93% yield as a yellow oil after purification by flash chromatography (silica gel, 12:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.47 (s, 3 H), 7.35 (d, *J*=8.0 Hz, 2 H), 7.54 (t, *J*=7.6 Hz, 1 H), 7.66 (m, 4 H), 7.88 (d, *J*=8.0 Hz, 1 H), 8.14 (d, *J*=8.6 Hz, 1 H), 8.61 (d, *J*=5.8 Hz, 1 H).

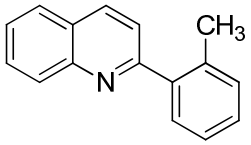
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 21.35 (s, 1 C), 119.77 (s, 1 C), 126.72 (s, 1 C), 126.96 (s, 1 C), 127.13 (s, 1 C), 127.74 (s, 1 C), 129.04 (s, 1 C), 129.87 (s, 1 C), 130.07 (s, 1 C), 136.37 (s, 1 C), 136.94 (s, 1 C), 138.58 (s, 1 C), 141.86 (s, 1 C), 160.66 (s, 1 C).

MS (70 eV, EI) m/z (%): 219 (80) $[M]^+$, 218 (100), 217 (21), 216 (20), 205 (11), 204 (59), 203 (11), 175 (9), 108 (13), 43 (13).

IR ATR ν (cm^{-1}): 3049, 2919, 2852, 1618, 1583, 1552, 1497, 1452, 1384, 1355, 1320, 1305, 1182, 1166, 1138, 1111, 1021, 974, 873, 848, 821, 799, 787, 749, 722, 677.

HRMS (EI) for **$C_{16}H_{13}N$** (219.1048) $[M]^+$: 219.1023.

Synthesis of 2-(*o*-tolyl)quinoline (33l):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**31f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, *o*-tolyl-magnesium bromide (**32b**; 2.3 equiv, 0.9 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 45 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 84% yield as a beige solid after purification by flash chromatography (silica gel, 5:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 78.3 – 80.4 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.43 (s, 3 H), 7.34 (s, 3 H), 7.54 (m, 3 H), 7.75 (t, *J*=7.7 Hz, 1 H), 7.87 (d, *J*=8.3 Hz, 1 H), 8.21 (m, 2 H).

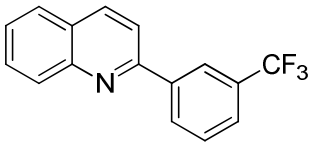
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 20.34 (s, 1 C), 122.37 (s, 1 C), 126.01 (s, 1 C), 126.44 (s, 1 C), 126.73 (s, 1 C), 127.49 (s, 1 C), 128.54 (s, 1 C), 129.50 (s, 1 C), 129.68 (s, 1 C), 129.70 (s, 1 C), 130.86 (s, 1 C), 136.00 (s, 1 C), 136.18 (s, 1 C), 140.56 (s, 1 C), 147.75 (s, 1 C), 160.22 (s, 1 C).

MS (70 eV, EI) m/z (%): 218 (100) $[M-H]^+$, 217 (27), 216 (8), 85 (27), 83 (35).

IR ATR ν (cm^{-1}): 2951, 2921, 2852, 1740, 1602, 1592, 1553, 1501, 1485, 1455, 1420, 1378, 1334, 1311, 1276, 1264, 1238, 1217, 1204, 1118, 1037, 1014, 976, 941, 836, 798, 772, 762, 754, 722, 688, 674.

HRMS (EI) for **$C_{16}H_{13}N$** (219.1048) $[M+H]^+$: 219.0957.

Synthesis of 2-(3-(trifluoromethyl)phenyl)quinoline (33m):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**31f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, (3-(trifluoromethyl)phenyl)magnesium bromide (**32e**; 2.3 equiv, 0.9 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 15 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 92% yield as a beige solid after purification by flash chromatography (silica gel, 5:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 76.5 – 78.5 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.56 (t, *J*=7.5 Hz, 1 H), 7.64 (t, *J*=7.7 Hz, 1 H), 7.75 (m, 2 H), 7.86 (m, 2 H), 8.22 (dd, *J*=15.5, 8.6 Hz, 2 H), 8.36 (d, *J*=7.7 Hz, 1 H), 8.48 (s, 1 H).

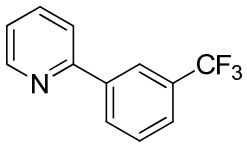
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 118.52 (s, 1 C), 124.16 (q, *J*=272.65 Hz), 124.39 (q, *J*=3.92 Hz), 125.84 (q, *J*=3.93 Hz), 126.74 (s, 1 C), 127.37 (s, 1 C), 127.48 (s, 1 C), 129.27 (s, 1 C), 129.81 (s, 1 C), 129.94 (s, 1 C), 130.66 (s, 1 C), 131.23 (q, *J*=32.26 Hz), 137.11 (s, 1 C), 140.35 (s, 1 C), 148.24 (s, 1 C), 155.52 (s, 1 C).

MS (70 eV, EI) m/z (%): 274 (19), 273 (100) $[M]^+$, 272 (29), 252 (10), 204 (21), 203 (6).

IR ATR ν (cm^{-1}): 3060, 2362, 1741, 1592, 1509, 1483, 1466, 1428, 1336, 1274, 1261, 1236, 1168, 1142, 1115, 1096, 1074, 1051, 806, 786, 757, 704, 693, 652.

HRMS (EI) for $C_{16}H_{10}F_3N$ (273.0765) $[M]^+$: 273.0763.

Synthesis of 2-(3-(trifluoromethyl)phenyl)pyridine (33n):

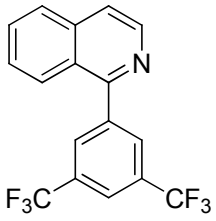


In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-bromopyridine (**31b**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were

dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, (3-(trifluoromethyl)phenyl)magnesium bromide (**32e**; 2.3 equiv, 0.9 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 2 h. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 66% yield as a yellow oil after purification by flash chromatography (silica gel, 5:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.28 (m, 1 H), 7.58 (t, *J*=7.7 Hz, 1 H), 7.67 (m, 1 H), 7.78 (m, 2 H), 8.18 (d, *J*=7.7 Hz, 1 H), 8.29 (s, 1 H), 8.72 (d, *J*=4.7 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.55 (s, 1C), 122.79 (s, 1C), 123.76 (q, *J*=3.93 Hz), 124.16 (q, *J*=272.36 Hz), 125.50 (q, *J*=3.93 Hz), 129.18 (s, 1C), 130.01 (s, 1C), 131,20 (q, *J*=32.54 Hz), 136.95 (s, 1C), 140.10 (s, 1C), 149,86 (s, 1C), 155.81 (s, 1C).
MS (70 eV, EI) m/z (%): 224 (10), 223 (100) $[M]^+$, 222 (12), 202 (7), 154 (21).
IR ATR ν (cm^{-1}): 3074, 3054, 3011, 1586, 1464, 1437, 1418, 1333, 1272, 1262, 1163, 1117, 1094, 1073, 1064, 1040, 991, 919, 826, 811, 773, 739, 696, 662.
HRMS (EI) for **$C_{12}H_8F_3N$** (223.0609) $[M]^+$: 223.0509.

Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)isoquinoline (33o):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**31g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, (3,5-bis(trifluoromethyl)phenyl)magnesium bromide (**32f**; 2.3 equiv, 1.0 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 5 h. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 75% yield as a beige solid after purification by flash chromatography (silica gel, 10:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 75.0 – 76.6 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.63 (t, *J*=7.9 Hz, 1 H), 7.76 (m, 2 H), 7.95 (d, *J*=8.3 Hz, 2 H), 8.03 (s, 1 H), 8.20 (s, 2 H), 8.65 (d, *J*=5.8 Hz, 1 H).

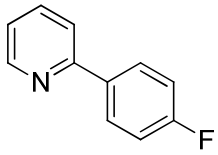
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 121.17 (s, 1C), 122.38 (m), 123.27 (q, *J*=272.72 Hz), 126.07 (s, 1C), 126.32 (s,1C), 127.44 (s, 1C), 128.19 (s, 1C), 130.14 (m), 130.52 (s, 1C), 131.83 (q, *J*=37.59 Hz), 136.95 (s, 1C), 141.56 (s, 1C), 142.29 (s, 1C), 157.22 (s, 1C).

MS (70 eV, EI) m/z (%): 342 (62), 341 (100) $[M]^+$, 320 (8), 272 (15), 271 (7).

IR ATR ν (cm^{-1}): 3059, 2360, 1623, 1567, 1368, 1335, 1275, 1184, 1164, 1123, 1107, 1069, 898, 877, 846, 829, 746, 714, 703, 690, 678.

HRMS (EI) for **$C_{17}H_9F_6N$** (341. 0639) $[M]^+$: 341.0549.

Synthesis of 2-(4-fluorophenyl)pyridine (33p):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-bromopyridine (**31b**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, (4-fluorophenyl)magnesium bromide (**32g**; 2.3 equiv, 1.0 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 5 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 68% yield as a beige solid after purification by flash chromatography (silica gel, 6:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 40.6 – 41.8 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.20 (m, 3 H), 7.72 (m, 2 H), 7.98 (m, 2 H), 8.67 (d, *J*=4.4 Hz, 1 H).

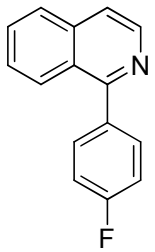
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 115.62 (d, *J*=21.63 Hz), 120.17 (s, 1C), 122,00 (s, 1C), 128.65 (d, *J*=8.26 Hz), 135.54 (d, *J*=4.4 Hz), 136.77 (s, 1C), 149.66 (s, 1C), 156.44 (s, 1C), 163.47 (d, *J*=248.25 Hz).

MS (70 eV, EI) m/z (%): 174 (11), 173 (100) $[M]^+$, 172 (50), 146 (7), 145 (5).

IR ATR ν (cm^{-1}): 3053, 2924, 2854, 1599, 1584, 1567, 1510, 1466, 1434, 1409, 1393, 1297, 1219, 1160, 1152, 1098, 989, 844, 826, 818, 773, 737, 724, 706.

HRMS (EI) for **$C_{11}H_8FN$** (173.0641) $[M]^+$: 173.0641.

Synthesis of 1-(4-fluorophenyl)isoquinoline (33q):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**31g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, ((4-fluorophenyl)magnesium bromide (**32g**; 2.3 equiv, 1.0 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 5 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 90% yield as a beige solid after purification by flash chromatography (silica gel, 8:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 79.8 – 81.5 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.22 (t, *J*=8.7 Hz, 2 H), 7.54 (t, *J*=7.6 Hz, 1 H), 7.68 (m, 4 H), 7.88 (d, *J*=8.3 Hz, 1 H), 8.06 (d, *J*=8.6 Hz, 1 H), 8.60 (d, *J*=5.8 Hz, 1 H).

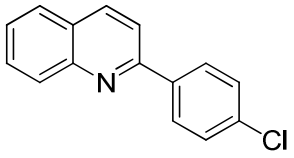
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 115.37 (d, *J*=21.64 Hz), 120.00 (s, 1C), 126.64 (s, 1C), 127.06 (s, 1C), 127.24 (s, 1C), 127.30 (s, 1C), 130.06 (s, 1C), 131.70 (d, *J*=8.26 Hz), 135.65 (d, *J*=3.41 Hz), 136.88 (s, 1C), 142.17 (s, 1C), 159.59 (s, 1C), 163.08 (d, *J*=247.96 Hz).

MS (70 eV, EI) m/z (%): 223 (100) $[M+H]^+$, 202 (7), 194 (4), 111 (3), 83 (22).

IR ATR ν (cm^{-1}): 3056, 2924, 2854, 1795, 1604, 1582, 1553, 1509, 1498, 1384, 1353, 1233, 1221, 1159, 975, 877, 844, 834, 804, 798, 757, 724, 674.

HRMS (EI) for **$C_{15}H_{10}FN$** (223.0797) $[M+H]^+$: 223.0701.

Synthesis of 2-(4-chlorophenyl)quinoline (33r):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**31f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, (4-chlorophenyl)magnesium bromide (**32h**; 2.3 equiv, 1.2 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 5 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 84% yield as a white solid after purification by flash chromatography (silica gel, 10:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 114.8 – 116.2 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.52 (m, 3 H), 7.76 (m, 3 H), 8.15 (m, 4 H).

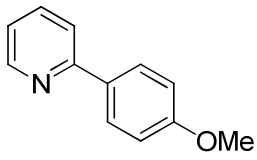
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 118.49 (s, 1 C), 126.47 (s, 1 C), 127.20 (s, 1 C), 127.47 (s, 1 C), 128.79 (s, 1 C), 129.99 (s, 1 C), 129.70 (s, 1 C), 129.81 (s, 1 C), 135.53 (s, 1 C), 136.91 (s, 1 C), 138.02 (s, 1 C), 148.22 (s, 1 C), 155.93 (s, 1 C).

MS (70 eV, EI) m/z (%): 241 (5), 239 (100) $[M]^+$, 203 (2), 102 (1).

IR ATR ν (cm^{-1}): 3055, 2361, 2338, 1596, 1588, 1577, 1552, 1486, 1430, 1399, 1285, 1089, 1050, 1008, 939, 815, 788, 770, 752, 732, 715, 672, 652.

HRMS (EI) for **$C_{15}H_{10}ClN$** (239.0502) $[M]^+$: 239.0507.

Synthesis of 2-(4-methoxyphenyl)pyridine (33s):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-bromopyridine (**31b**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, (4-methoxyphenyl)magnesium bromide (**32i**; 2.3 equiv, 1.3 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 10 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 82% yield as a white solid after purification by flash chromatography (silica gel, 5:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 58.7 – 60.4 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.86 (s, 3 H), 7.00 (d, *J*=8.8 Hz, 2 H), 7.18 (m, 1 H), 7.71 (m, 2 H), 7.95 (d, *J*=8.8 Hz, 2 H), 8.66 (d, *J*=4.4 Hz, 1 H).

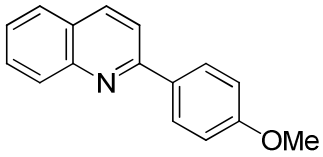
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.34 (s, 1 C), 114.14 (s, 1 C), 119.91 (s, 1 C), 121.42 (s, 1 C), 128.21 (s, 1 C), 131.71 (s, 1 C), 136.87 (s, 1 C), 149.28 (s, 1 C), 156.98 (s, 1 C), 160.53 (s, 1 C).

MS (70 eV, EI) m/z (%): 186 (13), 185 (100) $[M]^+$, 142 (26), 141 (16), 115 (5).

IR ATR ν (cm^{-1}): 3062, 2997, 2963, 2837, 1601, 1586, 1579, 1562, 1513, 1458, 1431, 1407, 1306, 1302, 1272, 1243, 1176, 1151, 1113, 1058, 1036, 1021, 1005, 838, 776, 736, 718.

HRMS (EI) for **$C_{12}H_{11}NO$** (185.0841) $[M]^+$: 185.0840.

Synthesis of 2-(4-methoxyphenyl)quinoline (33t):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**31f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, (4-methoxyphenyl)magnesium bromide (**32i**; 2.3 equiv, 1.3 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 5 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 87% yield as a white solid after purification by flash chromatography (silica gel, 7:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 123.7 – 125.6 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.87 (s, 3 H), 7.05 (d, *J*=8.8 Hz, 2 H), 7.49 (t, *J*=7.5 Hz, 1 H), 7.75 (m, 3 H), 8.16 (m, 4 H).

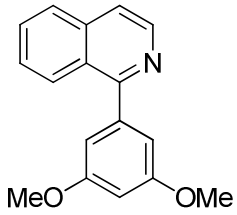
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.37 (s, 1 C), 114.23 (s, 1 C), 118.51 (s, 1 C), 125.90 (s, 1 C), 126.90 (s, 1 C), 127.43 (s, 1 C), 128.89 (s, 1 C), 129.49 (s, 1 C), 129.57 (s, 1 C), 132.18 (s, 1 C), 136.63 (s, 1 C), 148.24 (s, 1 C), 156.85 (s, 1 C), 160.84 (s, 1 C).

MS (70 eV, EI) m/z (%): 235 (100) $[M]^+$, 220 (18), 192 (17), 191 (18), 95 (3).

IR ATR ν (cm^{-1}): 3047, 2961, 2841, 1603, 1595, 1582, 1497, 1468, 1430, 1321, 1290, 1284, 1247, 1175, 1156, 1124, 1112, 1028, 1013, 948, 847, 834, 816, 789, 770, 761, 748, 726, 678.

HRMS (EI) for **$C_{16}H_{13}NO$** (235.0997) $[M]^+$: 235. 0993.

Synthesis of 1-(3,5-dimethoxyphenyl)isoquinoline (33u):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**31g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, (3,5-dimethoxyphenyl)magnesium bromide (**32j**; 2.3 equiv, 1.2 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 5 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 71% yield as a yellow oil after purification by flash chromatography (silica gel, 10:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.84 (s, 6 H), 6.61 (t, *J*=2.3 Hz, 1 H), 6.83 (d, *J*=2.4 Hz, 2 H), 7.52 (m, 1 H), 7.67 (m, 2 H), 7.86 (d, *J*=8.3 Hz, 1 H), 8.14 (d, *J*=8.6 Hz, 1 H), 8.59 (d, *J*=5.7 Hz, 1 H).

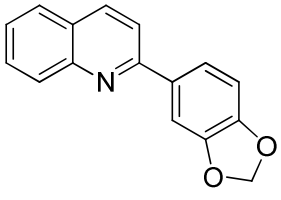
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.48 (s, 1 C), 101.04 (s, 1 C), 107.98 (s, 1 C), 120.08 (s, 1 C), 126.66 (s, 1 C), 126.91 (s, 1 C), 127.18 (s, 1 C), 127.57 (s, 1 C), 130.05 (s, 1 C), 136.80 (s, 1 C), 141.39 (s, 1 C), 141.99 (s, 1 C), 160.55 (s, 1 C), 160.66 (s, 1 C).

MS (70 eV, EI) m/z (%): 266 (13), 265 (100) $[M]^+$, 264 (91), 250 (19), 235 (14), 234 (22), 206 (11), 191 (13).

IR ATR ν (cm^{-1}): 3051, 3000, 2936, 2838, 1591, 1585, 1557, 1453, 1424, 1383, 1358, 1318, 1203, 1151, 1061, 1051, 1003, 927, 824, 799, 775, 750, 700, 686, 654.

HRMS (EI) for **$C_{17}H_{15}NO_2$** (265.1103) $[M]^+$: 265.1090.

Synthesis of 2-(benzo[*d*][1,3]dioxol-5-yl)quinoline (33v):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**31f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, benzo[*d*][1,3]dioxol-5-ylmagnesium bromide (**32k**; 2.3 equiv, 1.2 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 5 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 81% yield as a white solid after purification by flash chromatography (silica gel, 10:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 97.9 – 99.1 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.03 (s, 2 H), 6.95 (d, *J*=8.3 Hz, 1 H), 7.50 (t, *J*=7.0 Hz, 1 H), 7.72 (m, 5 H), 8.14 (dd, *J*=8.4, 4.0 Hz, 2 H).

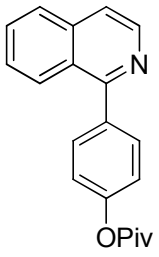
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 101.35 (s, 1 C), 107.91 (s, 1 C), 108.45 (s, 1 C), 118.56 (s, 1 C), 121.73 (s, 1 C), 126.03 (s, 1 C), 126.98 (s, 1 C), 127.39 (s, 1 C), 129.54 (s, 1 C), 129.62 (s, 1 C), 134.11 (s, 1 C), 136.64 (s, 1 C), 148.17 (s, 1 C), 148.38 (s, 1 C), 148.82 (s, 1 C), 156.62 (s, 1 C).

MS (70 eV, EI) m/z (%): 250 (15), 249 (100) $[M]^+$, 248 (15), 191 (12), 190 (9), 163 (2).

IR ATR ν (cm^{-1}): 3051, 3008, 2895, 2780, 1594, 1494, 1486, 1454, 1443, 1425, 1353, 1290, 1251, 1245, 1233, 1222, 1206, 1116, 1108, 1097, 1035, 930, 916, 906, 892, 837, 826, 813, 799, 782, 742, 718, 682.

HRMS (EI) for **$C_{16}H_{11}NO_2$** (249. 0790) $[M]^+$: 249.0782.

Synthesis of 4-(isoquinolin-1-yl)phenyl pivalate (33w):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**31g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, (4-(pivaloyloxy)phenyl)magnesium bromide (**32l**; 2.3 equiv, 0.8 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 15 min. The reaction

mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 80% yield as a white solid after purification by flash chromatography (silica gel, 4:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 97.1 – 96.3 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.41 (s, 9 H), 7.25 (d, *J*=8.6 Hz, 2 H), 7.54 (t, *J*=7.2 Hz, 1 H), 7.70 (m, 4 H), 7.88 (d, *J*=8.0 Hz, 1 H), 8.11 (d, *J*=8.3 Hz, 1 H), 8.60 (d, *J*=5.5 Hz, 1 H).

