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Iron-, Cobalt- and Chromium-Catalyzed Cross-Coupling Reactions of Aromatics and Heterocycles

von

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Erklärung

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Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe bearbeitet.

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2. Gutachter: Prof. Dr. Konstantin Karaghiosoff

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1) Kuzmina, O. M. & Knochel, P., Room-Temperature Chromium(II)-Catalyzed Direct Arylation of Pyridines, Aryl Oxazolines and Imines, *manuscript submitted.*
2) 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.
3) 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.
4) 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.

“Тупик — это отличный предлог, чтобы ломать стены”

(“Deadlock - it's a great excuse to break down the walls”)

Братья Стругацкие

(Brothers Strugackie)

Моей Бабушке и Маме

(To My Grandmother and Mother)

Table of Contents

List of Abbreviations

Ac	Acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
Alk	alkyl
Bn	benzyl
Boc	*t*-butyloxycarbonyl
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
dba	*trans*,*trans*-dibenzylideneacetone
DCB	2,3-dichlorobutane
DME	dimethoxyethane
DMPU	1,3-dimethyltetrahydropyrimidin-2(1*H*)-one
DG	directing group
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	heteroaryl
LDA	lithium diisopropylamide
M	molarity
m	meta
m	multiplet
MCPE	methoxycyclopentane
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
OTf	triflate
p	para
Ph	phenyl
Piv	pivaloyl
*i*Pr	*iso*-propyl
q	quartet
R	organic substituent
r.t.	room temperature
sat.	saturated
s	singulet
Tol	tolyl
tfp	tri-2-furylphosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMHD	2,2,6,6-tetramethyl-3,5-heptane-dionate
TMS	trimethylsilyl
TMP	2,2,6,6-tetramethylpiperidyl
TP	typical procedure

HRMS	high resolution mass spectroscopy
IR	infra-red
J	coupling constant (NMR)

A. Introduction

1. General Introduction

Over the past two centuries, the discoveries made in organic chemistry have led us to a world with vastly increased life expectancy due to the medical wonder drugs we are now able to produce.

Organometallic chemistry is at the same time an old and a new branch of chemistry. It is old because the first organometallic compound was prepared about 250 years ago; organometallic chemistry is new, since in the last 60 years organometallic compounds have become a subject of general interest, and the field is now recognized as an independent branch of chemistry.[1]

The history of organometallic chemistry could be described as a one of unexpected discoveries.[2] The first organometallic compound prepared was in 1760 by Louis Claude Cadet,[3] who worked on synthetic inks based on cobalt salts. He used cobalt minerals, which also contain arsenic. Reaction of arsenic(III) oxide and potassium acetate gave "Cadet´s fuming liquid", which contains cacodyloxide $[(CH_3)_2As]_2O$. Later, in 1840, R. W. Bunsen investigated these kind of compounds, which he called "alkarsines" more closely.[4]

The first olefin complex was prepared by William Christopher Zeise,[5] a Danish chemist, in 1827 by the reaction of ethanol with a mixture of $PtCl_2$ and $PtCl_4$ in the presence of KCl. It is interesting to mention that this was about at the same time as the first successful synthesis of urea in 1828 by F. Wöhler[6] and 40 years prior to the proposal of the Periodic Table by A. D. Mendeleev in 1869, who later, used organometallic compounds as the test cases for his Periodic Table.

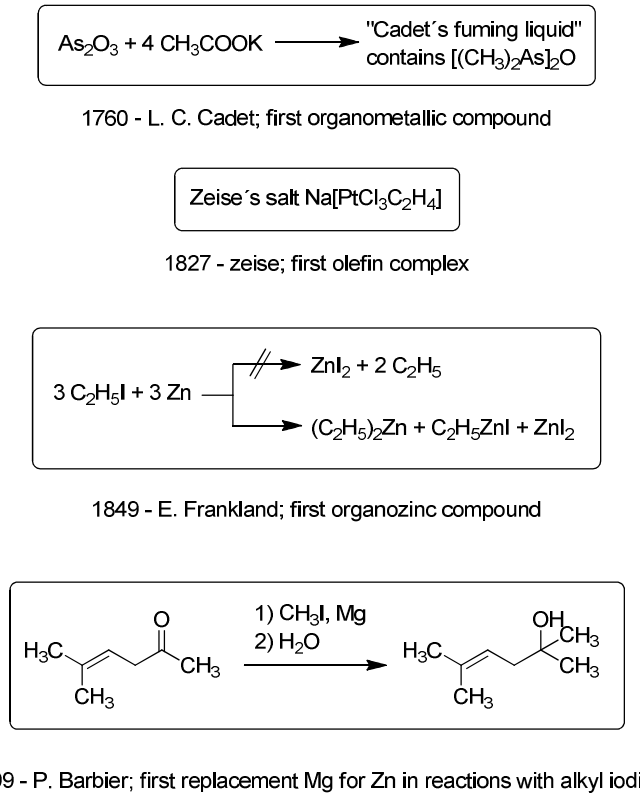
The compound prepared and formulated as $PtCl_2(C_2H_4)\cdot KCl\cdot H_2O$ by Zeise must have been regarded as quite bizarre at that time. How can ethylene, a gaseous compound under ordinary conditions combine with platinum? It is no wonder, that when the synthesis of this compound was reported, some of his contemporaries criticised Zeise.