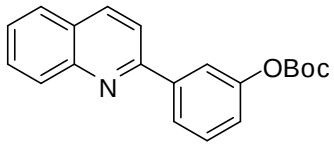
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.16 (s, 1 C), 39.17 (s, 1 C), 120.19 (s, 1 C), 121.50 (s, 1 C), 126.71 (s, 1 C), 127.01 (s, 1 C), 127.39 (s, 1 C), 127.52 (s, 1 C), 130.23 (s, 1 C), 131.01 (s, 1 C), 136.59 (s, 1 C), 136.93 (s, 1 C), 141.80 (s, 1 C), 151.58 (s, 1 C), 159.77 (s, 1 C), 177.00 (s, 1 C).

MS (70 eV, EI) m/z (%): 305 (68) $[M]^+$, 222 (12), 221 (70), 220 (100), 204 (22), 192 (20), 191 (35), 110 (26), 57 (32).

IR ATR ν (cm^{-1}): 3469, 2974, 2872, 1749, 1740, 1554, 1498, 1478, 1457, 1384, 1354, 1275, 1199, 1164, 1111, 1026, 1016, 974, 900, 882, 858, 844, 834, 820, 798, 788, 754, 726, 678.

HRMS (EI) for **$C_{20}H_{19}NO_2$** (305. 1416) $[M]^+$: 305. 1409.

Synthesis of *tert*-butyl 3-(quinolin-2-yl)phenyl carbonate (33x):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**31f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, (3-(*tert*-butoxycarbonyloxy)phenyl)magnesium bromide (**32m**; 2.3 equiv, 0.7 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 15 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 84% yield as a white solid after purification by flash chromatography (silica gel, 4:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 95.1 – 96.3 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.60 (s, 9 H), 7.29 (m, 1 H), 7.53 (t, *J*=7.9 Hz, 2 H), 7.73 (m, 1 H), 7.83 (m, 2 H), 8.04 (dd, *J*=4.1, 2.2 Hz, 2 H), 8.19 (m, 2 H).

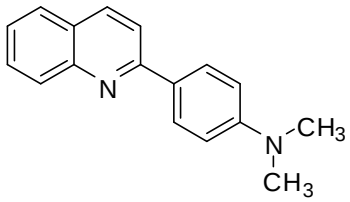
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.75 (s, 1 C), 83.58 (s, 1 C), 118.80 (s, 1 C), 120.43 (s, 1 C), 122.23 (s, 1 C), 124.80 (s, 1 C), 126.50 (s, 1 C), 127.30 (s, 1 C), 127.45 (s, 1 C), 129.71 (s, 1 C), 129.77 (s, 1 C), 136.93 (s, 1 C), 141.13 (s, 1 C), 148.12 (s, 1 C), 151.67 (s, 1 C), 151.83 (s, 1 C), 156.03 (s, 1 C).

MS (70 eV, EI) m/z (%): 321 (9) $[M]^+$, 222 (13), 221 (100), 220 (82), 204 (22), 191 (16), 57 (26).

IR ATR ν (cm^{-1}): 3496, 3076, 2982, 1747, 1598, 1454, 1445, 1369, 1295, 1274, 1264, 1252, 1242, 1183, 1142, 1083, 1047, 928, 869, 825, 804, 787, 780, 769, 742, 692, 686.

HRMS (EI) for **$C_{20}H_{19}NO_3$** (321. 1365) $[M]^+$: 321. 1360.

***N*,*N*-dimethyl-4-(quinolin-2-yl)aniline (3y) (CAS Number: 16032-41-0):**



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**31f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP2**. Then, (4-(dimethylamino)phenyl)magnesium bromide (**32n**; 2.3 equiv, 1.3 M) dissolved in THF was added dropwise at room temperature while stirring the reaction mixture for 5 min. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was separated and dried over Na_2SO_4. The product was obtained in 82% yield as a red solid after purification by flash chromatography (silica gel, 9:1 *i*-hexane/ethyl acetate + 0.5% triethylamine).

m.p.: 175.8 – 177.5 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.04 (s, 6 H), 6.84 (d, *J*=8.8 Hz, 2 H), 7.46 (t, *J*=7.2 Hz, 1 H), 7.69 (m, 1 H), 7.77 (d, *J*=7.9 Hz, 1 H), 7.83 (d, *J*=8.6 Hz, 1 H), 8.12 (dd, *J*=8.5, 6.6 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 40.34 (s, 1 C), 112.24 (s, 1 C), 118.26 (s, 1 C), 125.33 (s, 1 C), 126.69 (s, 1 C), 127.33 (s, 1 C), 127.37 (s, 1 C), 128.46 (s, 1 C), 129.33 (s, 1 C), 136.26 (s, 1 C), 148.41 (s, 1 C), 151.35 (s, 1 C), 157.33 (s, 1 C).

MS (70 eV, EI) m/z (%): 248 (100) $[M]^+$, 247 (35), 204 (11), 124 (4).

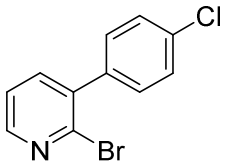
IR ATR ν (cm^{-1}): 3058, 2887, 2809, 1595, 1564, 1545, 1539, 1498, 1434, 1360, 1326, 1286, 1226, 1198, 1168, 1140, 1130, 1120, 947, 811, 789, 762.

HRMS (EI) for $C_{17}H_{16}N_2$ (248. 1313) $[M]^+$: 248.1309.

6. Ligand-Accelerated Fe- and Co-Catalyzed Cross-Coupling Reactions between *N*-Heterocyclic Halides and Arylmagnesium Reagents

6.1. Preparation of the Starting Materials

Synthesis of 2-bromo-3-(4-chlorophenyl)pyridine (35b):



Diisopropylamine (1.0 equiv, 20 mmol) in THF (50 mL) was cooled to -78 °C, and *n*-BuLi (1.0 equiv, 20 mmol) was added dropwise at -78 °C. The reaction mixture was stirred for 15 min at -78 °C, slowly warmed up to -5 °C and then cooled to -95 °C. A solution of 2-bromo-pyridine (1 equiv, 20 mmol) in THF (20 mL) was added dropwise, and the reaction mixture was stirred for 4 h at -95 °C. A solution of $ZnCl_2$ (1.1 equiv, 22 mmol, 1 M in THF) was added dropwise and the reaction mixture was warmed up to 25 °C. 1-Chloro-4-iodobenzene (0.75 equiv, 15 mmol) and $Pd(Ph_3P)_4$ (5 mol%) were added and the reaction mixture was heated to 50 °C for 2 h. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was dried with Na_2SO_4 and the crude material was purified by column chromatography (silica gel, 10:1 *i*-hexane/ethyl acetate) to furnish 2.01 g (50%) of the product as a pink solid.

m.p.: 136 – 139 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.29 - 7.48 (m, 5 H), 7.59 (dd, *J*=7.46, 1.66 Hz, 1 H), 8.38 (dd, *J*=4.56, 1.52 Hz, 1 H).

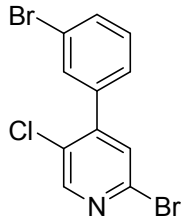
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 122.74 (s, 1 C), 128.56 (s, 1 C), 130.62 (s, 1 C), 134.56 (s, 1 C), 137.24 (s, 1 C), 138.60 (s, 1 C), 138.90 (s, 1 C), 142.21 (s, 1 C), 149.01 (s, 1 C)

MS (70 eV, EI) m/z (%): 267 (48), 190 (27), 188 (100), 153 (52), 152 (27), 126 (15).

IR ATR ν (cm^{-1}): 3045, 3036, 2000, 1911, 1572, 1554, 1494, 1442, 1408, 1376, 1301, 1098, 1090, 1053, 1020, 997, 833, 822, 803, 778, 744, 715, 700.

HRMS (EI) for **$C_{11}H_7BrClN$** (266.9450) $[M]^+$: 266.9444.

Synthesis of 2-bromo-4-(3-bromophenyl)-5-chloropyridine (35e):



Diisopropylamine (1.1 equiv, 16.5 mmol) in THF (24 mL) was cooled to -78 °C and *n*-BuLi (1.1 equiv, 16.5 mmol) was added dropwise at -78 °C. The reaction mixture was stirred for 15 minutes at -78 °C, slowly warmed up to -5 °C and then cooled to -78 °C. A solution of 2-bromo-5-chloropyridine (1 equiv, 15 mmol) in THF (7 mL) was added dropwise, and the reaction mixture was stirred for 2 h. A solution of $ZnCl_2$ (1.2 equiv, 18 mmol, 1 M in THF) was added at -78 °C and the reaction mixture was allowed to warm up to 25 °C. 1-Bromo-3-iodobenzene (1.1 equiv, 16.5 mmol) and $Pd(Ph_3P)_4$ (5 mol%) were added, and the reaction mixture was heated to 50 °C over night. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was dried with Na_2SO_4 and the crude material was purified by column chromatography (silica gel, 11:1 *i*-hexane/ethyl acetate) to furnish 3.6 g (68%) of the product as a yellow solid.

m.p.: 109 – 111 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.34 - 7.42 (m, 2 H), 7.47 (s, 1 H), 7.58 - 7.65 (m, 2 H), 8.45 (s, 1 H).

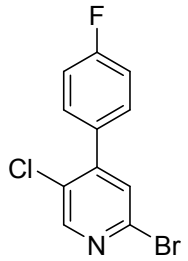
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 122.60 (s, 1 C), 127.47 (s, 1 C), 129.13 (s, 1 C), 129.74 (s, 1 C), 130.11 (s, 1 C), 131.68 (s, 1 C), 132.45 (s, 1 C), 137.09 (s, 1 C), 140.03 (s, 1 C), 148.61 (s, 1 C), 150.05 (s, 1 C).

MS (70 eV, EI) m/z (%): 345 (18), 268 (20), 267 (16), 187 (47), 152 (12).

IR ATR ν (cm^{-1}): 3045, 2361, 1564, 1512, 1443, 1412, 1322, 1282, 1112, 1095, 1067, 1023, 995, 920, 890, 880, 784, 746, 730, 691, 664.

HRMS (EI) for **$C_{11}H_6Br_2ClN$** (344.8556) $[M]^+$: 344.8541.

Synthesis of 2-bromo-5-chloro-4-(4-fluorophenyl)pyridine (35h):



Diisopropylamine (1.1 equiv, 16.5 mmol) in THF (24 mL) was cooled to -78 °C and *n*-BuLi (1.1 equiv, 16.5 mmol) was added dropwise at -78 °C. The reaction mixture was stirred for 15 minutes at -78 °C, slowly warmed up to -5 °C and then cooled to -78 °C. A solution of 2-bromo-5-chloropyridine (1 equiv, 15 mmol) in THF (7 mL) was added dropwise, and the reaction mixture was stirred for 2 h. A solution of $ZnCl_2$ (1.2 equiv, 18 mmol, 1 M in THF) was added at -78 °C and reaction mixture was allowed to warm up to 25 °C. 1-Fluoro-4-iodobenzene (1.1 equiv, 16.5 mmol) and $Pd(Ph_3P)_4$ (5 mol%) were added. The reaction mixture was heated to 50 °C over night. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was dried with Na_2SO_4 and the crude material was purified by column chromatography (silica gel, 10:1 *i*-hexane/ethyl acetate) to furnish 3 g (70%) of the product as a white solid.

m.p.: 130 – 132 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 11.25 (t, *J*=8.67 Hz, 2 H), 11.51 - 11.56 (m, 3 H), 12.50 (s, 1 H).

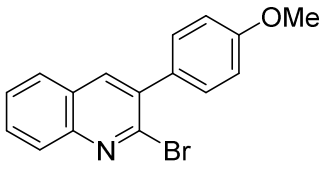
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 115.78 (d, *J*=21.88 Hz, 1 C) 129.22 (s, 1 C), 129.83 (s, 1 C), 130.82 (d, *J*=8.45 Hz, 1 C), 131.18 (d, *J*=3.07 Hz, 1 C), 139.99 (s, 1 C), 149.15 (s, 1 C), 149.99 (s, 1 C), 163.30 (d, *J*=250.29 Hz, 1 C).

MS (70 eV, EI) m/z (%): 285 (34), 206 (37), 171 (50), 144 (13), 73 (29), 61 (100).

IR ATR ν (cm^{-1}): 3076, 3041, 2362, 1907, 1773, 1604, 1569, 1507, 1446, 1334, 1234, 1223, 1159, 1109, 1098, 1020, 886, 843, 832.

HRMS (EI) for **$C_{11}H_6BrClFN$** (284.9356) $[M]^+$: 284.9332.

Synthesis of 2-bromo-3-(4-methoxyphenyl)quinoline (35i):



Diisopropylamine (1.1 equiv, 8.8 mmol) in THF (13 mL) was cooled to -78 °C and *n*-BuLi (1.1 equiv, 8.8 mmol) was added dropwise at -78 °C. The reaction mixture was stirred for 15 minutes at -78 °C, slowly warmed up to -5 °C and then cooled to -90 °C. A solution of 2-bromoquinoline (1 equiv, 8 mmol) in THF (4 mL) was added dropwise, and the reaction mixture was stirred for 4 h. A Solution of $ZnCl_2$ (1.2 equiv, 9.6 mmol, 1 M in THF) was added at -90 °C and reaction mixture was allowed to warm up to 25 °C. 1-Iodo-4-methoxybenzene (1.1 equiv, 8.8 mmol) and $Pd(Ph_3P)_4$ (5 mol%) were added. The reaction mixture was heated to 50 °C over night. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was dried with Na_2SO_4, and the crude material was purified by column chromatography (silica gel, 12:1 *i*-hexane/ethyl acetate) to produce 0.5 g (20%) of the product as a white solid.

m.p.: 91 – 95 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.89 (s, 3 H), 7.01 (m, 2 H), 7.44 (m, 2 H), 7.58 (ddd, *J*=8.11, 6.91, 1.19 Hz, 1 H), 7.73 (ddd, *J*=8.52, 6.97, 1.43 Hz, 1 H), 7.81 (dd, *J*=8.11, 1.19 Hz, 1 H), 8.03 (s, 1 H), 8.06 - 8.12 (m, 1 H).

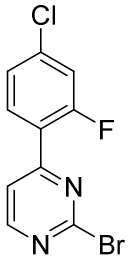
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.34 (s, 1 C), 113.64 (s, 1 C), 127.32 (s, 1 C), 127.34 (s, 1 C), 127.52 (s, 1 C), 128.41 (s, 1 C), 130.22 (s, 1 C), 130.94 (s, 1 C), 131.39 (s, 1 C), 136.77 (s, 1 C), 137.80 (s, 1 C), 143.23 (s, 1 C), 147.35 (s, 1 C), 159.67 (s, 1 C).

MS (70 eV, EI) m/z (%): 313 (31), 234 (22), 219 (14), 191 (11), 190 (14).

IR ATR ν (cm^{-1}): 3044, 2965, 2914, 2839, 1608, 1584, 1512, 1484, 1390, 1340, 1285, 1238, 1177, 1133, 1078, 1027, 1014, 958, 878, 827, 810, 794, 781, 767, 656.

HRMS (EI) for **$C_{16}H_{12}BrNO$** (313.0102) $[M]^+$: 313.0091.

Synthesis of 2-bromo-4-(4-chloro-2-fluorophenyl)pyrimidine (35l):



2-Bromopyridine (1 equiv, 6 mmol) in THF (6 mL) was reacted with a solution of TMPMgCl·LiCl (1.1 equiv, 6.6 mmol, 1.00 M in THF) at -55 °C for 1.5 h. A solution of $ZnCl_2$ (1.2 equiv, 7.2 mmol, 1 M in THF) was added, and the reaction mixture was allowed to warm up to 25 °C. 4-Chloro-2-fluoro-1-iodobenzene (1.3 equiv, 7.8 mmol), $Pd(dba)_2$ (3 mol%) and P(*o*-furyl)$_3$ (6 mol%) were added, and the reaction mixture was heated to 50 °C over night. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was dried with Na_2SO_4 and the crude material was purified by column chromatography (silica gel, 5:1 *i*-hexane/ethyl acetate) to furnish 1.7 g (78%) of the product as a white solid.

m.p.: 125 - 127 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.22 - 7.35 (m, 2 H), 7.83 (dd, *J*=5.36, 1.55 Hz, 1 H), 8.23 (t, *J*=8.46 Hz, 1 H), 8.62 (d, *J*=5.25 Hz, 1 H)

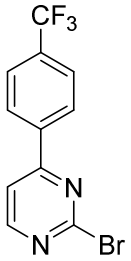
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 117.32 (d, J=26.37 Hz, 1 C), 119.33 (d, J=13.46 Hz, 1 C), 125.55 (s, 1 C), 131.84 (s, 1 C), 138.74 (d, J=10.94 Hz, 1 C), 153.29 (s, 1 C), 159.84 (s, 1 C), 161.19 (d, J=256.93 Hz), 161.63 (s, 1 C), 161.68 (s, 1 C).

MS (70 eV, EI) m/z (%): 285 (1), 88 (5), 73 (5), 70 (10), 61 (17).

IR ATR ν (cm^{-1}): 3112, 3101, 3032, 2360, 1612, 1561, 1527, 1483, 1418, 1402, 1348, 1345, 1340, 1212, 1191, 1172, 1086, 901, 858, 845, 820, 788, 771, 706, 661.

HRMS (EI) for **$C_{10}H_5BrClFN_2$** (285.9309) $[M]^+$: 285.9307.

Synthesis of 2-bromo-4-(4-(trifluoromethyl)phenyl)pyrimidine (35m):



2-Bromopyridine (1 equiv, 6 mmol) in THF (6 mL) was reacted with a solution of TMPMgCl·LiCl (1.1 equiv, 6.6 mmol, 1.00 M in THF) at -55 °C for 1.5 h. A solution of $ZnCl_2$ (1.2 equiv., 7.2 mmol, 1 M in THF) was added and the reaction mixture was allowed to warm up to 25 °C. 1-Iodo-4-(trifluoromethyl)benzene (1.3 equiv, 7.8 mmol), $Pd(dba)_2$ (3 mol%) and P(*o*-furyl)$_3$ (6 mol%) were added and the reaction mixture was heated to 50 °C over night. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was dried with Na_2SO_4 and the crude material was purified by column chromatography (silica gel, 4:1 *i*-hexane/ethyl acetate) to furnish 1.3 g (70%) of the product as a white solid.

m.p.: 89 – 93 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.73 (d, *J*=5.24 Hz, 1 H), 7.78 (m, *J*=8.23 Hz, 2 H), 8.20 (m, *J*=8.04 Hz, 2 H), 8.65 (d, *J*=5.05 Hz, 1 H).

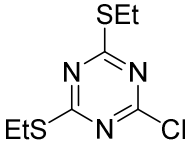
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 115.87 (s, 1 C), 123.67 (q, J=272.36 Hz, 1 C), 126.07 (q, J=3.93 Hz, 1 C), 127.80 (s, 1 C), 133.46 (q, J=32.82 Hz, 1 C), 138.27 (s, 1 C), 153.80 (s, 1 C), 160.03 (s, 1 C), 165.32 (s, 1 C).

MS (70 eV, EI) m/z (%): 223 (4), 171 (1), 88 (4), 73 (4), 70 (9).

IR ATR ν (cm^{-1}): 3132, 3060, 2362, 2332, 1563, 1430, 1320, 1180, 1171, 1162, 1119, 1077, 1055, 1018, 982, 842, 830, 816, 770, 764, 740, 702.

HRMS (EI) for **$C_{11}H_6BrF_3N_2$** (301.9666) $[M]^+$: 303.9646.

Synthesis of 2-chloro-4,6-bis(ethylthio)-1,3,5-triazine (35q):



BuLi (2.2 equiv, 475 mmol) was added to a solution of EtSH (2.5 equiv, 534 mmol) in THF (200 mL) at -78 °C. The mixture was immediately warmed to 25 °C. The milky-white mixture was transferred via syringe to a solution of cyanuric chloride (1 equiv, 216 mmol) in THF (50 mL) at -78 °C. The mixture was immediately warmed to 25 °C and quenched with NH_4Cl sat. aq. The mixture was extracted with Et_2O, dried with $MgSO_4$, filtered, and concentrated in vacuo to yield the crude substance as an orange oil, which was composed of the title compound mixed with 2,4,6-tris(ethylthio)-1,3,5-triazine. Purification was

accomplished using vacuum distillation (bp 97-98 °C, 0.001 mbar) to provide the titled compound as a pale yellow oil that was 18.7 g (37%) pure by GC analysis.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.35 (td, *J*=7.26, 2.90 Hz, 6 H), 2.93 - 3.26 (m, *J*=7.36, 7.36, 7.26, 2.90 Hz, 4 H).

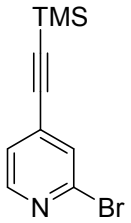
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.03 (s, 1 C), 25.13 (s, 1 C), 167.95 (s, 1 C), 182.82 (s, 1 C).

MS (70 eV, EI) m/z (%): 235 (100), 206 (18), 202 (23), 172 (40), 146 (60), 88 (30).

IR ATR ν (cm^{-1}): 2972, 2930, 2873, 1499, 1453, 1412, 1374, 1279, 1233, 1152, 1135, 1056, 966, 838, 787, 750.

HRMS (EI) for **$C_7H_{10}ClN_3S_2$** (235.0005) $[M]^+$: 234.9994.

Synthesis of 2-bromo-4-((trimethylsilyl)ethynyl)pyridine (35r):



Triethylamine (60 mL) and toluene (30 mL) were added to 2-bromo-4-iodopyridine (1 equiv, 9 mmol). $Pd(Ph_3P)_4$ (5 mol%) and CuI (10 mol%) were added and the reaction mixture was cooled to 0 °C. Trimethylsilylacetylene (1 equiv, 9 mmol) was added and the reaction mixture was stirred at room temperature over night. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was dried with Na_2SO_4 and the crude material was purified by column chromatography (silica gel, 9:1 *i*-hexane/ethyl acetate) to furnish 1.37 g (60%) of the product as a slightly yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.26 (s, 9 H), 7.24 (dd, *J*=5.11, 1.24 Hz, 1 H), 7.51 (s, 1 H), 8.30 (d, *J*=4.98 Hz, 1 H).

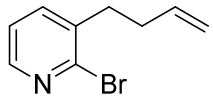
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -0.43 (s, 1 C), 100.32 (s, 1 C), 101.96 (s, 1 C), 124.71 (s, 1 C), 130.03 (s, 1 C), 133.74 (s, 1 C), 142.13 (s, 1 C), 149.82 (s, 1 C).

MS (70 eV, EI) m/z (%): 252 (5), 240 (63), 239 (10), 144 (5), 131 (4), 80 (9).

IR ATR ν (cm^{-1}): 2960, 2900, 2172, 1580, 1570, 1518, 1456, 1365, 1250, 1112, 1077, 983, 873, 835, 759, 710.

HRMS (EI) for **$C_{10}H_{12}BrNSi$** (252.9922) $[M]^+$: 253.9824.

Synthesis of 2-bromo-3-(but-3-en-1-yl)pyridine (35s):

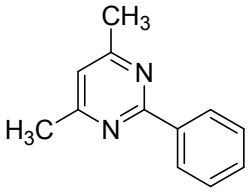


2-Bromo-3-(bromomethyl)pyridine (1 equiv, 1 mmol) was dissolved in THF (3 mL) and a solution of allyl magnesium chloride (1.1 equiv, 1.1 mmol, 1.2 M in THF) was added dropwise at -78 °C. The reaction mixture was allowed to warm up to room temperature over night. The reaction mixture was quenched with brine and extracted with EtOAc. The organic phase was dried with Na_2SO_4 and the crude material was purified by column chromatography (silica gel, 6:1 *i*-hexane/ethyl acetate) to furnish 81 mg (38%) of the product as a colorless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.40 (q, *J*=7.31 Hz, 2 H), 2.81 (t, *J*=7.75 Hz, 2 H), 4.84 - 5.22 (m, 2 H), 5.73 - 5.96 (m, *J*=16.96, 10.28, 6.65, 6.65 Hz, 1 H), 7.18 (dd, *J*=7.39, 4.77 Hz, 1 H), 7.48 (dd, *J*=7.39, 1.43 Hz, 1 H), 8.21 (dd, *J*=4.53, 1.67 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 33.08 (s, 1 C), 34.59 (s, 1 C), 115.86 (s, 1 C), 122.72 (s, 1 C), 136.82 (s, 1 C), 138.18 (s, 1 C), 138.32 (s, 1 C), 144.37 (s, 1 C), 147.63 (s, 1 C).
MS (70 eV, EI) m/z (%): 170 (100), 132 (82), 131 (39), 91 (24), 90 (18).
IR ATR ν (cm^{-1}): 3077, 2979, 2930, 2862, 1641, 1578, 1557, 1446, 1401, 1180, 1088, 1064, 1049, 994, 912, 796, 740, 674, 659.
HRMS (EI) for **$C_9H_{10}BrN$** (210.9997) $[M]^+$: 211.0013.

6.2. Preparation of the Title Compounds Using TP3:

Synthesis of 4,6-dimethyl-2-phenylpyrimidine (33g):

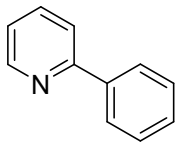


A solution of **32a** in THF (1.0 mmol, 2.0 equiv, 1.7 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **31h** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 5 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with

CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **33g** as a white powder.

Isolated yield: with $FeBr_3$: 89% (82 mg).
Reaction time: 5 min.
Solvent for purification: 10:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.
m.p.: 82.8 – 84.0 ºC.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.54 (s, 6 H), 6.92 (s, 1 H), 7.47 (m, 3 H), 8.43 (d, *J*=1.9 Hz, 1 H), 8.45 (d, *J*=4.4 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 24.11 (s, 1 C), 117.97 (s, 1 C), 128.24 (s, 1 C), 128.42 (s, 1 C), 130.31 (s, 1 C), 137.94 (s, 1 C), 164.06 (s, 1 C), 166.77 (s, 1 C).
MS (70 eV, EI) m/z (%): 185 (16), 184 (100) $[M]^+$, 169 (20), 104 (19), 103 (27), 77 (6).
IR ATR ν (cm^{-1}): 3068, 2924, 2853, 2361, 1595, 1574, 1550, 1534, 1442, 1434, 1379, 1364, 1342, 1173, 1025, 932, 854, 749, 693, 662.
HRMS (EI) for **$C_{12}H_{12}N2$** (184.1000) $[M]^+$: 184.0995.

Synthesis of 2-phenylpyridine (33a):



A solution of **32a** in THF (1.0 mmol, 2.0 equiv, 1.7 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **31a** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **33a** as a colorless oil.

Isolated yield: with $FeBr_3$: 89% (69 mg).

Reaction time: 15 min.

Solvent for purification: 6:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.23 (m, 1 H), 7.45 (m, 3 H), 7.75 (m, 2 H), 8.01 (m, 2 H), 8.70 (d, *J*=4.7 Hz, 1 H).

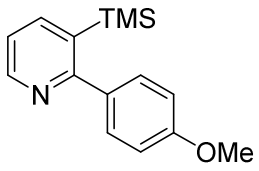
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.60 (s, 1 C), 122.10 (s, 1 C), 126.92 (s, 1 C), 128.74 (s, 1 C), 128.99 (s, 1 C), 136.84 (s, 1 C), 139.24 (s, 1 C), 149.53 (s, 1 C), 157.39 (s, 1 C).

MS (70 eV, EI) m/z (%): 155 (100) $[M]^+$, 154 (60), 128 (10), 127 (10), 77 (9), 59 (10), 43 (7).

IR ATR ν (cm^{-1}): 3062, 3036, 3008, 2927, 1586, 1580, 1564, 1468, 1449, 1424, 1293, 1152, 1074, 1020, 988, 800, 737, 692.

HRMS (EI) for **$C_{11}H_9N$** (155.1735) $[M]^+$: 155.1731.

Synthesis of 2-(4-methoxyphenyl)-3-(trimethylsilyl)pyridine (34a):



A solution of **32i** in THF (1.0 mmol, 2.0 equiv, 1.3 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35a** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34a** as a colorless oil.

Isolated yield: with $FeBr_3$: 91% (117 mg).

with $CoCl_2$: 85% (109 mg).

Reaction time: 15 min.

Solvent for purification: 4:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.05 (s, 9 H), 3.84 (s, 3 H), 6.94 (m, *J*=8.85 Hz, 2 H), 7.20 (dd, *J*=7.46, 4.70 Hz, 1 H), 7.34 (m, *J*=8.57 Hz, 2 H), 7.89 (dd, *J*=7.60, 1.80 Hz, 1 H), 8.59 (dd, *J*=4.70, 1.94 Hz, 1 H).

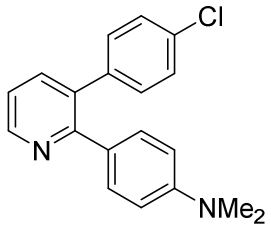
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 0.25 (s, 1 C), 55.29 (s, 1 C), 113.29 (s, 1 C), 121.02 (s, 1 C), 130.11 (s, 1 C), 133.30 (s, 1 C), 136.29 (s, 1 C), 143.17 (s, 1 C), 148.91 (s, 1 C), 159.62 (s, 1 C), 165.10 (s, 1 C).

MS (70 eV, EI) m/z (%): 257 (91), 242 (100), 227 (23), 211 (6), 199 (13).

IR ATR ν (cm^{-1}): 3045, 2954, 2898, 2836, 1609, 1548, 1515, 1402, 1298, 1245, 1172, 1038, 1025, 832, 809, 787, 753, 731, 688, 656.

HRMS (EI) for **$C_{15}H_{19}NOSi$** (257.1236) $[M]^+$: 257.1222.

Synthesis of 4-(3-(4-chlorophenyl)pyridin-2-yl)-*N*,*N*-dimethylaniline (34b):



A solution of **32n** in THF (1.0 mmol, 2.0 equiv, 1.2 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35b** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34b** as a slightly yellow oil.

Isolated yield: with $FeBr_3$: 82% (127 mg)
with $CoCl_2$: 77% (119 mg)

Reaction time: 15 min.

Solvent for purification: 9:1 dichloromethane/ethyl acetate + 0.5% triethylamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.95 (s, 6 H), 6.59 (d, *J*=8.85 Hz, 2 H), 7.08 - 7.35 (m, 7 H), 7.61 (dd, *J*=7.74, 1.66 Hz, 1 H), 8.65 (dd, *J*=4.70, 1.66 Hz, 1 H).

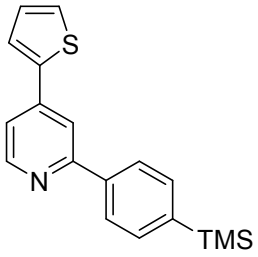
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 40.28 (s, 1 C), 111.63 (s, 1 C), 120.91 (s, 1 C), 127.49 (s, 1 C), 128.56 (s, 1 C), 130.75 (s, 1 C), 130.85 (s, 1 C), 132.97 (s, 1 C), 133.96 (s, 1 C), 138.32 (s, 1 C), 139.32 (s, 1 C), 148.51 (s, 1 C), 150.10 (s, 1 C), 157.19 (s, 1 C).

MS (70 eV, EI) m/z (%): 308 (100), 307 (45), 291 (19), 153 (9), 136 (12).

IR ATR ν (cm^{-1}): 3037, 2885, 2855, 2801, 1606, 1576, 1524, 1489, 1425, 1394, 1353, 1193, 1168, 1090, 999, 945, 834, 821, 799, 778, 758, 728, 718, 704.

HRMS (EI) for **$C_{19}H_{17}ClN_2$** (308.1080) $[M]^+$: 308.1060.

4-(thiophen-2-yl)-2-(4-(trimethylsilyl)phenyl)pyridine (34c):



A solution of **32o** in THF (1.0 mmol, 2.0 equiv, 1.2 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35c** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34c** as a slightly yellow oil.

Isolated yield: with $FeBr_3$: 65% (101 mg).

with $CoCl_2$: 70% (108 mg).

Reaction time: 15 min.

Solvent for purification: 9:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.33 (s, 9 H), 7.17 (dd, *J*=5.13, 3.70 Hz, 1 H), 7.44 (d, *J*=5.25 Hz, 2 H), 7.54 - 7.60 (m, 1 H), 7.67 (m, *J*=8.11 Hz, 2 H), 7.92 (s, 1 H), 8.02 (m, *J*=8.11 Hz, 2 H), 8.68 (d, *J*=5.01 Hz, 1 H).

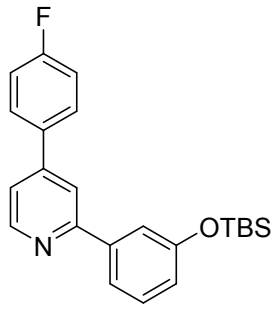
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -1.12 (s, 1 C), 117.00 (s, 1 C), 118.52 (s, 1 C), 125.31 (s, 1 C), 126.19 (s, 1 C), 127.10 (s, 1 C), 128.43 (s, 1 C), 133.79 (s, 1 C), 139.57 (s, 1 C), 141.53 (s, 1 C), 141.67 (s, 1 C), 142.16 (s, 1 C), 150.26 (s, 1 C), 158.32 (s, 1 C).

MS (70 eV, EI) m/z (%): 309 (20), 296 (9), 295 (27), 294 (100).

IR ATR ν (cm^{-1}): 3073, 3021, 2953, 2895, 1593, 1554, 1467, 1405, 1246, 1107, 989, 837, 815, 799, 785, 759, 754, 720, 699, 679.

HRMS (EI) for **$C_{18}H_{19}NSSi$** (309.1007) $[M]^+$: 309.0977.

Synthesis of 2-(3-((tert-butyldimethylsilyl)oxy)phenyl)-4-(4-fluorophenyl)pyridine (34d):



A solution of **32p** in THF (1.0 mmol, 2.0 equiv, 1.05 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35d** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34d** as a slightly yellow oil.

Isolated yield: with $FeBr_3$: 71% (131 mg).
with $CoCl_2$: 79% (145 mg).

Reaction time: 15 min.

Solvent for purification: 9:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.26 (s, 6 H), 1.03 (s, 9 H), 6.93 (dd, *J*=7.99, 1.79 Hz, 1 H), 7.21 (t, *J*=8.58 Hz, 2 H), 7.31 - 7.44 (m, 2 H), 7.54 (d, *J*=2.15 Hz, 1 H), 7.58 - 7.74 (m, 3 H), 7.84 (s, 1 H), 8.73 (d, *J*=5.25 Hz, 1 H).

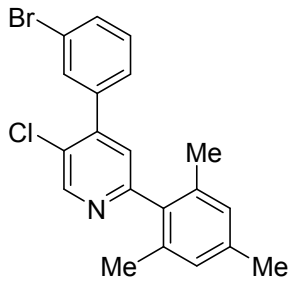
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.32 (s, 1 C), 18.23 (s, 1 C), 25.73 (s, 1 C), 116.15 (d, *J*=21.60 Hz, 1 C), 118.63 (s, 1 C), 118.88 (s, 1 C), 120.08 (s, 1 C), 120.69 (s, 1 C), 128.85 (d, *J*=8.41 Hz, 1 C), 129.70 (s, 1 C), 134.63 (s, 1 C), 134.68 (s, 1 C), 140.94 (s, 1 C), 148.18 (s, 1 C), 150.11 (s, 1 C), 156.15 (s, 1 C), 157.99 (s, 1 C), 163.42 (d, J=249.08 Hz, 1 C).

MS (70 eV, EI) m/z (%): 322 (100), 281 (41), 209 (13), 207 (83), 97 (12).

IR ATR ν (cm^{-1}): 3064, 2955, 2930, 2895, 2858, 1597, 1581, 1512, 1464, 1444, 1270, 1253, 1233, 1204, 1160, 948, 825, 779, 724, 693, 666.

HRMS (EI) for **$C_{23}H_{26}FNOSi$** (379.1768) $[M]^+$: 379.1756.

Synthesis of 4-(3-bromophenyl)-5-chloro-2-mesitylpyridine (34e):



A solution of **32q** in THF (1.0 mmol, 2.0 equiv, 1.1 M) was added dropwise to a suspension of $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35e** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 5 h before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34e** as a slightly yellow oil.

Isolated yield: with $CoCl_2$: 82% (159 mg).

Reaction time: 5 h.

Solvent for purification: 10:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.04 - 2.13 (m, 6 H), 2.34 (s, 3 H), 6.95 (s, 2 H), 7.21 - 7.24 (m, 1 H), 7.33 - 7.41 (m, 1 H), 7.44 - 7.51 (m, 1 H), 7.55 - 7.65 (m, 1 H), 7.65 - 7.73 (m, 1 H), 8.76 - 8.81 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 20.33 (s, 1 C), 21.18 (s, 1 C), 122.53 (s, 1 C), 126.20 (s, 1 C), 127.80 (s, 1 C), 128.01 (s, 1 C), 128.54 (s, 1 C), 130.06 (s, 1 C), 132.01 (s, 1 C), 135.59

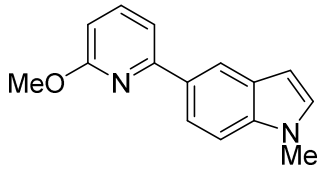
(s, 1 C), 135.69 (s, 1 C), 136.29 (s, 1 C), 137.98 (s, 1 C), 138.58 (s, 1 C), 146.11 (s, 1 C), 150.09 (s, 1 C), 158.85 (s, 1 C).

MS (70 eV, EI) m/z (%): 386 (100), 384 (74), 255 (5), 230 (24), 127 (8).

IR ATR ν (cm^{-1}): 2966, 2918, 2858, 1612, 1577, 1563, 1525, 1478, 1455, 1355, 1106, 1093, 1073, 1025, 996, 907, 881, 851, 840, 786, 732, 697, 679, 658.

HRMS (EI) for **$C_{20}H_{17}BrClN$** (385.0233) $[M]^+$:384.0152.

Synthesis of 5-(6-methoxypyridin-2-yl)-1-methyl-1*H*-indole (34f):



A solution of **32r** in THF (1.0 mmol, 2.0 equiv, 0.9 M) was added dropwise to a suspension of $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35f** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 1 h before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34f** as a slightly yellow solid.

Isolated yield: with $CoCl_2$: 65% (77 mg).

Reaction time: 1 h.

Solvent for purification: 4:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

m.p.: 99 – 108 °C.

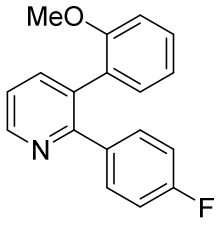
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.83 (s, 3 H), 4.10 (s, 3 H), 6.59 (dd, *J*=3.04, 0.83 Hz, 1 H), 6.65 (dd, *J*=8.16, 0.69 Hz, 1 H), 7.09 (d, *J*=3.04 Hz, 1 H), 7.37 - 7.43 (m, 2 H), 7.63 (dd, *J*=8.02, 7.46 Hz, 1 H), 7.99 (dd, *J*=8.57, 1.66 Hz, 1 H), 8.37 (dd, *J*=1.66, 0.55 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 32.93 (s, 1 C), 53.17 (s, 1 C), 101.85 (s, 1 C), 107.76 (s, 1 C), 109.18 (s, 1 C), 112.39 (s, 1 C), 119.54 (s, 1 C), 120.79 (s, 1 C), 128.77 (s, 1 C), 129.51 (s, 1 C), 130.75 (s, 1 C), 137.32 (s, 1 C), 139.04 (s, 1 C), 156.15 (s, 1 C), 163.63 (s, 1 C).

MS (70 eV, EI) m/z (%): 238 (64), 237 (48), 209 (12), 207 (13), 104 (5).

IR ATR ν (cm^{-1}): 3001, 2944, 1591, 1580, 1566, 1463, 1446, 1428, 1419, 1410, 1335, 1321, 1278, 1243, 1178, 1150, 1081, 1061, 1020, 986, 940, 893, 859, 788, 767, 735, 726, 662.
HRMS (EI) for **$C_{15}H_{14}N_2O$** (238.1106) $[M]^+$:238.1097.

Synthesis of 2-(4-fluorophenyl)-3-(2-methoxyphenyl)pyridine (34g):



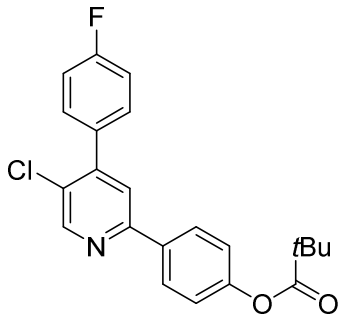
A solution of **32g** in THF (1.0 mmol, 2.0 equiv, 1.05 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35g** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34g** as a slightly yellow oil.

Isolated yield: with $FeBr_3$: 77% (108 mg).
with $CoCl_2$: 79% (110 mg).
Reaction time: 15 min.
Solvent for purification: 9:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.42 (s, 3 H), 6.78 (d, *J*=8.22 Hz, 1 H), 6.84 - 7.05 (m, 3 H), 7.16 (dd, *J*=7.40, 1.53 Hz, 1 H), 7.23 - 7.41 (m, 4 H), 7.69 (dd, *J*=7.63, 1.53 Hz, 1 H), 8.67 (dd, *J*=4.75, 1.47 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 54.96 (s, 1 C), 111.05 (s, 1 C), 114.42 (d, *J*=21.35 Hz, 1 C), 120.84 (s, 1 C), 121.87 (s, 1 C), 128.75 (s, 1 C), 129.36 (s, 1 C), 130.54 (d, *J*=8.26 Hz, 1 C), 131.14 (s, 1 C), 132.73 (s, 1 C), 137.06 (s, 1 C), 139.10 (s, 1 C), 148.21 (s, 1 C), 155.98 (s, 1 C), 157.02 (s, 1 C), 162.36 (d, *J*=246.54 Hz, 1 C).
MS (70 eV, EI) m/z (%): 279 (15), 278 (15), 264 (4), 248 (9), 235 (4).

IR ATR ν (cm^{-1}): 3050, 2958, 2936, 2836, 1895, 1599, 1580, 1510, 1495, 1462, 1436, 1420, 1273, 1220, 1181, 1157, 1124, 1107, 1094, 1050, 1025, 1015, 999, 839, 824, 811, 802, 780, 751, 718, 678.