The first organometallic compound having a direct metal-to-alkyl σ-bond was synthesized by E. Frankland,[7] a student of Bunsen´s at Marburg, in 1849. What Frankland was trying to prove, was the existence of organic radicals. Reasoning that abstraction of iodine from ethyl

[1] *Basic Organometallic Chemistry*, I. Haiduc, J. J. Zuckerman, Walter de Gruyter, Berlin, **1985.**
[2] *Organotransition metal Chemistry. Fundemental Concepts and Applications*; A. Yamamoto, Wiley-VCH: Weinheim, **1986.**
[3] L. C. Cadet de Gassicourt, *Mem. Mat. Phys.* **1760**, *3*, 363.
[4] R. Bunsen, *Liebigs Ann. Chem.* **1837**, *24*, 471.
[5] W. C. Zeise, *Pogg. Ann.* **1827**, *9*, 632.
[6] F. Wöhler, *Annalen der Physik und Chemie* **1828**, *88*, 253.
[7] E. Frankland, *Liebigs Ann. Chem.* **1849**, *71*, 171.

iodide by zinc should give an ethyl radical, he heated a mixture of ethyl iodide and zinc. He obtained a volatile, colorless liquid and first thought that he had demonstrated the occurrence of a radical. However, the determination of the molecular weight showed that it was not an ethyl radical, but butane that was formed by the decomposition of an ethylzinc compound generated by the reaction of zinc with ethyl iodide.

This experiment, which was called “the most fruitful failure”, led to a method for preparing alkylzinc compounds. A number of discoveries of different organometallic compounds such as bis-alkylmercury, bis-alkyltin, bis-alkylboron, allylaluminum iodides, organochlosilanes, halide-free magnesium alkyls passed by, until P. Barbier in 1890 replaced zinc with magnesium in reactions with alkyl iodides.[8] His student V. Grignard went on with this investigation and expanded significantly the usage of organo-magnesium reagents,[9] which were subsequently named Grignard reagents. Since then, Grignard reagents became a powerful tool in organic synthesis (Scheme 1).



Scheme 1. Some important discoveries in the history of organometallic chemistry

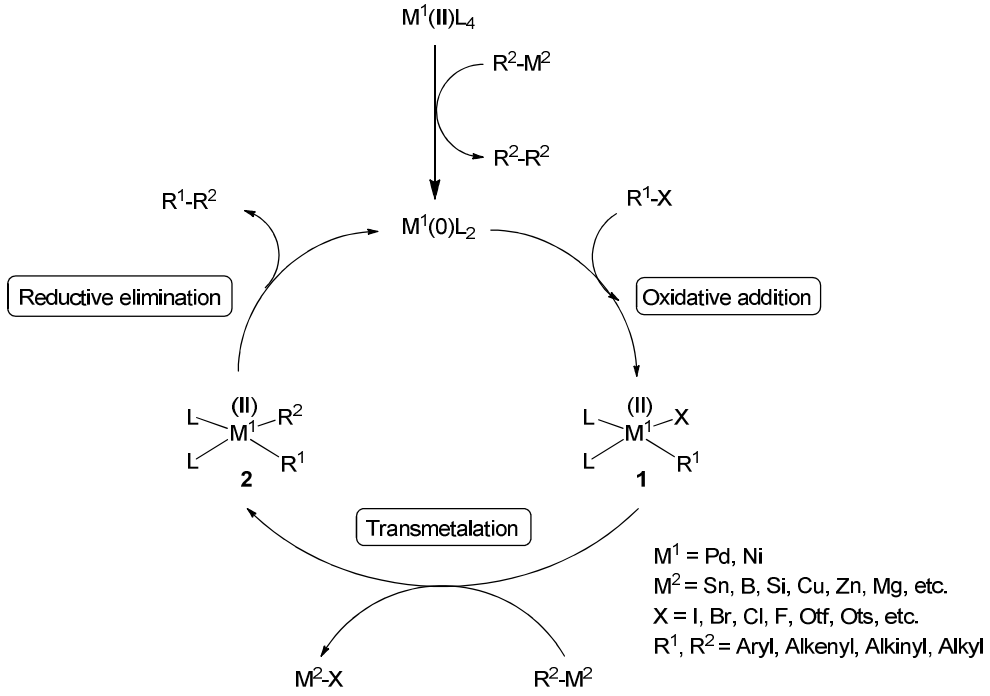
[8] P. A. Barbier, *C. R. Acad. Sci.* **1899**, *128*, 110.
[9] V. Grignard, *C. R. Acad. Sci.* **1900**, *130*, 1322.