HRMS (EI) for **$C_{18}H_{14}FNO$** (279.1059) $[M]^+$: 278.0958.

Synthesis of 4-(5-chloro-4-(4-fluorophenyl)pyridin-2-yl)phenyl pivalate (34h):



A solution of **32l** in THF (1.0 mmol, 2.0 equiv, 0.8 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35h** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34h** as a white thick oil.

Isolated yield: with $FeBr_3$: 65% (125 mg).

Reaction time: 15 min.

Solvent for purification: 15:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.39 (s, 9 H), 7.12 - 7.25 (m, 4 H), 7.48 - 7.56 (m, 2 H), 7.64 - 7.69 (m, 1 H), 8.02 (d, *J*=8.57 Hz, 2 H), 8.72 (s, 1 H).

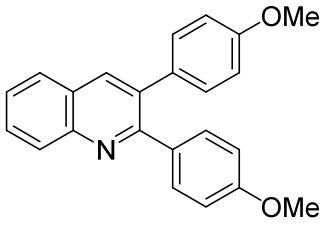
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.13 (s, 1 C), 39.15 (s, 1 C), 115.60 (d, *J*=21.64 Hz, 1 C), 121.93 (s, 1 C), 127.45 (s, 1 C), 127.91 (s, 1 C), 128.03 (s, 1 C), 128.71 (s, 1 C), 130.86 (d, *J*=8.26 Hz, 1 C), 132.74 (s, 1 C), 132.79 (s, 1 C), 135.47 (s, 1 C), 147.19 (s, 1 C), 149.83 (s, 1 C), 152.19 (s, 1 C), 155.15 (s, 1 C), 163.07 (d, *J*=249.10 Hz, 1 C), 176.88 (s, 1 C).

MS (70 eV, EI) m/z (%): 383 (14), 300 (18), 299 (100), 264 (11), 85 (14).

IR ATR ν (cm^{-1}): 2975, 2874, 1747, 1606, 1507, 1480, 1460, 1366, 1276, 1231, 1200, 1163, 1102, 1022, 1014, 908, 895, 856, 836, 816, 800, 788, 757, 729.

HRMS (EI) for **$C_{22}H_{19}ClFNO_2$** (383.1088) $[M]^+$: 383.1083.

Synthesis of 2,3-bis(4-methoxyphenyl)quinoline (34i):



A solution of **32i** in THF (1.0 mmol, 2.0 equiv, 1.3 M) was added dropwise to a suspension of $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35i** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34i** as a slightly yellow oil.

Isolated yield: with $CoCl_2$: 78% (133 mg).

Reaction time: 15 min.

Solvent for purification: 4:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.81 (s, 3 H), 3.82 (s, 3 H), 6.77 - 6.90 (m, 5H), 7.16 - 7.19 (m, 2 H), 7.42 - 7.44 (m, 2 H), 7.54 (ddd, *J*=8.04, 6.97, 1.17 Hz, 1 H), 7.70 - 7.75 (m, 1 H), 7.84 (dd, *J*=8.19, 1.17 Hz, 1 H), 8.14 (s, 1 H).

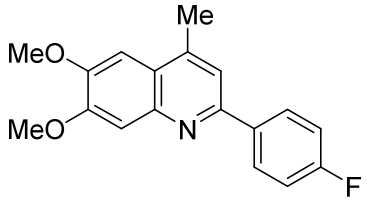
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 59.35 (s, 1 C), 59.42 (s, 1 C), 117.57 (s, 1 C), 117.90 (s, 1 C), 130.74 (s, 1 C), 131.28 (s, 1 C), 131.42 (s, 1 C), 132.80 (s, 1 C), 133.76 (s, 1 C), 134.89 (s, 1 C), 135.63 (s, 1 C), 136.24 (s, 1 C), 137.00 (s, 1 C), 138.23 (s, 1 C), 141.91 (s, 1 C), 147.53 (s, 1 C), 159.32 (s, 1 C), 163.00 (s, 1 C), 163.84 (s, 1 C).

MS (70 eV, EI) m/z (%): 340 (100), 326 (11), 297 (14), 254 (12), 163 (5).

IR ATR ν (cm^{-1}): 2999, 2955, 2945, 2917, 2835, 1607, 1511, 1483, 1463, 1455, 1422, 1402, 1370, 1289, 1242, 1173, 1144, 1109, 1027, 965, 829, 809, 792, 782, 757, 746, 731, 714, 666.

HRMS (EI) for **$C_{23}H_{19}NO_2$** (341.1416) $[M]^+$:340.1336.

Synthesis of 2-(4-fluorophenyl)-6,7-dimethoxy-4-methylquinoline (34j):



A solution of **32g** in THF (1.0 mmol, 2.0 equiv, 1.05 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35j** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34j** as a slightly yellow solid.

Isolated yield: with $FeBr_3$: 82% (122 mg).
with $CoCl_2$: 67% (100 mg).

Reaction time: 15 min.

Solvent for purification: 9:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

m.p.: 164 – 168 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.70 (s, 3 H), 4.05 (s, 3 H), 4.06 (s, 3 H), 7.12 - 7.23 (m, 3 H), 7.54 (d, *J*=2.76 Hz, 2 H), 8.09 (dd, *J*=8.98, 5.39 Hz, 2 H).

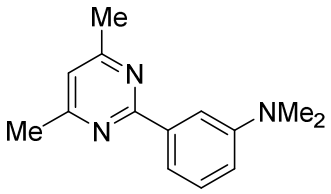
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 19.26 (s, 1 C), 56.02 (s, 1 C), 56.17 (s, 1 C), 101.46 (s, 1 C), 108.56 (s, 1 C), 115.64 (d, *J*=21.64 Hz, 1 C), 117.99 (s, 1 C), 122.38 (s, 1 C), 129.06 (d, *J*=8.54 Hz, 1 C), 135.88 (s, 1 C), 143.36 (s, 1 C), 144.79 (s, 1 C), 149.46 (s, 1 C), 152.36 (s, 1 C), 153.96 (s, 1 C), 163.48 (d, *J*=247.96 Hz, 1 C).

MS (70 eV, EI) m/z (%): 297 (100), 282 (14), 254 (24), 252 (6), 211 (10).

IR ATR ν (cm^{-1}): 2923, 2854, 2833, 1623, 1597, 1503, 1489, 1465, 1433, 1422, 1399, 1353, 1260, 1246, 1208, 1189, 1166, 1150, 1096, 1065, 1034, 1014, 1000, 994, 910, 862, 850, 836, 808, 771, 726, 668.

HRMS (EI) for **$C_{18}H_{16}FNO_2$** (297.1165) $[M]^+$:297.1165.

Synthesis of 3-(4,6-dimethylpyrimidin-2-yl)-*N*,*N*-dimethylaniline (34k):



A solution of **32s** in THF (1.0 mmol, 2.0 equiv, 1.15 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **31h** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 30 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34k** as a brownish solid.

Isolated yield: with $FeBr_3$: 78% (89 mg).
with $CoCl_2$: 63% (72 mg).

Reaction time: 30 min.

Solvent for purification: 9:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

m.p.: 105 – 108 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.54 (s, 6 H), 3.05 (s, 6 H), 6.92 (s, 2 H), 7.35 (t, *J*=7.88 Hz, 1 H), 7.77 - 7.92 (m, 2 H).

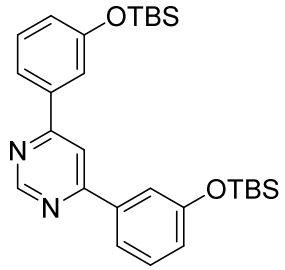
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 24.18 (s, 1 C), 40.91 (s, 1 C), 112.49 (s, 1 C), 114.95 (s, 1 C), 117.16 (s, 1 C), 117.79 (s, 1 C), 129.13 (s, 1 C), 138.86 (s, 1 C), 150.82 (s, 1 C), 164.71 (s, 1 C), 166.57 (s, 1 C).

MS (70 eV, EI) m/z (%): 227 (100), 212 (53), 184 (18), 114 (7), 43 (55).

IR ATR ν (cm^{-1}): 2986, 2918, 2887, 2800, 1600, 1586, 1570, 1539, 1494, 1486, 1436, 1414, 1396, 1362, 1345, 1319, 1233, 1177, 1064, 996, 955, 864, 775, 766, 697.

HRMS (EI) for **$C_{14}H_{17}N_3$** (227.1422) $[M]^+$:227.1417.

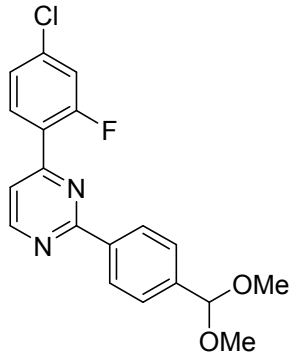
Synthesis of 4,6-bis(3-((*tert*-butyldimethylsilyl)oxy)phenyl)pyrimidine (34l):



A solution of **32p** in THF (2.0 mmol, 4.0 equiv, 1.1 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35k** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34l** as a red liquid.

Isolated yield: with $FeBr_3$: 95% (234 mg).
Reaction time: 15 min, using 4 equiv of Grignard reagent.
Solvent for purification: 9:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.
MS (70 eV, EI) m/z (%): 492 (11), 436 (36), 435 (100), 393 (19), 379 (9), 189 (23).
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.27 (s, 12 H), 1.03 (s, 18 H), 7.01 (dd, *J*=7.87, 1.83 Hz, 2 H), 7.40 (t, *J*=7.97 Hz, 2 H), 7.65 (d, *J*=1.83 Hz, 2 H), 7.72 (d, *J*=7.87 Hz, 2 H), 8.02 (s, 1 H), 9.32 (s, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.32 (s, 1 C), 18.24 (s, 1 C), 25.72 (s, 1 C), 112.98 (s, 1 C), 118.89 (s, 1 C), 120.17 (s, 1 C), 122.56 (s, 1 C), 129.99 (s, 1 C), 138.58 (s, 1 C), 156.37 (s, 1 C), 159.14 (s, 1 C), 164.47 (s, 1 C).
IR ATR ν (cm^{-1}): 2955, 2943, 2886, 2858, 1572, 1521, 1491, 1471, 1461, 1277, 1252, 1229, 1199, 1001, 968, 939, 870, 833, 777, 734, 708, 687, 666.
HRMS (EI) for **$C_{28}H_{40}N_2O_2Si_2$** (492.2628) $[M]^+$:492.2615.

Synthesis of 4-(4-chloro-2-fluorophenyl)-2-(4-(dimethoxymethyl)phenyl)pyrimidine (34m):



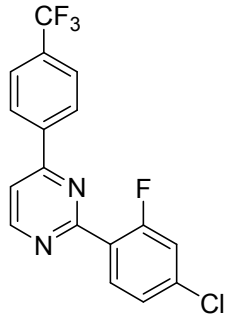
A solution of **32t** in THF (1.0 mmol, 2.0 equiv, 0.9 M) was added dropwise to a suspension of or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35l** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34m** as a white solid.

Isolated yield: with $CoCl_2$: 68% (122 mg).
Reaction time: 15 min.
Purification: purified by HPLC with a column Chromolith SemiPrep RP-18e, 100-10 nm; 15 % H_2O/85 % CH_3CN; flow rate 8 ml/min.
m.p.: 89 – 91 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.36 (s, 6 H), 5.49 (s, 1 H), 7.18 - 7.30 (m, 1 H), 7.34 (dddd, *J*=8.48, 6.38, 2.00, 0.68 Hz, 1 H), 7.60 (d, *J*=8.19 Hz, 1 H), 7.66 - 7.81 (m, 1 H), 7.95 - 8.09 (m, 1 H), 8.36 (td, *J*=8.38, 2.53 Hz, 1 H), 8.48 - 8.59 (m, 1 H), 8.65 - 8.76 (m, 1 H), 8.87 (dd, *J*=17.45, 5.36 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 52.61 (s, 1 C), 102.69 (s, 1 C), 117.24 (d, *J*=21.77 Hz, 1C), 125.39 (s, 1 C), 127.02 (s, 1 C), 128.11 (s, 1 C), 128.76 (s, 1 C), 129.88 (s, 1 C), 137.75 (s, 1 C), 140.72 (s, 1 C), 142.91 (s, 1 C), 158.15 (s, 1 C), 159.27 (s, 1 C), 161.31 (d, J=255.47 Hz, 1C), 163.38 (s, 1 C), 164.26 (s, 1 C).
MS (70 eV, EI) m/z (%): 358 (1), 327 (100), 311 (18), 283 (8), 154 (1), 130(5).

IR ATR ν (cm^{-1}): 2980, 2959, 2932, 2830, 1607, 1584, 1576, 1558, 1548, 1484, 1432, 1407, 1380, 1348, 1286, 1207, 1189, 1099, 1078, 1050, 1018, 982, 900, 851, 822, 810, 786, 738, 722, 712, 665.

HRMS (EI) for **$C_{19}H_{16}ClFN_2O_2$** (358.0884) $[M]^+$:358.0872.

Synthesis of 2-(4-chloro-2-fluorophenyl)-4-(4-(trifluoromethyl)phenyl)pyrimidine (34n):



A solution of **32u** in THF (1.0 mmol, 2.0 equiv, 1.0 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35m** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34n** as a white solid.

Isolated yield: with $FeBr_3$: 61% (108 mg).
with $CoCl_2$: 60% (106 mg).

Reaction time: 15 min.

Solvent for purification: 4:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

m.p.: 120 – 122 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.24 - 7.32 (m, 2 H), 7.67 (d, *J*=5.28 Hz, 1 H), 7.79 (m, *J*=8.14 Hz, 2 H), 8.20 (t, *J*=8.36 Hz, 1 H), 8.30 (m, *J*=8.14 Hz, 2 H), 8.94 (d, *J*=5.28 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 114.93 (s, 1 C), 117.71 (d, J=26.19 Hz, 1 C), 123.86 (q, J=272.44, 1 C), 124.64 (d, J=3.99 Hz, 1 C), 124.92 (d, J=8.83 Hz, 1 C), 125.96 (q, J=3.70 Hz, 1 C), 127.60 (s, 1 C), 132.71 (s, 1 C), 132.75 (s, 1 C), 132.81 (q, J=32.74 Hz, 1 C), 137.12 (d,

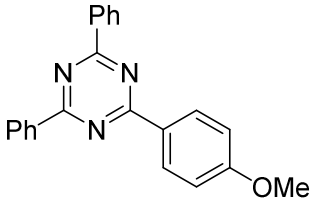
J= 10.25 Hz, 1 C), 139.83 (q, J=1.14 Hz, 1 C), 158.28 (s, 1 C), 161.33 (d, J=260.48 Hz, 1 C), 162.60 (s, 1 C), 162.75 (s, 1 C), 162.82 (s, 1 C).

MS (70 eV, EI) m/z (%): 354 (31), 352 (100), 197 (34), 170 (36), 157 (10).

IR ATR ν (cm^{-1}): 1607, 1576, 1558, 1550, 1488, 1414, 1374, 1323, 1308, 1285, 1278, 1218, 1191, 1172, 1142, 1106, 1087, 1065, 1038, 1014, 902, 854, 838, 820, 792, 768, 718, 711.

HRMS (EI) for **$C_{17}H_9ClF_4N_2$** (352.0390) $[M]^+$:352.0383.

Synthesis of 2-(4-methoxyphenyl)-4,6-diphenyl-1,3,5-triazine (34o):



A solution of **32i** in THF (1.0 mmol, 2.0 equiv, 1.3 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35n** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34o** as a white solid.

Isolated yield: with $FeBr_3$: 81% (137 mg).
with $CoCl_2$: 79% (134 mg).

Reaction time: 15 min.

Solvent for purification: 10:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

m.p.: 144 – 146 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.94 (s, 3 H), 7.08 (d, *J*=8.79 Hz, 2 H), 7.39 - 7.81 (m, 6 H), 8.62 - 9.07 (m, 6 H).

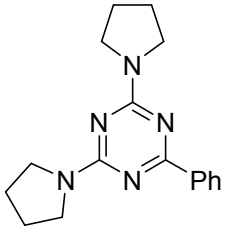
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.45 (s, 1 C), 113.94 (s, 1 C), 128.55 (s, 1 C), 128.77 (s, 1 C), 128.87 (s, 1 C), 130.85 (s, 1 C), 132.31 (s, 1 C), 136.40 (s, 1 C), 163.31 (s, 1 C), 171.18 (s, 1 C), 171.38 (s, 1 C).

MS (70 eV, EI) m/z (%): 339 (63), 214 (44), 199 (35), 171 (12), 133 (41), 103 (24).

IR ATR ν (cm^{-1}): 3312, 3038, 3015, 2958, 2840, 2362, 2331, 1605, 1499, 1438, 1274, 1249, 1183, 1040, 1012, 823, 809, 781, 770, 690.

HRMS (EI) for **$C_{22}H_{17}N_3O$** (339.1372) $[M]^+$:339.1366.

2-phenyl-4,6-di(pyrrolidin-1-yl)-1,3,5-triazine (34p):



A solution of **32a** in THF (1.0 mmol, 2.0 equiv, 1.7 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35o** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 50 °C for 12 h before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34p** as a white solid.

Isolated yield: with $FeBr_3$: 76% (112 mg).

Reaction time: 12 h at 50 °C.

Solvent for purification: 10:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

m.p.: 137 – 139 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.96 (ddd, *J*=6.28, 3.48, 3.26 Hz, 8 H), 3.61 (br. s., 4 H), 3.72 (br. s., 4 H), 7.35 - 7.52 (m, 3 H), 8.38 - 8.50 (m, 2 H).

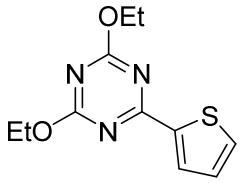
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 25.35 (s, 1 C), 45.98 (s, 1 C), 127.97 (s, 1 C), 128.21 (s, 1 C), 130.69 (s, 1 C), 138.07 (s, 1 C), 163.62 (s, 1 C), 169.50 (s, 1 C).

MS (70 eV, EI) m/z (%): 295 (88), 267 (100), 253 (25), 239 (19), 226 (39), 197 (13).

IR ATR ν (cm^{-1}): 2969, 2871, 2361, 1557, 1540, 1507, 1491, 1471, 1454, 1383, 1338, 1293, 1279, 1238, 1221, 1180, 1167, 1154, 1008, 863, 815, 795, 780, 702.

HRMS (EI) for **$C_{17}H_{21}N_5$** (295.1797) $[M]^+$:295.1792.

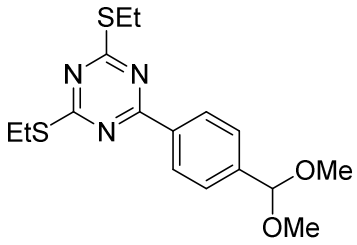
Synthesis of 2,4-diethoxy-6-(thiophen-2-yl)-1,3,5-triazine (34q):



A solution of **32v** in THF (1.0 mmol, 2.0 equiv, 0.8 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35p** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 12 h before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34q** as a yellow solid.

Isolated yield: with $FeBr_3$: 84% (105 mg).
with $CoCl_2$: 79% (99 mg).
Reaction time: 12 h.
Solvent for purification: 10:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.
m.p.: 79 – 81 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.33 - 1.55 (m, 6 H), 4.52 (q, *J*=7.08 Hz, 4 H), 7.14 (dd, *J*=4.97, 3.80 Hz, 1 H), 7.56 (dd, *J*=4.97, 1.27 Hz, 1 H), 8.14 (dd, *J*=3.80, 1.27 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.29 (s, 1 C), 64.22 (s, 1 C), 128.27 (s, 1 C), 131.71 (s, 1 C), 132.29 (s, 1 C), 140.81 (s, 1 C), 170.59 (s, 1 C), 172.03 (s, 1 C).
MS (70 eV, EI) m/z (%): 251 (6), 207 (6), 110 (10), 71 (35), 61 (14).
IR ATR ν (cm^{-1}): 3102, 2983, 2927, 1531, 1490, 1466, 1439, 1416, 1378, 1346, 1324, 1290, 1233, 1218, 1121, 1100, 1078, 1044, 1034, 1008, 866, 841, 811, 754, 714, 692, 671.
HRMS (EI) for **$C_{11}H_{13}N_3O_2S$** (251.0728) $[M]^+$:251.0725.

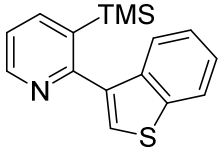
Synthesis of 2-(4-(dimethoxymethyl)phenyl)-4,6-bis(ethylthio)-1,3,5-triazine (34r):



A solution of **32t** in THF (1.0 mmol, 2.0 equiv, 0.9 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35q** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34r** as a colorless oil.

Isolated yield: with $FeBr_3$: 61% (107 mg).
Reaction time: 15 min.
Solvent for purification: 6:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.45 (t, *J*=7.46 Hz, 6 H), 3.22 (q, *J*=7.46 Hz, 4 H), 3.34 (s, 6 H), 5.47 (s, 1 H), 7.56 (d, *J*=8.29 Hz, 2 H), 8.45 (d, *J*=8.57 Hz, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.39 (s, 1 C), 24.85 (s, 1 C), 52.63 (s, 1 C), 102.51 (s, 1 C), 126.95 (s, 1 C), 128.88 (s, 1 C), 135.21 (s, 1 C), 142.59 (s, 1 C), 167.94 (s, 1 C), 181.30 (s, 1 C).
MS (70 eV, EI) m/z (%): 351 (43), 320 (53), 230 (6), 146 (11), 75 (11).
IR ATR ν (cm^{-1}): 2962, 2947, 2829, 1483, 1410, 1377, 1348, 1309, 1284, 1235, 1205, 1098, 1051, 1018, 984, 971, 912, 898, 847, 832, 796, 751, 733, 690.
HRMS (EI) for **$C_{16}H_{21}N_3O_2S_2$** (351.1075) $[M]^+$:351.1061.

Synthesis of 2-(benzo[*b*]thiophen-3-yl)-3-(trimethylsilyl)pyridine (34s):



A solution of **32w** in THF (1.0 mmol, 2.0 equiv, 0.8 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35a** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 24 h before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34s** as a yellow oil.

Isolated yield: with $FeBr_3$: 64% (90 mg).
with $CoCl_2$: 66% (93 mg).

Reaction time: 24 h.

Solvent for purification: 9:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.00 (s, 9 H), 7.28 - 7.42 (m, 4 H), 7.49 - 7.55 (m, 1 H), 7.87 - 7.93 (m, 1 H), 7.99 (dt, *J*=7.74, 1.52 Hz, 1 H), 8.72 (dt, *J*=3.04, 1.52 Hz, 1 H).

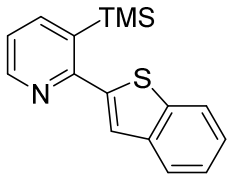
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -0.15 (s, 1 C), 121.89 (s, 1 C), 122.43 (s, 1 C), 123.43 (s, 1 C), 124.42 (s, 1 C), 124.55 (s, 1 C), 125.39 (s, 1 C), 135.44 (s, 1 C), 138.94 (s, 1 C), 139.48 (s, 1 C), 139.68 (s, 1 C), 143.21 (s, 1 C), 149.46 (s, 1 C), 159.75 (s, 1 C).

MS (70 eV, EI) m/z (%): 283 (36), 268 (100), 250 (10), 227 (21), 126 (14).

IR ATR ν (cm^{-1}): 3051, 3028, 2952, 2896, 1564, 1550, 1458, 1431, 1399, 1338, 1262, 1248, 1221, 1041, 953, 833, 797, 782, 752, 731, 712, 696.

HRMS (EI) for **$C_{16}H_{17}NSSi$** (283.0851) $[M]^+$:283.0840.

Synthesis of 2-(benzo[*b*]thiophen-2-yl)-3-(trimethylsilyl)pyridine (34t):

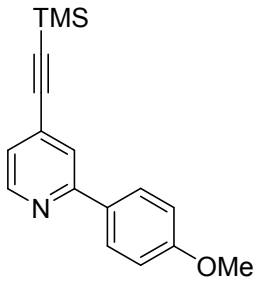


A solution of **32x** in THF (1.0 mmol, 2.0 equiv, 0.8 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35a** (0.5 mmol, 1.0 equiv) in *t*BuOMe

(2.5 mL) at 25 °C. The suspension was stirred at 50 °C for 12 h (for $FeBr_3$) or at 25 °C for 12 h (for $CoCl_2$) before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34t** as a yellow oil.

Isolated yield: with $FeBr_3$: 61% (86 mg).
with $CoCl_2$: 66% (93 mg).
Reaction time: for $FeBr_3$: 12 h at 50 °C.
for $CoCl_2$: 12 h at 25 °C.
Solvent for purification: 4:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.23 (s, 9 H), 7.25 - 7.30 (m, 1 H), 7.35 - 7.41 (m, 2 H), 7.42 (s, 1 H), 7.78 - 7.84 (m, 1 H), 7.86 - 7.91 (m, 1 H), 7.96 (dd, *J*=9.40, 1.11 Hz, 1 H), 8.66 (dd, *J*=3.04, 1.11 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 0.28 (s, 1 C), 122.01 (s, 1 C), 122.29 (s, 1 C), 123.88 (s, 1 C), 124.20 (s, 1 C), 124.37 (s, 1 C), 124.71 (s, 1 C), 134.24 (s, 1 C), 139.61 (s, 1 C), 140.62 (s, 1 C), 143.54 (s, 1 C), 145.80 (s, 1 C), 149.23 (s, 1 C), 158.26 (s, 1 C).
MS (70 eV, EI) m/z (%): 283 (32), 270 (10), 268 (100), 252 (8), 238 (19), 127 (7).
IR ATR ν (cm^{-1}): 3052, 3027, 2953, 2896, 1561, 1548, 1458, 1391, 1248, 1166, 1156, 1129, 1041, 958, 835, 829, 798, 783, 743, 725, 709, 685.
HRMS (EI) for **$C_{16}H_{17}NSSi$** (283.0851) $[M]^+$:283.0837.

Synthesis of 2-(4-methoxyphenyl)-4-((trimethylsilyl)ethynyl)pyridine (34u):

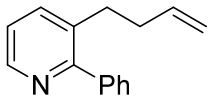


A solution of **32i** in THF (1.0 mmol, 2.0 equiv, 1.3 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35r** (0.5 mmol, 1.0 equiv) in *t*BuOMe

(2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 30 min before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34u** as a slightly yellow oil.

Isolated yield: with $FeBr_3$: 38% (53 mg).
with $CoCl_2$: 62% (87 mg).
Reaction time: 30 min.
Solvent for purification: 8:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.29 (s, 9 H), 3.86 (s, 3 H), 6.98 (dd, *J*=8.82, 1.19 Hz, 2 H), 7.18 (dt, *J*=5.01, 1.43 Hz, 1 H), 7.70 (d, *J*=0.72 Hz, 1 H), 7.95 (dd, *J*=8.58, 1.19 Hz, 2 H), 8.58 (d, *J*=5.01 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -0.26 (s, 1 C), 55.34 (s, 1 C), 99.26 (s, 1 C), 102.51 (s, 1 C), 114.12 (s, 1 C), 122.00 (s, 1 C), 123.33 (s, 1 C), 128.17 (s, 1 C), 131.31 (s, 1 C), 131.72 (s, 1 C), 149.43 (s, 1 C), 157.15 (s, 1 C), 160.68 (s, 1 C).
MS (70 eV, EI) m/z (%): 281 (68), 266 (100), 251 (6), 223 (8), 133 (12).
IR ATR ν (cm^{-1}): 2958, 2900, 2837, 2160, 1609, 1592, 1578, 1535, 1514, 1466, 1422, 1385, 1274, 1247, 1219, 1196, 1174, 1112, 1031, 890, 839, 826, 800, 758, 728, 700.
HRMS (EI) for **$C_{17}H_{19}NOSi$** (281.1236) $[M]^+$:281.1220.

Synthesis of 3-(but-3-en-1-yl)-2-phenylpyridine (34v):



A solution of **32a** in THF (1.0 mmol, 2.0 equiv, 1.7 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **35s** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 1 h before being quenched with $NaHCO_3$ sat. aq. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 25 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, NaCl sat. aq. was added, and the

mixture was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34v** as a colorless oil.

Isolated yield: with $FeBr_3$: 62% (65 mg).
with $CoCl_2$: 78% (81 mg).

Reaction time: 1 h.

Solvent for purification: 4:1 *i*-hexane/ethyl acetate + 0.5 % triethylamine.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.18 - 2.34 (m, 2 H), 2.71 - 2.83 (m, 2 H), 4.81 - 5.02 (m, 2 H), 5.63 - 5.79 (m, 1 H), 7.21 - 7.28 (m, 1 H), 7.36 - 7.52 (m, 5 H), 7.61 (dd, *J*=7.88, 1.80 Hz, 1 H), 8.53 (dd, *J*=4.70, 1.66 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 31.81 (s, 1 C), 34.57 (s, 1 C), 115.34 (s, 1 C), 122.13 (s, 1 C), 127.84 (s, 1 C), 128.17 (s, 1 C), 128.78 (s, 1 C), 129.09 (s, 1 C), 134.60 (s, 1 C), 137.30 (s, 1 C), 140.62 (s, 1 C), 146.97 (s, 1 C), 158.97 (s, 1 C).

MS (70 eV, EI) m/z (%): 209 (42), 208 (51), 180 (15), 168 (25). 167 (100),

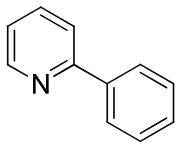
IR ATR ν (cm^{-1}): 3060, 3027, 2977, 2925, 2860, 1640, 1579, 1564, 1495, 1453, 1433, 1421, 1019, 995, 912, 791, 749, 732, 699.

HRMS (EI) for **$C_{15}H_{15}N$** (209.1204) $[M]^+$:208.1126.

7. Efficient Chromium(II)-Catalyzed Cross-Coupling Reactions Between Csp^2-Centers

7.1. Preparation of the Title Compounds Using TP4

Synthesis of 2-phenylpyridine (33a):



A solution of **32a** in THF (1.2 mmol, 1.2 equiv, 1.7 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **31a** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$,

filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **33a** as a colorless oil.

Isolated yield: 90% (140 mg)

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 6:1 (+0.5% NEt_3).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.23 (m, 1 H), 7.45 (m, 3 H), 7.75 (m, 2 H), 8.01 (m, 2 H), 8.70 (d, *J*=4.7 Hz, 1 H).

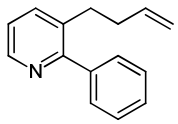
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.6, 122.1, 126.9, 128.7, 128.9, 136.8, 139.2, 149.5, 157.4.

MS (70 eV, EI) m/z (%): 155 (100) $[M]^+$, 154 (60), 128 (10), 127 (10), 77 (9), 59 (10), 43 (7).

IR ATR ν (cm^{-1}): 3062, 3036, 3008, 2927, 1586, 1580, 1564, 1468, 1449, 1424, 1293, 1152, 1074, 1020, 988, 800, 737, 692.

HRMS (EI) for **$C_{11}H_9N$** (155.1735) $[M]^+$: 155.1731.

Synthesis of 3-(but-3-en-1-yl)-2-phenylpyridine (34v):



A solution of **32a** in THF (1.2 mmol, 1.2 equiv, 1.7 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **35s** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34v** as a colorless oil.

Isolated yield: 95% (199 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 6:1 (+0.5% NEt_3).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.18 - 2.32 (m, 2 H), 2.68 - 2.84 (m, 2 H), 4.86 - 5.00 (m, 2 H), 5.63 - 5.80 (m, 1 H), 7.21 (dd, *J*=7.76, 4.77 Hz, 1 H), 7.32 - 7.54 (m, 5 H), 7.57 - 7.64 (m, 1 H), 8.53 (dd, *J*=4.86, 1.31 Hz, 1 H).

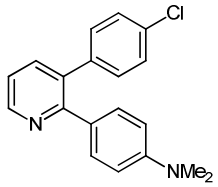
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 31.8, 34.6, 115.4, 122.1, 127.9, 128.2, 128.8, 134.6, 137.3, 140.6, 147.0, 159.0.

MS (70 eV, EI) m/z (%): 209 (42), 208 (51), 180 (15), 168 (25). 167 (100).

IR ATR ν (cm^{-1}): 3060, 3027, 2977, 2925, 2860, 1640, 1579, 1564, 1495, 1453, 1433, 1421, 1019, 995, 912, 791, 749, 732, 699.

HRMS (EI) for **$C_{15}H_{15}N$** (209.1204) $[M]^+$:209.1191.

Synthesis of 4-(3-(4-chlorophenyl)pyridin-2-yl)-*N*,*N*-dimethylaniline (34b):



A solution of **32n** in THF (1.2 mmol, 1.2 equiv, 1.2 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **35b** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 90 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34b** as a slightly yellow oil.

Isolated yield: 80% (247 mg).

Reaction time: 90 min.

Solvent for purification: dichloromethane/ethyl acetate 9:1 (+0.5% NEt_3).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.95 (s, 6 H), 6.59 (d, *J*=8.85 Hz, 2 H), 7.08 - 7.35 (m, 7 H), 7.61 (dd, *J*=7.74, 1.66 Hz, 1 H), 8.65 (dd, *J*=4.70, 1.66 Hz, 1 H).

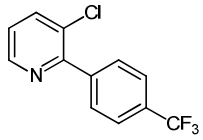
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 40.3, 111.6, 120.9, 127.5, 128.6, 130.8, 130.9, 132.9, 133.9, 138.3, 139.3, 148.5, 150.1, 157.2.

MS (70 eV, EI) m/z (%): 308 (100), 307 (45), 291 (19), 153 (9), 136 (12).

IR ATR ν (cm^{-1}): 3037, 2885, 2855, 2801, 1606, 1576, 1524, 1489, 1425, 1394, 1353, 1193, 1168, 1090, 999, 945, 834, 821, 799, 778, 758, 728, 718, 704.

HRMS (EI) for **$C_{19}H_{17}ClN_2$** (308.1080) $[M]^+$: 308.1060.

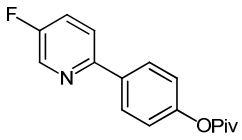
Synthesis of 3-chloro-2-(4-(trifluoromethyl)phenyl)pyridine (37a):



A solution of **32y** in THF (1.2 mmol, 1.2 equiv, 0.9 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **35t** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **37a** as a white solid.

Isolated yield: 76% (195 mg).
Reaction time: 15 min.
Solvent for purification: *i*-hexane/ethyl acetate 8:1 (+0.5% NEt_3).
m.p.: 53.0-54.0 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.27 (dd, *J*=8.02, 4.70 Hz, 1 H), 7.69 - 7.78 (m, 2 H), 7.79 - 7.92 (m, 3 H), 8.62 (dd, *J*=4.70, 1.66 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 123.7, 124.0 (q, *J*=272.1 Hz), 125.0 (q, *J*=3.9 Hz), 129.8, 130.3, 130.8 (q, *J*=32.5 Hz), 138.3, 141.6, 147.8, 155.1.
MS (70 eV, EI) m/z (%): 257 (46), 237 (28), 222 (98), 81 (13), 71 (16), 43 (100).
IR ATR ν (cm^{-1}): 3052, 1616, 1564, 1436, 1428, 1402, 1324, 1164, 1132, 1108, 1090, 1066, 1040, 1026, 1012, 848, 792, 768, 758, 736, 690.
HRMS (EI) for **$C_{12}H_7ClF_3N$** (257.0219) $[M]^+$: 257.0219.

Synthesis of 4-(5-fluoropyridin-2-yl)phenyl pivalate (37b):



A solution of **32l** in THF (1.2 mmol, 1.2 equiv, 0.8 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **35u** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and

concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **37b** as a white solid.

Isolated yield: 66% (180 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 6:1 (+0.5% NEt_3).

m.p.: 76.6-76.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.38 (s, 9 H), 7.16 (m, 2 H), 7.46 (td, *J*=8.43, 3.32 Hz, 1 H), 7.69 (dd, *J*=8.85, 4.42 Hz, 1 H), 7.95 (m, 2 H), 8.53 (d, *J*=2.76 Hz, 1 H)

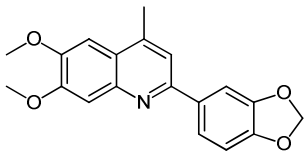
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.1, 39.1, 121.1, 121.2, 121.8, 123.5, 123.7, 127.8, 135.8, 137.5, 137.8, 151.8, 152.9, 152.9, 157.1, 160.5, 176.9.

MS (70 eV, EI) m/z (%): 273 (9), 190 (11), 189 (100), 160 (4), 159 (3).

IR ATR ν (cm^{-1}): 2982, 2966, 2932, 2908, 2890, 1750, 1742, 1600, 1470, 1416, 1396, 1382, 1368, 1276, 1264, 1224, 1198, 1166, 1112, 1026, 1010, 974, 960, 942, 924, 898, 834, 826, 810, 796, 750.

HRMS (EI) for **$C_{16}H_{16}FNO_2$** (273.1165) $[M]^+$: 273.1154.

Synthesis of 2-(benzo[*d*][1,3]dioxol-5-yl)-6,7-dimethoxy-4-methylquinoline (37c):



A solution of **32k** in THF (1.2 mmol, 1.2 equiv, 1.1 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **35j** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 1 h before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **37c** as a yellow solid.

Isolated yield: 74% (239 mg).

Reaction time: 1 h.

Solvent for purification: *i*-hexane/ethyl acetate 3:1 (+0.5% NEt_3).

m.p.: 195-221 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.67 (s, 3 H), 4.04 (d, *J*=5.53 Hz, 6 H), 6.02 (s, 2 H), 6.92 (d, *J*=8.29 Hz, 1 H), 7.13 (s, 1 H), 7.50 (d, *J*=5.81 Hz, 2 H), 7.59 (dd, *J*=8.16, 1.80 Hz, 1 H), 7.65 (d, *J*=1.94 Hz, 1 H).

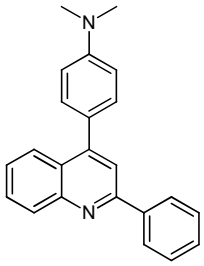
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 19.2, 56.0, 56.1, 101.2, 101.5, 107.7, 108.4, 108.6, 117.9, 121.3, 122.2, 134.3, 143.0, 144.8, 148.2, 148.4, 149.3, 152.2, 154.5.

MS (70 eV, EI) m/z (%): 323 (100), 308 (18), 280 (15), 278 (6), 161 (9).

IR ATR ν (cm^{-1}): 2922, 2898, 2834, 1618, 1604, 1592, 1494, 1486, 1476, 1466, 1450, 1432, 1416, 1382, 1352, 1336, 1240, 1222, 1206, 1166, 1138, 1114, 1066, 1048, 1028, 998, 926, 876, 862, 852, 834, 808.

HRMS (EI) for **$C_{19}H_{17}NO_4$** (323.1158) $[M]^+$: 323.1149.

Synthesis of *N*,*N*-dimethyl-4-(2-phenylquinolin-4-yl)aniline (37d):



A solution of **32n** in THF (1.2 mmol, 1.2 equiv, 1.1 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **35v** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **37d** as a red solid.

Isolated yield: 78% (253 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 8:1 (+0.5% NEt_3).

m.p.: 152.0-154.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.06 (s, 6 H), 6.89 (dd, *J*=8.71, 1.80 Hz, 2 H), 7.43 - 7.59 (m, 6 H), 7.70 - 7.77 (m, 1 H), 7.83 (d, *J*=1.66 Hz, 1 H), 8.09 (d, *J*=8.29 Hz, 1 H), 8.19 - 8.30 (m, 3 H).

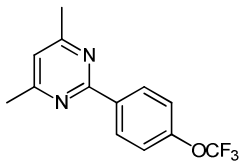
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 40.4, 112.2, 113.1, 119.1, 125.9, 126.1, 127.0, 127.6, 128.8, 129.2, 129.3, 130.0, 130.6, 139.9, 148.9, 149.5, 150.6, 156.9.

MS (70 eV, EI) m/z (%): 324 (100), 323 (42), 307 (16), 280 (13), 240 (63), 225 (23), 161 (15), 119 (14).

IR ATR ν (cm^{-1}): 2922, 2866, 2806, 1610, 1592, 1542, 1524, 1504, 1492, 1460, 1442, 1424, 1414, 1402, 1356, 1226, 1196, 1162, 1138, 1120, 1064, 944, 818, 808, 788, 772, 762, 694, 680.

HRMS (EI) for **$C_{23}H_{20}N_2$** (324.1626) $[M]^+$: 324.1621.

Synthesis of 4,6-dimethyl-2-(4-(trifluoromethoxy)phenyl)pyrimidine (37e):



A solution of **32z** in THF (1.2 mmol, 1.2 equiv, 0.8 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **31h** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 2 h before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **37e** as a white solid.

Isolated yield: 71% (190 mg).

Reaction time: 2 h.

Solvent for purification: *i*-hexane/ethyl acetate 6:1 (+0.5% NEt_3).

m.p.: 66.0-67.4 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.53 (s, 6 H), 6.93 (s, 1 H), 7.29 (d, *J*=8.29 Hz, 2 H), 8.48 (d, *J*=8.57 Hz, 2 H).

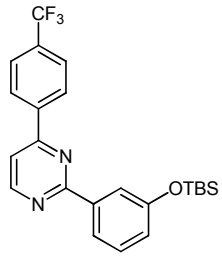
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 24.1, 118.2, 120.5, 120.5 (q, *J*=257.6 Hz), 129.9, 136.6, 150.9, 162.8, 166.9.

MS (70 eV, EI) m/z (%): 269 (13), 268 (100), 253 (12), 189 (15), 187 (20).

IR ATR ν (cm^{-1}): 1602, 1582, 1544, 1504, 1434, 1368, 1288, 1256, 1196, 1148, 1102, 1030, 1012, 958, 920, 874, 866, 852, 810, 786, 734, 680.

HRMS (EI) for **$C_{13}H_{11}F_3N_2O$** (268.0823) $[M]^+$: 268.0803.