The history of organometallic chemistry continues with the discovery by Paul Sabatier in 1910, who showed that finely divided metals such as nickel, palladium or platinum could catalyze the hydrogenation of alkenes. This discovery was a great advance for the use of transition metals in organic synthesis.[10] However, a real turning point was the determination of the structure of ferrocene by Wilkinson and Fischer[11] many years later. A clear image and the high stability of ferrocene gave chemists the possibility of studying and better understanding these kind of organometallic compounds. These discoveries coupled with tremendous advances such as nuclear magnetic resonance (NMR)[12] and X-ray crystallography[13] paved the way for the investigation of transition-metal complexes, their reactivity and usage in synthetic chemistry. The era of transition metal-catalyzed chemistry had begun.

The work of Nobel Laureates such as Sharpless,[14] Noyori[15] and Knowles[16] (2001), Grubbs[17], Schrock[18] and Chawin[19] (2005) and, most recently, Heck,[20] Negishi[21] and Suzuki[22] (2010), made the approaches of this area one of the most applicable in synthetic organic chemistry. Transition metal-catalyzed cross-coupling type reactions represent one of the most powerful tools for the synthesis of any desired molecular structures.

Over the last decades, Pd, Ni and Cu-catalyzed cross-couplings were widely applied due to the generality and high functional-group tolerance. A great number of natural products, building blocks for supramolecular chemistry and self-assembly, organic materials and polymers were produced using these metals as catalysts in cross-coupling reactions.[23] Most of the palladium or nickel-catalyzed reactions are believed to follow a similar catalytic cycle (Scheme 2).

[10] *Organic Synthesis Using Transition Metals*; Bates, R. John Wiley & Sons Ltd., United Kingdom **2012**.
[11] Wilkinson, *J. Am. Chem. Soc.* **1954**, 76, 209.
[12] *Nuclear Magnetic Resonance*; Hore, P.J. Oxford University Press, Oxford, **1995**.
[13] *Understanding Single-Crystal X-ray Crystallography*; Bennett, D. W. Wiley-VCH: Weinheim, **2010**.
[14] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
[15] a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Douchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932; b) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117.
[16] Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.
[17] Dias, E. L.; Nqyuyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, 119, 3887.
[18] McCullough, L. G.; Schrock, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 4067.
[19] Martinato, A.; Chauvin, Y.; Lefebvre, G. *Compt. Rend.* **1964**, *258*, 4271.
[20] Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.
[21] Baba, S., Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729.
[22] Suzuki, A. *Pure Appl. Chem*. **1991**, *63*, 419.
[23] Metal-Catalyzed Cross-Coupling Reactions; de Meijere, A.; Diederich, F. Wiley-VCH: Weinheim, **2004.**



Scheme 2. General mechanism for palladium- or nickel-catalyzed cross-coupling reactions

The first step of the catalysis includes the *in situ* reduction of the precatalyst $M^1(II)L_4$ and the generation of the active species of the catalyst $M^1(0)L_2$, due to the excess of the organometallic reagent R^2-M^2. Next, the oxidative addition of the C-X bond of the electrophile R^1-X to $M^1(0)L_2$ leads to the formation of the complex **1**. As a consequence of transmetalation, R^2 goes to M^1 and the complex **2** is created. The last step is a reductive elimination, whereby the cross-coupling product R^1-R^2 is produced and the catalyst $M^1(0)L_2$ is regenerated.[24]

The catalytic species can be formed *in situ* using metal sources such as $Pd_2(dba)_3$, $Pd(OAc)_2$ or $Ni(dppe)Cl_2$ in the presence of an appropriate ligand. It also can be introduced as a performed catalyst such as $Pd(Ph_3)_4$, $Pd(P^tBu_3)_2$ or $Ni(COD)_2$.