Synthesis of 2-(3-((tert-butyldimethylsilyl)oxy)phenyl)-4-(4-(trifluoromethyl)-phenyl)-pyrimidine (37f):



A solution of **32p** in THF (1.2 mmol, 1.2 equiv, 1.0 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **35m** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **37f** as a slightly yellow oil.

Isolated yield: 80% (366 mg)

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 8:1 (+0.5% NEt_3).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.29 (s, 6 H), 1.05 (s, 9 H), 7.02 (dd, *J*=7.60, 2.07 Hz, 1 H), 7.40 (t, *J*=7.88 Hz, 1 H), 7.63 (d, *J*=5.25 Hz, 1 H), 7.81 (m, *J*=8.02 Hz, 2 H), 8.08 (dd, *J*=2.21, 1.66 Hz, 1 H), 8.17 - 8.22 (m, *J*=7.78, 1.11, 0.81, 0.81 Hz, 1 H), 8.33 (m, *J*=8.02 Hz, 2 H), 8.90 (d, *J*=5.25 Hz, 1 H).

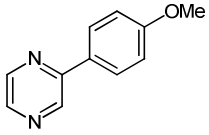
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.3, 18.3, 25.7, 107.6, 108.4, 112.6, 114.8, 119.9, 121.4, 122.9, 123.9 (q, *J*=272.6 Hz), 125.9 (q, *J*=3.9 Hz), 127.6, 129.6, 129.9, 132.4, 140.3, 156.1, 156.7, 158.0, 162.5, 164.5.

MS (70 eV, EI) m/z (%): 430 (7), 374 (26), 373 (100), 224 (4), 167 (23).

IR ATR ν (cm^{-1}): 2958, 2932, 2860, 1712, 1566, 1550, 1452, 1426, 1410, 1382, 1362, 1326, 1284, 1272, 1256, 1220, 1168, 1146, 1128, 1094, 1070, 950, 838, 810, 784.

HRMS (EI) for **$C_{23}H_{25}F_3N_2OSi$** (430.1688) $[M]^+$: 430.1682.

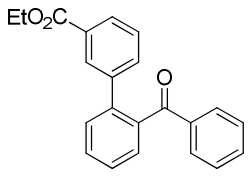
Synthesis of 2-(4-methoxyphenyl)pyrazine (37g):



A solution of **32i** in THF (1.2 mmol, 1.2 equiv, 1.3 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **31j** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 30 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **37g** as a white solid.

Isolated yield: 72% (134 mg).
Reaction time: 30 min.
Solvent for purification: *i*-hexane/ethyl acetate 6:1 (+0.5% NEt_3).
m.p.: 93.8-95.2 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.87 (s, 3 H), 6.98 - 7.07 (m, 2 H), 7.95 - 8.01 (m, 2 H), 8.43 (d, *J*=2.49 Hz, 1 H), 8.58 (dd, *J*=2.49, 1.38 Hz, 1 H), 8.97 (d, *J*=1.38 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.4, 114.5, 128.3, 128.8, 141.5, 141.9, 144.0, 152.5, 161.2.
MS (70 eV, EI) m/z (%): 186 (19), 149 (7), 133 (7), 109 (6), 83 (8), 71 (8), 69 (24).
IR ATR ν (cm^{-1}): 2956, 2914, 2836, 1604, 1586, 1516, 1474, 1458, 1424, 1400, 1302, 1246, 1178, 1148, 1108, 1078, 1034, 1014, 834, 818, 750.
HRMS (EI) for **$C_{11}H_{10}N_2O$** (186.0793) $[M]^+$: 186.0785.

Synthesis of Ethyl 2'-benzoyl-[1,1'-biphenyl]-3-carboxylate (41a):



A solution of **39** in THF (1.2 mmol, 1.2 equiv, 0.8 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **38** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **41a** as a white solid.

Isolated yield: 79% (261 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/diethyl ether 9:1.

m.p.: 65.1-66.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.98 (t, *J*=1.7 Hz, 1 H), 7.85 (dt, *J*=7.8, 1.5 Hz, 1 H), 7.69 – 7.38 (m, 8 H), 7.32 - 7.23 (m, 3 H), 4.32 (q, *J*=7.2 Hz, 2 H), 1.33 (t, *J*=7.1 Hz, 3 H).

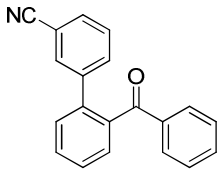
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 198.3, 166.1, 140.3, 140.2, 138.9, 137.3, 133.3, 132.9, 130.5, 130.5, 130.1, 129.9, 129.8, 128.9, 128.4, 128.2, 128.1, 127.4, 60.9, 14.2.

MS (70 eV, EI) m/z (%): 330 (100), 285 (37), 257 (53), 253 (30), 207 (97), 152 (30), 105 (83), 77 (45).

IR ATR ν (cm^{-1}): 3054, 2971, 2912, 1714, 1662, 1595, 1580, 1567, 1447, 1440, 1428, 1306, 1283, 1264, 1238, 1180, 1167, 1153, 1120, 1112, 1106, 1075, 1054, 1033, 1023, 1000, 937, 923, 894, 882, 861, 805, 768, 747, 712, 704, 695, 669.

HRMS (EI) for **$C_{22}H_{18}O_3$** (330.1256) $[M]^+$: 330.1247.

Synthesis of 2'-benzoyl-[1,1'-biphenyl]-3-carbonitrile (41b):



A solution of **40** in THF (0.7 mmol, 0.7 equiv, 0.5 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **38** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 2 h before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **41b** as colorless oil.

Isolated yield: 71% (261 mg).

Reaction time: 2 h.

Solvent for purification: *i*-hexane/ethyl acetate 95:5.

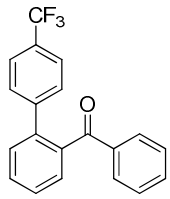
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.68 – 7.51 (m, 6H), 7.50 – 7.41 (m, 4H), 7.39 – 7.22 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 197.8, 141.5, 138.9, 138.8, 137.2, 133.4, 133.3, 132.2, 130.9, 130.8, 130.1, 129.9, 129.2, 129.0, 128.4, 128.0, 118.5, 112.5.

MS (70 eV, EI) m/z (%): 283 (98), 282 (28), 206 (79), 151 (25), 105 (100), 77 (53).

IR ATR ν (cm^{-1}): 3061, 3028, 2230, 1661, 1595, 1579, 1470, 1448, 1412, 1314, 1284, 1276, 1264, 1177, 1152, 1110, 1074, 1026, 1000, 928, 905, 846, 802, 757, 727, 707, 690.
HRMS (EI) for **$C_{20}H_{13}NO$** (283.0997) $[M]^+$: 283.0988.

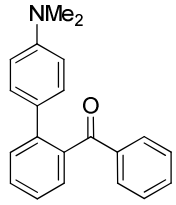
Synthesis of phenyl(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)methanone (41c):



A solution of **32y** in THF (1.2 mmol, 1.2 equiv, 0.9 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **38** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **41c** as colorless oil.

Isolated yield: 93% (305 mg).
Reaction time: 15 min.
Solvent for purification: *i*-hexane/ethyl acetate 96:4.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.71 - 7.66 (m, 2 H), 7.65 - 7.43 (m, 7 H), 7.42 - 7.26 (m, 4 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 198.1, 143.9, 139.9, 138.9, 137.3, 133.2, 130.6, 130.1, 129.9, 129.4 (q, *J*=32.5 Hz), 129.3, 128.9, 128.3, 127.7, 125.2 (q, *J*=3.9 Hz), 124.1 (q, *J*=272.1 Hz).
MS (70 eV, EI) m/z (%): 326 (100), 325 (27), 249 (91), 201 (34), 152 (24), 105 (74), 77 (42).
IR ATR ν (cm^{-1}): 3063, 1663, 1618, 1597, 1581, 1450, 1405, 1322, 1281, 1260, 1162, 1120, 1114, 1068, 1020, 1006, 926, 843, 806, 764, 737, 709, 698.
HRMS (EI) for **$C_{20}H_{13}F_3O$** (326.0918) $[M]^+$: 326.0904.

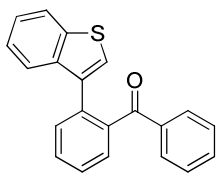
Synthesis of (4'-(dimethylamino)-[1,1'-biphenyl]-2-yl)(phenyl)methanone (41d):



A solution of **32n** in THF (1.2 mmol, 1.2 equiv, 1.1 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **38** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **41d** as an orange solid.

Isolated yield: 94% (282 mg).
Reaction conditions: 15 min.
Solvent for purification: *i*-hexane/ethyl acetate 97:3 (+ 4% Et_3N).
m.p.: 112.4-113.8 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.75 - 7.68 (m, 2 H), 7.58 - 7.45 (m, 3 H), 7.44 - 7.35 (m, 2 H), 7.33 - 7.24 (m, 2 H), 7.21 - 7.14 (m, 2 H), 6.62 - 6.53 (m, 2 H), 2.87 (s, 6 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 199.3, 149.7, 141.2, 138.6, 137.5, 132.7, 130.2, 129.9, 129.8, 129.8, 128.6, 128.1, 128.1, 126.0, 112.3, 40.4.
MS (70 eV, EI) m/z (%): 302 (21), 301 (100), 300 (36), 77 (12).
IR ATR ν (cm^{-1}): 2924, 2854, 2802, 1663, 1611, 1594, 1580, 1570, 1525, 1479, 1447, 1349, 1315, 1293, 1281, 1247, 1222, 1204, 1168, 1161, 1150, 1130, 1104, 1062, 1028, 945, 938, 932, 921, 879, 823, 804, 775, 766, 726, 720, 703, 690, 676.
HRMS (EI) for **$C_{21}H_{19}NO$** (301.1467) $[M]^+$: 301.1452.

Synthesis of (2-(benzo[*b*]thiophen-3-yl)phenyl)(phenyl)methanone (41e):

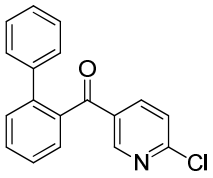


A solution of **32w** in THF (1.2 mmol, 1.2 equiv, 0.9 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **38** (1 mmol, 1.0 equiv)

in THF (5 mL) at 25 °C. The suspension was stirred at 50 °C for 2 h before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **41e** as a red solid.

Isolated yield: 89% (305 mg).
Reaction conditions: 2 h, 50 °C.
Solvent for purification: *i*-hexane/ethyl acetate 96:4.
m.p.: 121.2-123.1 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.75 - 7.49 (m, 8 H), 7.38 - 7.20 (m, 3 H), 7.18 (s, 1 H), 7.05 - 7.13 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 198.5, 140.1, 139.9, 138.3, 137.2, 135.6, 134.5, 132.4, 130.4, 130.3, 129.1, 129.1, 127.8, 127.7, 126.0, 124.3, 124.3, 122.7, 122.5.
MS (70 eV, EI) m/z (%): 314 (100), 313 (21), 285 (19), 234 (76), 165 (30), 105 (21), 77 (27).
IR ATR ν (cm^{-1}): 1663, 1593, 1577, 1448, 1424, 1316, 1285, 1270, 1255, 1210, 1183, 1163, 1147, 1062, 944, 926, 836, 808, 764, 758, 733, 717, 704.
HRMS (EI) for **$C_{21}H_{14}OS$** (314.0765) $[M]^+$: 314.0755.

Synthesis of [1,1'-biphenyl]-2-yl(6-chloropyridin-3-yl)methanone (43):



A solution of **32a** in THF (1.2 mmol, 1.2 equiv, 1.7 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **42** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **43** as white crystals.

Isolated yield: 72% (211 mg).
Reaction time: 15 min.
Solvent for purification: *i*-hexane/diethyl ether 2:1.
m.p.: 108.6-111.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.42 (dd, *J*=2.5, 0.6 Hz, 1 H), 7.81 (dd, *J*=8.3, 2.5 Hz, 1 H), 7.68 - 7.48 (m, 4 H), 7.24 - 7.12 (m, 6 H).

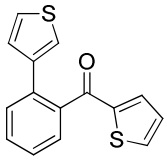
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 196.3, 154.8, 151.2, 141.2, 139.6, 138.9, 137.6, 131.8, 131.4, 130.1, 129.1, 129.0, 128.6, 127.8, 127.7, 123.8.

MS (70 eV, EI) m/z (%): 293 (97), 292 (100), 266 (11), 264 (26), 182 (10), 153 (30), 152 (50), 151 (13), 140 (18).

IR ATR ν (cm^{-1}): 1671, 1594, 1576, 1564, 1478, 1460, 1448, 1433, 1376, 1363, 1289, 1276, 1266, 1251, 1139, 1115, 1100, 1076, 1052, 1041, 1020, 1008, 970, 961, 926, 918, 884, 844, 786, 774, 752, 744, 715, 699.

HRMS (EI) for **$C_{18}H_{12}ClNO$** (293.0613) $[M]^+$: 293.0569.

Synthesis of thiophen-2-yl(2-(thiophen-3-yl)phenyl)methanone (46):



A solution of **45** in THF (1.2 mmol, 1.2 equiv, 0.8 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **44** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **46** as a brownish solid.

Isolated yield: 90% (165 mg).

Reaction conditions: 15 min.

Solvent for purification: *i*-hexane/diethyl ether 9:1.

m.p.: 68.8-70.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.65 - 7.47 (m, 4 H), 7.45 - 7.38 (m, 1 H), 7.28 - 7.17 (m, 3 H), 7.09 (dd, *J*=4.8, 1.5 Hz, 1 H), 6.94 (dd, *J*=4.8, 3.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 190.8, 144.5, 140.5, 138.7, 135.2, 134.8, 134.7, 130.3, 129.7, 128.2, 128.1, 127.9, 127.0, 125.9, 123.4.

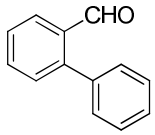
MS (70 eV, EI) m/z (%): 270 (100), 269 (33), 241 (32), 237 (85), 115 (31), 111 (38).

IR ATR ν (cm^{-1}): 3094, 2923, 2853, 1628, 1595, 1567, 1511, 1481, 1443, 1407, 1366, 1354, 1295, 1268, 1258, 1231, 1195, 1164, 1149, 1106, 1085, 1052, 1042, 1026, 889, 859, 842, 804, 795, 779, 756, 748, 728, 723, 706, 697, 669.

HRMS (EI) for **$C_{15}H_{10}OS_2$** (270.0173) $[M]^+$: 270.0169.

7.2. Preparation of the Title Compounds Using TP5

Synthesis of [1,1'-biphenyl]-2-carbaldehyde (48a):



A solution of **32a** in THF (1.2 mmol, 1.2 equiv, 1.7 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and imine **47** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with an aq. solution of HCl (2 M) and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **48a** as a yellow oil.

Isolated yield: 84% (152 mg).

Reaction conditions: 15 min.

Solvent for purification: *i*-hexane/diethyl ether 9:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 10.00 (d, *J*=0.8 Hz, 1 H), 8.04 (dd, *J*=7.7, 1.4 Hz, 1 H), 7.64 (td, *J*=7.5, 1.5 Hz, 1 H), 7.52 - 7.43 (m, 5 H), 7.41 - 7.37 (m, 2 H).

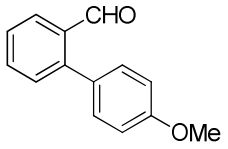
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 192.4, 146.0, 137.7, 133.7, 133.5, 130.8, 130.1, 128.4, 128.1, 127.8, 127.6.

MS (70 eV, EI) m/z (%): 182 (72), 181 (100), 154 (19), 153 (41), 152 (49), 76 (13).

IR ATR ν (cm^{-1}): 3060, 3028, 2845, 2752, 1688, 1655, 1596, 1498, 1473, 1453, 1437, 1392, 1301, 1252, 1194, 1160, 1101, 1075, 1048, 1033, 1008, 919, 827, 778, 756, 745, 700.

HRMS (EI) for **$C_{13}H_{10}O$** (182.0732) $[M]^+$: 182.0701.

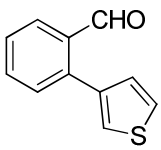
Synthesis of 4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (48b):



A solution of **32i** in THF (1.2 mmol, 1.2 equiv, 1.3 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and imine **47** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with an aq. solution of HCl (2 M) and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **48b** as a yellow oil.

Isolated yield: 69% (152 mg).
Reaction conditions: 15 min.
Solvent for purification: *i*-hexane/diethyl ether 95:5.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 10.00 (t, *J*=0.7 Hz, 1 H), 8.00 (dt, *J*=7.8, 0.7 Hz, 1 H), 7.65 - 7.57 (m, 1 H), 7.49 - 7.40 (m, 2 H), 7.34 - 7.25 (m, 2 H), 7.04 - 6.97 (m, 2 H), 3.87 (d, *J*=0.8 Hz, 3 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 192.6, 159.7, 145.6, 133.8, 133.5, 131.3, 130.8, 130.0, 127.6, 127.3, 113.9, 55.4.
MS (70 eV, EI) m/z (%): 212 (100), 211 (30), 197 (20), 181 (27), 169 (59), 168 (19), 152 (21), 140 (20), 139 (51), 115 (57).
IR ATR ν (cm^{-1}): 3031, 2957, 2935, 2837, 2750, 1688, 1657, 1609, 1596, 1578, 1514, 1474, 1449, 1442, 1391, 1297, 1271, 1243, 1192, 1177, 1160, 1112, 1100, 1047, 1033, 1016, 1000, 833, 803, 763, 742, 713.
HRMS (EI) for **$C_{14}H_{12}O_2$:** (212.0837) $[M]^+$: 212.0838.

Synthesis of 2-(thiophen-3-yl)benzaldehyde (48c):



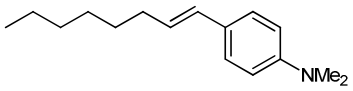
A solution of **45** in THF (1.2 mmol, 1.2 equiv, 0.8 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and imine **47** (1 mmol,

1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 16 h before being quenched with an aq. solution of HCl (2 M) and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **48c** as a yellow oil.

Isolated yield: 75% (140 mg).
Reaction conditions: 16 h.
Solvent for purification: *i*-hexane/diethyl ether 95:5.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 10.10 (d, *J*=0.6 Hz, 1 H), 8.03 - 7.97 (m, 1 H), 7.65 - 7.58 (m, 1 H), 7.51 - 7.42 (m, 3 H), 7.29 (dd, *J*=2.9, 1.2 Hz, 1 H), 7.21 - 7.17 (m, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 192.3, 140.4, 138.3, 134.0, 133.6, 130.6, 129.3, 127.8, 127.6, 126.3, 125.0.
MS (70 eV, EI) m/z (%): 188 (100), 160 (100), 159 (24), 158 (21), 116 (20), 115 (85), 43 (31).
IR ATR ν (cm^{-1}): 3099, 2847, 2750, 1683, 1596, 1570, 1474, 1447, 1406, 1389, 1362, 1270, 1243, 1194, 1160, 1100, 1082, 1047, 1028, 859, 830, 813, 792, 756, 731, 684, 653.
HRMS (EI) for **$C_{11}H_8OS$:** (188.0296) $[M]^+$: 188.0300.

7.3. Preparation of the Title Compounds Using TP6

Synthesis of (*E*)-*N*,*N*-dimethyl-4-(oct-1-en-1-yl)aniline (50a):



A solution of **32n** in THF (1.5 mmol, 1.5 equiv, 1.2 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and alkenyl iodide **49** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **50a** as a slightly yellow oil.

Isolated yield: 70% (162 mg).
Reaction time: 15 min.
Solvent for purification: *i*-hexane/ethyl acetate 9:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.84 - 0.96 (m, 3 H), 1.23 - 1.52 (m, 8 H), 2.10 - 2.26 (m, 2 H), 2.95 (s, 6 H), 5.97 - 6.10 (m, 1 H), 6.30 (d, *J*=16.03 Hz, 1 H), 6.66 - 6.74 (m, 2 H), 7.21 - 7.29 (m, 2 H).

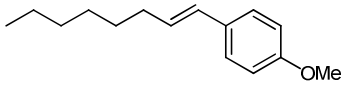
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.1, 22.7, 28.9, 29.7, 31.8, 33.1, 40.7, 112.8, 126.7, 127.2, 129.4, 149.6.

MS (70 eV, EI) m/z (%): 232 (15), 231 (100), 161 (26), 160 (40), 145 (14), 134 (30).

IR ATR ν (cm^{-1}): 2954, 2923, 2871, 2852, 2801, 1610, 1519, 1480, 1466, 1454, 1444, 1348, 1221, 1187, 1164, 1129, 1061, 961, 947, 831, 801, 725.

HRMS (EI) for **$C_{16}H_{25}N$** (231.1987) $[M]^+$: 231.1964.

Synthesis of (*E*)-1-methoxy-4-(oct-1-en-1-yl)benzene (50b):



A solution of **32i** in THF (1.5 mmol, 1.5 equiv, 1.3 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and alkenyl iodide **49** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **50b** as a colorless oil.

Isolated yield: 75% (164 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 20:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.87 - 0.99 (m, 3 H), 1.28 - 1.52 (m, 8 H), 2.14 - 2.27 (m, 2 H), 3.81 (s, 3 H), 6.04 - 6.17 (m, 1 H), 6.29 - 6.39 (m, 1 H), 6.85 (m, 2 H), 7.29 (m, 2 H).

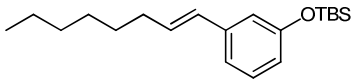
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.1, 22.7, 28.9, 29.5, 31.8, 33.0, 55.3, 113.9, 126.9, 129.0, 129.1, 130.8, 158.6.

MS (70 eV, EI) m/z (%): 218 (27), 148 (14), 147 (100), 134 (19), 121 (24), 115 (10), 91 (16).

IR ATR ν (cm^{-1}): 2955, 2924, 2871, 2854, 2836, 1608, 1510, 1465, 1441, 1287, 1244, 1174, 1105, 1037, 963, 840, 803, 758, 724.

HRMS (EI) for **$C_{15}H_{22}O$** (218.1671) $[M]^+$: 218.1666.

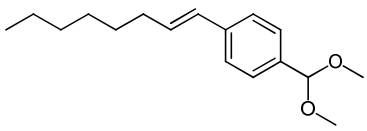
Synthesis of (*E*)-*tert*-butyldimethyl(3-(oct-1-en-1-yl)phenoxy)silane (50c):



A solution of **32p** in THF (1.5 mmol, 1.5 equiv, 1.0 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and alkenyl iodide **49** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **50c** as a colorless oil.

Isolated yield: 80% (255 mg).
Reaction time: 15 min.
Solvent for purification: *i*-hexane.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.22 (s, 6 H), 0.87 - 0.97 (m, 3 H), 1.02 (s, 9 H), 1.22 - 1.58 (m, 8 H), 2.22 (q, *J*=7.28 Hz, 2 H), 6.15 - 6.26 (m, 1 H), 6.30 - 6.38 (m, 1 H), 6.70 (dd, *J*=8.02, 2.21 Hz, 1 H), 6.94 - 7.00 (m, 1 H), 7.12 - 7.28 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.4, 14.1, 18.2, 22.6, 25.7, 28.9, 29.3, 31.8, 33.0, 117.5, 118.5, 119.1, 120.1, 129.5, 131.3, 139.5, 155.8.
MS (70 eV, EI) m/z (%): 318 (13), 262 (20), 261 (100), 163 (9), 151 (6).
IR ATR ν (cm^{-1}): 2956, 2928, 2857, 1597, 1578, 1490, 1472, 1464, 1439, 1277, 1252, 1170, 1156, 1001, 965, 939, 916, 876, 837, 778, 713, 688, 665.
HRMS (EI) for **$C_{20}H_{34}OSi$** (318.2379) $[M]^+$: 318.2376.

Synthesis of (*E*)-1-(dimethoxymethyl)-4-(oct-1-en-1-yl)benzene (50d):



A solution of **32t** in THF (1.5 mmol, 1.5 equiv, 0.9 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and alkenyl iodide **49** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **50d** as a colorless oil.

Isolated yield: 69% (181 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 20:1.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.81 - 0.87 (m, 3 H), 1.23 - 1.32 (m, 6 H), 1.36 - 1.45 (m, 2 H), 2.15 (q, *J*=6.63 Hz, 2 H), 3.32 (s, 6 H), 5.33 (s, 1 H), 6.24 - 6.39 (m, 2 H), 7.28 (m, 2 H), 7.36 (m, 2 H).

^{13}C NMR (75 MHz, DMSO) δ/ppm: 14.4, 22.5, 28.8, 29.2, 31.6, 32.9, 52.8, 102.9, 125.9, 127.2, 129.6, 131.7, 137.1, 137.9.

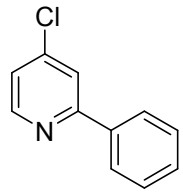
MS (70 eV, EI) m/z (%): 216 (24), 133 (11), 132 (100), 131 (30), 117 (66), 91 (24).

IR ATR ν (cm^{-1}): 2954, 2927, 2856, 1689, 1609, 1577, 1466, 1422, 1379, 1286, 1268, 1208, 1170, 1107, 1016, 893, 856, 828, 804, 790, 762, 733, 724, 702.

HRMS (EI) for **$C_{17}H_{26}O_2$** (262.1933) $[M]^+$: 262.1916.

7.4. Preparation of the Title Compounds Using TP7 and TP8

Synthesis of 4-chloro-2-phenylpyridine (52a):



A solution of **32a** in THF (1.2 mmol, 1.2 equiv, 1.7 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51a** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52a** as a slightly yellow oil.

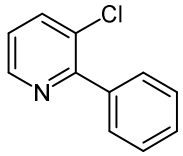
Isolated yield: 80% (152 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 6:1 (+0.5% NEt_3).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.21 - 7.29 (m, 1 H), 7.41 - 7.57 (m, 3 H), 7.74 (dd, *J*=1.94, 0.55 Hz, 1 H), 7.90 - 8.08 (m, 2 H), 8.59 (dd, *J*=5.25, 0.55 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.83 (s, 1 C), 122.27 (s, 1 C), 126.98 (s, 1 C), 128.85 (s, 1 C), 129.60 (s, 1 C), 138.10 (s, 1 C), 144.74 (s, 1 C), 150.46 (s, 1 C), 158.98 (s, 1 C):
MS (70 eV, EI) m/z (%): 189 (51) $[M]^+$, 188 (14), 154 (27), 127 (12), 70 (11), 43 (100).
IR ATR ν (cm^{-1}): 3044, 2358, 1571, 1549, 1497, 1462, 1442, 1382, 1112, 1096, 1072, 1053, 872, 823, 802, 771, 728, 703, 690, 668, 659.
HRMS (EI) for **$C_{11}H_8ClN$** (189.0345) $[M]^+$: 189.0337.

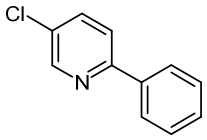
Synthesis of 3-chloro-2-phenylpyridine (52b):



A solution of **32a** in THF (1.2 mmol, 1.2 equiv, 1.7 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51b** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52b** as a slightly yellow oil.

Isolated yield: 76% (144 mg).
Reaction time: 15 min.
Solvent for purification: *i*-hexane/ethyl acetate 6:1 (+0.5% NEt_3).
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.22 (dd, *J*=8.02, 4.70 Hz, 1 H), 7.43 - 7.53 (m, 3 H), 7.72 - 7.84 (m, 3 H), 8.61 (dd, *J*=4.70, 1.38 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 123.02 (s, 1 C), 128.02 (s, 1 C), 128.81 (s, 1 C), 129.32 (s, 1 C), 130.16 (s, 1 C), 138.06 (s, 1 C), 138.19 (s, 1 C), 147.55 (s, 1 C), 156.58 (s, 1 C).
MS (70 eV, EI) m/z (%): 189 (22), 154 (50), 61 (18), 43 (100).
IR ATR ν (cm^{-1}): 3057, 3042, 2362, 1570, 1553, 1496, 1450, 1431, 1415, 1222, 1181, 1131, 1089, 1075, 1031, 1016, 1002, 974, 918, 794, 786, 761, 737, 694, 681, 668, 659, 654.
HRMS (EI) for **$C_{11}H_8ClN$** (189.0345) $[M]^+$: 189.0344.

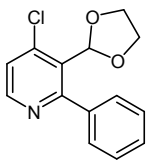
Synthesis of 5-chloro-2-phenylpyridine (52c):



A solution of **32a** in THF (1.2 mmol, 1.2 equiv, 1.7 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51c** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52c** as white crystals.

Isolated yield: 87% (165 mg).
Reaction time: 15 min.
Solvent for purification: *i*-hexane/ethyl acetate 6:1 (+0.5% NEt_3).
m.p.: 65.8-67.8 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.42 - 7.52 (m, 3 H), 7.66 - 7.69 (m, 1 H), 7.71 - 7.74 (m, 1 H), 7.95 - 8.01 (m, 2 H), 8.65 (dd, *J*=2.34, 0.78 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 121.11 (s, 1 C), 126.79 (s, 1 C), 128.85 (s, 1 C), 129.28 (s, 1 C), 130.59 (s, 1 C), 136.45 (s, 1 C), 138.16 (s, 1 C), 148.46 (s, 1 C), 155.53 (s, 1 C).
MS (70 eV, EI) m/z (%): 191 (33), 189 (100), 154 (41), 127 (13).
IR ATR ν (cm^{-1}): 3062, 3037, 2360, 1574, 1554, 1460, 1456, 1442, 1436, 1419, 1365, 1290, 1136, 1112, 1074, 1022, 1007, 991, 979, 929, 920, 853, 834, 774, 755, 730, 707, 690, 676, 672, 668, 663, 658, 655, 653.
HRMS (EI) for **$C_{11}H_8ClN$** (189.0345) $[M]^+$: 189.0340.

Synthesis of 4-chloro-3-(1,3-dioxolan-2-yl)-2-phenylpyridine (52d):

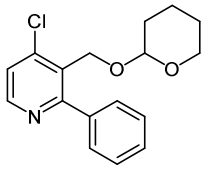


A solution of **32a** in THF (1.2 mmol, 1.2 equiv, 1.7 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51d** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 30 min before being

quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52d** as a white solid.

Isolated yield: 67% (175 mg).
Reaction time: 30 min.
Solvent for purification: *i*-hexane/ethyl acetate 4:1 (+0.5% NEt_3).
m.p.: 59.3-61.0 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.85 - 4.02 (m, 2 H), 4.02 - 4.20 (m, 2 H), 5.97 (s, 1 H), 7.30 - 7.67 (m, 6 H), 8.54 (d, *J*=5.25 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 65.82 (s, 1 C), 101.38 (s, 1 C), 124.97 (s, 1 C), 127.46 (s, 1 C), 128.02 (s, 1 C), 128.54 (s, 1 C), 129.43 (s, 1 C), 139.06 (s, 1 C), 145.17 (s, 1 C), 149.86 (s, 1 C), 162.12 (s, 1 C).
MS (70 eV, EI) m/z (%): 218 (30), 216 (89), 191 (33), 189 (100), 183 (26), 154 (47).
IR ATR ν (cm^{-1}): 2971, 2894, 2362, 1559, 1552, 1452, 1446, 1379, 1222, 1171, 1103, 1057, 1018, 973, 962, 938, 922, 862, 844, 838, 810, 792, 771, 763, 724, 707, 702, 685, 673, 668, 661, 656, 653.
HRMS (EI) for **$C_{14}H_{12}ClNO_2$** (261.0557) $[M]^+$: 261.0554.

Synthesis of 4-chloro-2-phenyl-3-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)pyridine (52e):



A solution of **32a** in THF (1.2 mmol, 1.2 equiv, 1.7 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51e** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 30 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52e** as a colorless oil.

Isolated yield: 76% (231 mg).
Reaction time: 30 min.

Solvent for purification: *i*-hexane/ethyl acetate 4:1 (+0.5% NEt_3).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.52 - 1.92 (m, 6 H), 3.46 - 3.55 (m, 1 H), 3.79 - 3.90 (m, 1 H), 4.39 (d, *J*=10.50 Hz, 1 H), 4.77 (t, *J*=3.04 Hz, 1 H), 4.83 (d, *J*=10.50 Hz, 1 H), 7.36 (d, *J*=5.25 Hz, 1 H), 7.41 - 7.51 (m, 3 H), 7.62 - 7.71 (m, 2 H), 8.52 (d, *J*=5.25 Hz, 1 H).

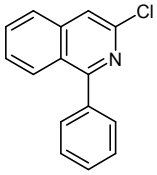
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 18.92 (s, 1 C), 25.41 (s, 1 C), 30.41 (s, 1 C), 61.69 (s, 1 C), 64.56 (s, 1 C), 99.00 (s, 1 C), 123.55 (s, 1 C), 128.10 (s, 1 C), 128.67 (s, 1 C), 129.17 (s, 1 C), 129.32 (s, 1 C), 139.39 (s, 1 C), 146.82 (s, 1 C), 149.27 (s, 1 C), 162.12 (s, 1 C).

MS (70 eV, EI) m/z (%): 219 (16), 204 (30), 202 (100), 167 (14), 85 (33).

IR ATR ν (cm^{-1}): 2940, 2894, 2362, 2338, 1560, 1548, 1496, 1452, 1438, 1410, 1378, 1348, 1200, 1182, 1174, 1131, 1118, 1103, 1076, 1068, 1055, 1037, 1022, 1001, 989, 962, 938, 922, 905, 890, 869, 843, 837, 818, 816, 810, 793, 779, 757, 732, 730, 724, 700, 686, 668, 653.

HRMS (EI) for **$C_{17}H_{18}ClNO_2$** (303.1026) $[M]^+$: 303.0949.

Synthesis of 3-chloro-1-phenylisoquinoline (52f):



A solution of **32a** in THF (1.2 mmol, 1.2 equiv, 1.7 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51f** (1 mmol, 1.0 equiv) in CPME (5 mL) at 25 °C. The suspension was stirred at 25 °C for 1 h before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52f** as a slightly yellow solid.

Isolated yield: 71% (170 mg).

Reaction time: 1 h.

Solvent for purification: *i*-hexane/ethyl acetate 3:1 (+0.5% NEt_3).

m.p.: 75.9-77.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.47 - 7.60 (m, 4 H), 7.67 - 7.75 (m, 4 H), 7.79 - 7.84 (m, 1 H), 8.10 (d, *J*=8.57 Hz, 1 H).

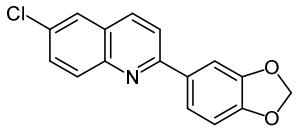
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 118.89 (s, 1 C), 125.49 (s, 1 C), 126.25 (s, 1 C), 127.34 (s, 1 C), 127.79 (s, 1 C), 128.41 (s, 1 C), 129.07 (s, 1 C), 130.04 (s, 1 C), 130.90 (s, 1 C), 138.21 (s, 1 C), 138.96 (s, 1 C), 144.76 (s, 1 C), 161.49 (s, 1 C).

MS (70 eV, EI) m/z (%): 239 (100), 202 (71), 176 (18), 151 (15), 101 (17).

IR ATR ν (cm^{-1}): 3054, 3028, 2363, 2331, 1616, 1572, 1570, 1560, 1558, 1542, 1489, 1443, 1430, 1396, 1385, 1376, 1359, 1319, 1307, 1269, 1215, 1147, 1077, 1069, 1028, 999, 978, 974, 964, 922, 874, 854, 850, 799, 766, 757, 749, 724, 698, 677, 668, 658, 653.

HRMS (EI) for **$C_{15}H_{10}ClN$** (239.0502) $[M]^+$: 239.0477.

Synthesis of 2-(benzo[*d*][1,3]dioxol-5-yl)-6-chloroquinoline (52g):



A solution of **32k** in THF (1.2 mmol, 1.2 equiv, 1.1 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51g** (1 mmol, 1.0 equiv) in CPME (5 mL) at 25 °C. The suspension was stirred at 25 °C for 1 h before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52g** as a white solid.

Isolated yield: 82% (232 mg).

Reaction time: 1 h.

Solvent for purification: *i*-hexane/ethyl acetate 8:1 (+0.5% NEt_3).

m.p.: 159.2-160.9 °C.

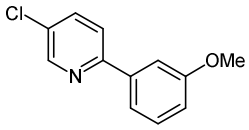
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.05 (s, 2 H), 6.95 (d, *J*=8.02 Hz, 1 H), 7.64 (ddd, *J*=8.71, 2.35, 2.21 Hz, 2 H), 7.70 - 7.83 (m, 3 H), 8.06 (dd, *J*=8.71, 2.63 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 101.41 (s, 1 C), 107.77 (s, 1 C), 108.48 (s, 1 C), 119.32 (s, 1 C), 121.74 (s, 1 C), 126.06 (s, 1 C), 127.49 (s, 1 C), 130.50 (s, 1 C), 131.10 (s, 1 C), 131.61 (s, 1 C), 133.58 (s, 1 C), 135.68 (s, 1 C), 146.52 (s, 1 C), 148.45 (s, 1 C), 149.03 (s, 1 C), 156.78 (s, 1 C).

MS (70 eV, EI) m/z (%): 283 (100), 225 (14), 190 (25), 44 (20).

IR ATR ν (cm^{-1}): 2903, 2366, 2336, 1593, 1548, 1507, 1499, 1481, 1455, 1438, 1351, 1329, 1293, 1287, 1256, 1241, 1214, 1190, 1145, 1120, 1111, 1072, 1036, 948, 936, 924, 913, 894, 881, 861, 830, 824, 815, 809, 788, 775, 724, 706, 653.
HRMS (EI) for **$C_{16}H_{10}ClNO_2$** (283.0400) $[M]^+$: 283.0389.

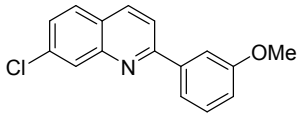
Synthesis of 5-chloro-2-(3-methoxyphenyl)pyridine (52h):



A solution of **53** in THF (1.2 mmol, 1.2 equiv, 1.2 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51c** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 30 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52h** as a white powder.

Isolated yield: 71% (156 mg).
Reaction time: 30 min.
Solvent for purification: *i*-hexane/Et_2O 9:1 (+0.5% NEt_3).
m.p.: 60.2-62.8 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.90 (s, 3 H), 6.99 (dd, *J*=8.16, 2.63 Hz, 1 H), 7.39 (t, *J*=8.02 Hz, 1 H), 7.49 - 7.59 (m, 2 H), 7.64 - 7.75 (m, 2 H), 8.64 (d, *J*=2.49 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.38 (s, 1 C), 111.97 (s, 1 C), 115.28 (s, 1 C), 119.13 (s, 1 C), 121.23 (s, 1 C), 129.82 (s, 1 C), 130.69 (s, 1 C), 136.41 (s, 1 C), 139.63 (s, 1 C), 148.40 (s, 1 C), 155.30 (s, 1 C), 160.11 (s, 1 C).
MS (70 eV, EI) m/z (%): 219 (66), 190 (50), 176 (11), 154 (50), 141 (36), 113 (17).
IR ATR ν (cm^{-1}): 3002, 2956, 2834, 2360, 2331, 1608, 1586, 1575, 1554, 1471, 1459, 1430, 1370, 1365, 1302, 1292, 1227, 1219, 1208, 1182, 1176, 1168, 1111, 1053, 1035, 1010, 894, 889, 885, 876, 858, 855, 848, 840, 836, 824, 791, 755, 749, 689, 668.
HRMS (EI) for **$C_{12}H_{10}ClNO$** (219.0451) $[M]^+$: 219.0435.

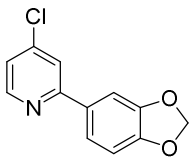
Synthesis of 7-chloro-2-(3-methoxyphenyl)quinoline (52i):



A solution of **53** in THF (1.2 mmol, 1.2 equiv, 1.2 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51h** (1 mmol, 1.0 equiv) in CPME (5 mL) at 25 °C. The suspension was stirred at 25 °C for 2 h before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52i** as a white solid.

Isolated yield: 72% (194 mg).
Reaction time: 2 h.
Solvent for purification: *i*-hexane/ethyl acetate 9:1 (+0.5% NEt_3).
m.p.: 66.2-67.5 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.94 (s, 3 H), 7.04 (ddd, *J*=6.91, 1.66, 1.38 Hz, 1 H), 7.41 - 7.51 (m, 2 H), 7.68 - 7.80 (m, 3 H), 7.86 (d, *J*=8.29 Hz, 1 H), 8.12 - 8.22 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.41 (s, 1 C), 112.71 (s, 1 C), 115.69 (s, 1 C), 119.15 (s, 1 C), 119.96 (s, 1 C), 125.58 (s, 1 C), 127.28 (s, 1 C), 128.62 (s, 1 C), 128.70 (s, 1 C), 129.83 (s, 1 C), 135.44 (s, 1 C), 136.49 (s, 1 C), 140.59 (s, 1 C), 148.56 (s, 1 C), 157.95 (s, 1 C), 160.16 (s, 1 C).
MS (70 eV, EI) m/z (%): 269 (71), 268 (100), 239 (45), 204 (12), 190 (16).
IR ATR ν (cm^{-1}): 2940, 2920, 2830, 2359, 1611, 1597, 1587, 1557, 1545, 1483, 1469, 1456, 1436, 1329, 1308, 1292, 1278, 1241, 1218, 1188, 1183, 1157, 1152, 1133, 1087, 1069, 1046, 1037, 997, 927, 880, 871, 849, 837, 806, 778, 766, 692, 674, 668, 659.
HRMS (EI) for **$C_{16}H_{12}ClNO$** (269.0607) $[M]^+$: 268.0524.

Synthesis of 2-(benzo[*d*][1,3]dioxol-5-yl)-4-chloropyridine (52j):



A solution of **32k** in THF (1.2 mmol, 1.2 equiv, 1.1 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51a** (1 mmol, 1.0 equiv)

in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52j** as a white solid.

Isolated yield: 77% (179 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 8:1 (+0.5% NEt_3).

m.p.: 108.5-111.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.03 (s, 2 H), 6.90 (d, *J*=8.02 Hz, 1 H), 7.19 (dd, *J*=5.25, 1.94 Hz, 1 H), 7.45 - 7.53 (m, 2 H), 7.63 (d, *J*=1.94 Hz, 1 H), 8.53 (d, *J*=5.25 Hz, 1 H).

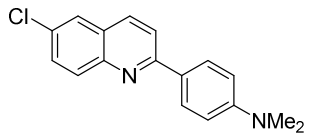
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 101.42 (s, 1 C), 107.34 (s, 1 C), 108.48 (s, 1 C), 120.17 (s, 1 C), 121.16 (s, 1 C), 121.78 (s, 1 C), 132.50 (s, 1 C), 144.63 (s, 1 C), 148.37 (s, 1 C), 148.97 (s, 1 C), 150.27 (s, 1 C), 158.41 (s, 1 C).

MS (70 eV, EI) m/z (%): 233 (100), 140 (19), 113 (13).

IR ATR ν (cm^{-1}): 2894, 2359, 1573, 1550, 1500, 1493, 1462, 1442, 1378, 1351, 1278, 1257, 1216, 1114, 1108, 1037, 934, 888, 869, 865, 861, 834, 815, 811, 780, 734, 719, 717, 701, 686, 684, 668.

HRMS (EI) for **$C_{12}H_8ClNO_2$** (233.0244) $[M]^+$: 233.0244.

Synthesis of 4-(6-chloroquinolin-2-yl)-*N*,*N*-dimethylaniline (52k):



A solution of **32n** in THF (1.2 mmol, 1.2 equiv, 1.2 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51g** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 3 h before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52k** as a beige solid.

Isolated yield: 71% (199 mg).

Reaction time: 3 h.

Solvent for purification: *i*-hexane/ethyl acetate 8:1 (+0.5% NEt_3).

m.p.: 188.0-188.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.06 (s, 6 H), 6.84 (d, *J*=9.12 Hz, 2 H), 7.61 (dd, *J*=8.98, 2.35 Hz, 1 H), 7.75 (d, *J*=2.49 Hz, 1 H), 7.84 (d, *J*=8.85 Hz, 1 H), 7.97 - 8.15 (m, 4 H).

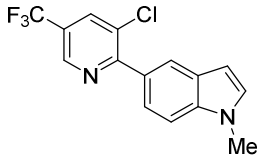
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 40.29 (s, 1 C), 112.18 (s, 1 C), 119.01 (s, 1 C), 126.04 (s, 1 C), 126.94 (s, 1 C), 127.19 (s, 1 C), 128.43 (s, 1 C), 130.16 (s, 1 C), 130.75 (s, 1 C), 130.84 (s, 1 C), 135.31 (s, 1 C), 146.76 (s, 1 C), 151.48 (s, 1 C), 157.50 (s, 1 C).

MS (70 eV, EI) m/z (%): 282 (100), 281 (47), 266 (9), 238 (11).

IR ATR ν (cm^{-1}): 2915, 2830, 2366, 1613, 1597, 1539, 1484, 1470, 1457, 1437, 1330, 1310, 1288, 1279, 1240, 1231, 1220, 1202, 1188, 1168, 1157, 1152, 1133, 1067, 1062, 1046, 1037, 949, 941, 930, 882, 871, 849, 838, 825, 809, 794, 778, 767, 760, 757, 693, 681, 675, 668.

HRMS (EI) for **$C_{17}H_{15}ClN_2$** (282.0924) $[M]^+$: 282.0921.

Synthesis of 5-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-1-methyl-1*H*-indole (52l):



A solution of **32r** in THF (1.2 mmol, 1.2 equiv, 1.0 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51i** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 50 °C for 1 h before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52l** as a beige solid.

Isolated yield: 56% (174 mg).

Reaction conditions: 1 h, 50 °C.

Solvent for purification: *i*-hexane/ethyl acetate 6:1 (+0.5% NEt_3).

m.p.: 83.9-85.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.85 (s, 3 H), 6.60 (d, *J*=3.04 Hz, 1 H), 7.13 (d, *J*=3.04 Hz, 1 H), 7.44 (d, *J*=8.57 Hz, 1 H), 7.68 (dd, *J*=8.85, 1.66 Hz, 1 H), 8.08 (dd, *J*=18.94, 2.07 Hz, 2 H), 8.87 (d, *J*=1.94 Hz, 1 H).

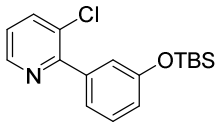
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 32.95 (s, 1 C), 102.06 (s, 1 C), 108.91 (s, 1 C), 122.76 (s, 1 C), 122.95 (q, *J*=272.73 Hz), 123.04 (s, 1 C), 125.07 (q, J=33.59 Hz), 128.10 (s, 1 C), 128.21 (s, 1 C), 129.87 (s, 1 C), 130.06 (s, 1 C), 135.18 (q, J=3.42 Hz, 1 C), 137.21 (s, 1 C), 144.00 (q, J=3.99 Hz, 1 C), 161.15 (s, 1 C).

MS (70 eV, EI) m/z (%): 310 (100), 275 (16), 111 (13), 97 (16), 85 (15).

IR ATR ν (cm^{-1}): 2923, 2853, 2357, 1596, 1485, 1455, 1443, 1437, 1325, 1310, 1293, 1288, 1280, 1271, 1243, 1232, 1220, 1202, 1188, 1181, 1153, 1133, 1118, 1109, 1093, 1066, 1027, 1004, 1003, 949, 941, 937, 931, 916, 899, 887, 884, 871, 848, 839, 825, 814, 809, 793, 783, 771, 766, 758, 752, 735, 730, 724, 718, 708, 693, 681, 676, 668, 660, 652.

HRMS (EI) for **$C_{15}H_{10}ClF3N_2$** (310.0485) $[M]^+$: 310.0472.

Synthesis of 2-(3-((tert-butyldimethylsilyl)oxy)phenyl)-3-chloropyridine (52m):



A solution of **32p** in THF (1.2 mmol, 1.2 equiv, 1.1 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51b** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52m** as a colorless oil.

Isolated yield: 82% (262 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/Et_2O 9:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.24 (s, 6 H), 1.01 (s, 9 H), 6.93 (dt, *J*=7.26, 2.18 Hz, 1 H), 7.17 - 7.25 (m, 2 H), 7.28 - 7.38 (m, 2 H), 7.79 (dd, *J*=8.02, 1.66 Hz, 1 H), 8.59 (dd, *J*=4.56, 1.52 Hz, 1 H).

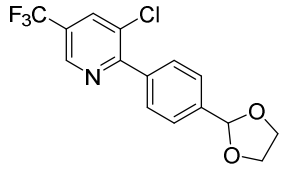
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.38 (s, 1 C), 18.18 (s, 1 C), 25.69 (s, 1 C), 120.53 (s, 1 C), 121.07 (s, 1 C), 122.34 (s, 1 C), 123.01 (s, 1 C), 129.11 (s, 1 C), 130.14 (s, 1 C), 138.03 (s, 1 C), 139.47 (s, 1 C), 147.47 (s, 1 C), 155.20 (s, 1 C), 156.36 (s, 1 C).

MS (70 eV, EI) m/z (%): 319 (13), 264 (38), 262 (100), 226 (9).

IR ATR ν (cm^{-1}): 2955, 2928, 2857, 2360, 2338, 1602, 1581, 1570, 1486, 1471, 1462, 1439, 1419, 1415, 1406, 1306, 1272, 1259, 1251, 1243, 1227, 1199, 1130, 1029, 1001, 937, 884, 830, 816, 791, 778, 760, 723, 696, 685, 677, 668, 662.

HRMS (EI) for **$C_{17}H_{22}ClNOSi$** (319.1159) $[M]^+$: 319.1154.

Synthesis of 2-(4-(1,3-dioxolan-2-yl)phenyl)-3-chloro-5-(trifluoromethyl)pyridine (52n):



A solution of **54** in THF (1.2 mmol, 1.2 equiv, 1.1 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51i** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52n** as a white powder.

Isolated yield: 71% (233 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 8:1 (+0.5% NEt_3).

m.p.: 72.4-74.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 4.02 - 4.22 (m, 4 H), 5.92 (s, 1 H), 7.63 (m, 2 H), 7.80 (m, 2 H), 8.05 (d, *J*=1.36 Hz, 1 H), 8.85 (dd, *J*=2.05, 0.88 Hz, 1 H).

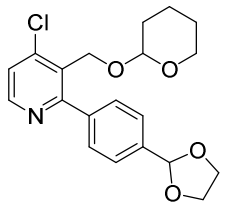
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 65.34 (s, 1 C), 103.22 (s, 1 C), 122.70 (q, J=272.93 Hz), 126.12 (q, J=33.59 Hz), 126.28 (s, 1 C), 129.47 (s, 1 C), 130.25 (s, 1 C), 135.30 (q, J=3.65 Hz), 137.68 (s, 1 C), 139.47 (s, 1 C), 144.21 (q, J=4.03 Hz), 159.49 (q, J=1.54 Hz).

MS (70 eV, EI) m/z (%): 329 (19), 328 (69), 286 (16), 271 (14), 257 (100), 222 (81), 73 (62).

IR ATR ν (cm^{-1}): 2899, 2361, 2339, 1599, 1380, 1324, 1309, 1216, 1153, 1119, 1093, 1081, 1069, 1028, 1014, 988, 981, 970, 957, 941, 911, 858, 843, 835, 824, 768, 735, 731, 695, 685.

HRMS (EI) for **$C_{15}H_{11}ClF_3NO_2$** (329.0430) $[M]^+$: 328.0355.

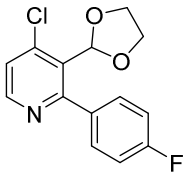
Synthesis of 2-(4-(1,3-dioxolan-2-yl)phenyl)-4-chloro-3-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)pyridine (52o):



A solution of **54** in THF (1.2 mmol, 1.2 equiv, 1.1 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51e** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 30 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52o** as a colorless oil.

Isolated yield: 66% (248 mg).
Reaction conditions: 30 min.
Solvent for purification: *i*-hexane/ethyl acetate 3:1 (+0.5% NEt_3).
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.51 - 1.90 (m, 6 H), 3.45 - 3.60 (m, 1 H), 3.78 - 3.95 (m, 1 H), 3.99 - 4.22 (m, 4 H), 4.37 (d, *J*=10.78 Hz, 1 H), 4.73 - 4.91 (m, 2 H), 5.90 (s, 1 H), 7.36 (d, *J*=5.25 Hz, 1 H), 7.57 (m, 2 H), 7.71 (m, 2 H), 8.52 (d, *J*=5.25 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 18.95 (s, 1 C), 25.39 (s, 1 C), 30.44 (s, 1 C), 61.80 (s, 1 C), 64.54 (s, 1 C), 65.25 (s, 1 C), 99.02 (s, 1 C), 103.38 (s, 1 C), 123.64 (s, 1 C), 126.23 (s, 1 C), 129.26 (s, 1 C), 129.35 (s, 1 C), 138.47 (s, 1 C), 140.15 (s, 1 C), 146.86 (s, 1 C), 149.33 (s, 1 C), 161.64 (s, 1 C).
MS (70 eV, EI) m/z (%): 291 (25), 274 (40), 230 (13), 202 (36), 166 (16), 73 (100).
IR ATR ν (cm^{-1}): 2941, 2884, 2366, 2334, 1561, 1548, 1446, 1412, 1385, 1363, 1349, 1200, 1182, 1130, 1117, 1078, 1064, 1053, 1036, 1023, 989, 966, 941, 905, 890, 880, 869, 824, 816, 788, 775, 754, 729, 712, 710, 707, 693, 689, 687, 685, 681, 675, 668, 659, 658, 654.
HRMS (EI) for **$C_{20}H_{22}ClNO_4$** (375.1237) $[M]^+$: 374.1157.

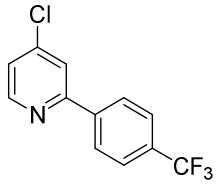
Synthesis of 4-chloro-3-(1,3-dioxolan-2-yl)-2-(4-fluorophenyl)pyridine (52p):



A solution of **32g** in THF (1.2 mmol, 1.2 equiv, 1.0 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51d** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 30 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52p** as white crystals.

Isolated yield: 79% (221 mg).
Reaction conditions: 30 min.
Solvent for purification: *i*-hexane/ethyl acetate 4:1 (+0.5% NEt_3).
m.p.: 76.2-79.0 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.88 - 4.13 (m, 4 H), 5.95 (s, 1 H), 7.06 - 7.20 (m, 2 H), 7.36 (d, *J*=5.25 Hz, 1 H), 7.45 - 7.60 (m, 2 H), 8.52 (d, *J*=5.25 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 65.80 (s, 1 C), 101.26 (s, 1 C), 114.84 (s, 1 C), 115.13 (s, 1 C), 124.99 (s, 1 C), 127.50 (s, 1 C), 131.28 (s, 1 C), 131.39 (s, 1 C), 135.19 (s, 1 C), 135.24 (s, 1 C), 145.28 (s, 1 C), 149.84 (s, 1 C), 161.03 (s, 1 C), 161.35 (s, 1 C), 164.64 (s, 1 C):
MS (70 eV, EI) m/z (%): 236 (29), 234 (84), 220 (11), 207 (100), 183 (42), 171 (22), 144 (17).
IR ATR ν (cm^{-1}): 2983, 2899, 2360, 2344, 1603, 1564, 1556, 1511, 1457, 1381, 1234, 1224, 1213, 1179, 1159, 1154, 1102, 1096, 1057, 1019, 1013, 984, 971, 958, 940, 883, 846, 832, 821, 776, 726, 720, 691, 668.
HRMS (EI) for **$C_{14}H_{11}ClFNO_2$** (279.0462) $[M]^+$: 278.0372.

Synthesis of 4-chloro-2-(4-(trifluoromethyl)phenyl)pyridine (52q):

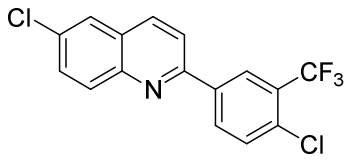


A solution of **32y** in THF (1.2 mmol, 1.2 equiv, 1.0 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51a** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 30 min before being

quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52q** as white crystals.

Isolated yield: 92% (237 mg).
Reaction conditions: 30 min.
Solvent for purification: *i*-hexane/diethyl ether 9:1.
m.p.: 44.9-46.6 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.31 (dd, *J*=5.25, 1.11 Hz, 1 H), 7.69 - 7.80 (m, 3 H), 8.05 - 8.16 (m, 2 H), 8.62 (d, *J*=5.25 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 121.17 (s, 1 C), 123.10 (s, 1 C), 124.03 (q, J=272.35 Hz), 125.78 (q, J=3.65 Hz), 127.27 (s, 1 C), 131.41 (q, J=32.54 Hz), 141.37 (q, J=1.40 Hz), 145.02 (s, 1 C), 150.70 (s, 1 C), 157.34 (s, 1 C).
MS (70 eV, EI) m/z (%): 257 (100), 222 (50), 202 (12), 188 (15), 43 (47).
IR ATR ν (cm^{-1}): 2366, 2334, 1617, 1572, 1549, 1380, 1323, 1315, 1265, 1168, 1105, 1095, 1069, 1047, 1013, 988, 977, 956, 849, 840, 829, 818, 785, 765, 750, 739, 728, 706, 690, 668, 662.
HRMS (EI) for **$C_{12}H_7ClF_3N$:** (257.0219) $[M]^+$: 257.0211.

Synthesis of 6-chloro-2-(4-chloro-3-(trifluoromethyl)phenyl)quinoline (52r):



A solution of **55** in THF (1.2 mmol, 1.2 equiv, 1.0 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51g** (1 mmol, 1.0 equiv) in CPME (5 mL) at 25 °C. The suspension was stirred at 25 °C for 1 h before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52r** as a white powder.

Isolated yield: 87% (299 mg).
Reaction conditions: 1 h.
Solvent for purification: *i*-hexane/ethyl acetate 12:1 (+0.5% NEt_3).

m.p.: 118.8-121.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.62 - 7.73 (m, 2 H), 7.82 (d, *J*=2.21 Hz, 1 H), 7.87 (d, *J*=8.57 Hz, 1 H), 8.10 (d, *J*=8.85 Hz, 1 H), 8.17 (d, *J*=8.29 Hz, 1 H), 8.26 (dd, *J*=8.29, 2.21 Hz, 1 H), 8.54 (d, *J*=2.21 Hz, 1 H).

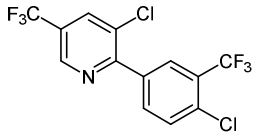
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 118.89 (s, 1 C), 122.84 (q, J=273.30 Hz), 126.16 (s, 1 C), 126.52 (q, J=5.41 Hz), 127.89 (s, 1 C), 128.73, 128.94 (q, J=31.60 Hz), 131.05 (s, 1 C), 131.34 (s, 1 C), 131.91 (s, 1 C), 132.68 (s, 1 C), 133.48 (q, J=1.71 Hz), 136.31 (s, 1 C), 137.86 (s, 1 C), 146.53 (s, 1 C), 154.52 (s, 1 C).

MS (70 eV, EI) m/z (%): 341 (100), 308 (10), 306 (28), 286 (14), 272 (12).

IR ATR ν (cm^{-1}): 2926, 2860, 2360, 2331, 1595, 1476, 1411, 1328, 1321, 1315, 1276, 1259, 1251, 1236, 1164, 1155, 1133, 1123, 1113, 1075, 1056, 1034, 948, 904, 899, 874, 848, 827, 811, 781, 775, 729, 675, 668, 664, 658.

HRMS (EI) for **$C_{16}H_8Cl_2F_3N$:** (340.9986) $[M]^+$: 340.9969.

Synthesis of 3-chloro-2-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)pyridine (52s):



A solution of **55** in THF (1.2 mmol, 1.2 equiv, 1.0 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51i** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 30 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52s** as a colorless oil.

Isolated yield: 66% (239 mg).

Reaction time: 30 min.

Solvent for purification: *i*-hexane/ethyl acetate 15:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.65 (d, *J*=8.02 Hz, 1 H), 7.95 (dd, *J*=8.57, 2.21 Hz, 1 H), 8.09 (d, *J*=1.94 Hz, 1 H), 8.17 (d, *J*=1.94 Hz, 1 H), 8.88 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 122.47 (q, J=273.20 Hz), 122.57 (q, J=273.48 Hz), 126.92 (q, J=33.94 Hz), 128.57 (q, J=31.70 Hz), 128.87 (q, J=5.33 Hz), 130.22, 131.32,

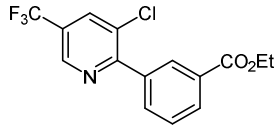
133.64, 133.89 (q, J=1.68 Hz), 135.60, 135.65 (q, J=3.65 Hz), 144.50 (q, J=3.93 Hz), 157.10 (q, J=1.68 Hz).

MS (70 eV, EI) m/z (%): 359 (81), 339 (14), 324 (100), 304 (17), 290 (12).

IR ATR ν (cm^{-1}): 2362, 2342, 1602, 1487, 1456, 1413, 1380, 1329, 1315, 1295, 1278, 1260, 1238, 1214, 1127, 1113, 1099, 1079, 1038, 1031, 910, 873, 836, 813, 766, 737, 718, 665.

HRMS (EI) for **$C_{13}H_5Cl_2F_6N$** (358.9703) $[M]^+$: 358.9690.

Synthesis of ethyl 3-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)benzoate (52t):



A solution of **39** in THF (1.2 mmol, 1.2 equiv, 0.6 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **51i** (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **52t** as a slightly yellow oil.

Isolated yield: 70% (231 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 9:1 (+0.5% NEt_3).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.41 (t, *J*=7.19 Hz, 3 H), 4.42 (q, *J*=7.19 Hz, 2 H), 7.59 (t, *J*=7.88 Hz, 1 H), 7.96 (dt, *J*=7.74, 1.52 Hz, 1 H), 8.07 (d, *J*=2.21 Hz, 1 H), 8.18 (dt, *J*=7.95, 1.42 Hz, 1 H), 8.46 (t, *J*=1.80 Hz, 1 H), 8.87 (d, *J*=1.11 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.30 (s, 1 C), 61.22 (s, 1 C), 122.62 (q, J=272.92 Hz), 126.44 (q, J=33.66 Hz), 128.34 (s, 1 C), 130.31 (s, 1 C), 130.58 (s, 1 C), 130.65 (s, 1 C), 130.69 (s, 1 C), 133.56 (s, 1 C), 135.37 (q, J=3.65 Hz), 137.17 (s, 1 C), 144.33 (q, J=3.39 Hz), 158.92 (q, J=1.40 Hz), 165.98 (s, 1 C).

MS (70 eV, EI) m/z (%): 329 (33), 301 (22), 284 (100), 257 (55), 221 (15).

IR ATR ν (cm^{-1}): 2982, 2367, 2335, 1718, 1717, 1600, 1368, 1322, 1312, 1285, 1249, 1223, 1214, 1160, 1131, 1093, 1082, 1075, 1036, 1020, 1001, 912, 847, 820, 741, 710, 693, 668, 662.

HRMS (EI) for **$C_{15}H_{11}ClF_3NO_2$** (329.0430) $[M]^+$: 329.0419.