Many ligand families for palladium or nickel are available today. Electron-rich phosphine ligands facilitate the oxidative addition through increasing the electron density of the catalyst´s active complex. Electron-poor ligands facilitate transmetalation as well as reductive elimination. The choice of the ligand depends on which step of catalytic cycle is rate limiting. The oxidative addition of aryliodides usually proceeds fast; thereby electron-poor ligands are

[24] a) Handbook of Functionalized Organometallics, (Hrsg.: P. Knochel), Wiley-VCH, Weinheim, **2005**; b) Metal Catalyzed Cross-Coupling Reactions, 2nd Ed., (Hrsg.: A. de Meijere, F. Diederich), Wiley-VCH: Weinheim, **2004**; c) Handbook of Organopalladium Chemistry for Organic Synthesis, (Hrsg.: E. Negishi), Wiley-Interscience, New York, **2002**; d) Transition Metal for Organic Synthesis, 2nd Ed., (Hrsg.: M. Beller, C. Bolm), Wiley-VCH, Weincheim, **2004**

mostly used. Whereas the cross-coupling reaction with arylchlorides commonly requires electron-rich ligands to accelerate the oxidative addition.

Coupled with the right ligand, palladium and nickel catalyzed cross-coupling reactions represent a powerful tool in synthetic organic chemistry today. However, due to economic and ecological disadvantages there is still exists a need for the examination of alternative catalysts. It is not a secret that the price of the most applicable palladium –catalyst, also for the large scale reactions, is around $300 per ounce. At the same time, the toxicity of nickel prevents application of nickel-catalyzed processes for consumer goods and health-care products.[25] Moreover, both palladium and nickel catalitic systems require the addition of complicated and expensive ligands.

2. Iron-Catalyzed Cross-Coupling Reactions

Iron catalysts have recently received a lot of attention due to a number of advantages, which this metal brings. For instance, for $100 one can buy 0.5 g of ruthenium, 2.0 g of platinum, 2.2 g of gold, 5571 g of nickel, 15 000 g of copper and, finally, 500 000 g of iron.[26] Iron is the most abundant metal in the universe and the second-most abundant metal in the earth´s crust. Furthermore, iron is the most abundant transition metal in the human body (4g/person) and it is an essential metal in the life cycle of all living things. This factor actually represents a big advantage for using iron catalysts in health-care related chemistry, since no severe toxicity and side effects exist.

The environmentally friendly properties and moderate price make iron the catalyst of the future and therefore provide ample motivation for further developments in the field of iron-catalyzed cross-coupling.

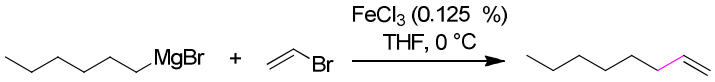
The first iron-catalyzed homo-coupling reaction of aryl Grignard reagents was described by Kharash and Fields as far back as 1941.[27] Although, the true epoch started in the 1970´s, predating the palladium and nickel relatives, with Kochi investigating the reaction between alkenyl halides and Grignard reagents.[28] Kochi also proposed the first mechanistic rationale for iron-catalyzed cross-coupling with an analogy to palladium and nickel catalytic cycles. This mechanistic rationale includes the formation of a reduced iron complex, which

[25] a) *Handbook of the Toxicity of Metals*; Friberg L.; Nordberg, G. F.; Vouk, V. B. Elsevier, Amsterdam, **1986**; b) Hughes, M. N. *Compr. Coord, Chem.* **1987**, *67*, 643; c) *Nickel and the Skin: Absorbtion, Immunology, Epidemiology, and Metallurgy*; Hostynek, J. J.; Maibach, H. I. CRC Press, Boca Raton, **2002**.
[26] For prices of the metals see: http://www.boerse-go.de.
[27] Kharash, M. S., Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316.
[28] a) Kumada, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487; b) Kochi, J. K.; *Acc. Chem. Res.* **1974**, *7*, 351.

undergoes oxidative addition of the organohalide, with subsequent transmetalation from the organomagnesium species and reductive elimination to give the cross-coupling product. During 1990´s, iron-catalyzed cross-couplings (with the exception of a few publications) received little attention, until in the early 2000´s Fürstner and Leitner breathed new life into the development of this field. They reported a highly selective iron-catalyzed cross-coupling of aryl halides and alkyl Grignard reagents in the presence of NMP as co-solvent.[29] This work paved the way for a number of publications, which continue to increase each year. All these discoveries made a strong foundation for a better development of iron-catalyzed cross-couplings, which today represent an effective tool for the C-C and C-X-bond formation with good tolerance of functional groups.

2.1 Cross-Coupling of Alkenyl Electrophiles with Grignard Reagents

In 1971 Kochi reported that an excess of alken-1-yl halides react with Grignard reagents in the presence of catalytic amount of $FeCl_3$ to give at 0 °C or 25 °C the cross-coupling products in good yields (up to 89 %) and stereoselectivity after several hours (see Scheme 3).[28]

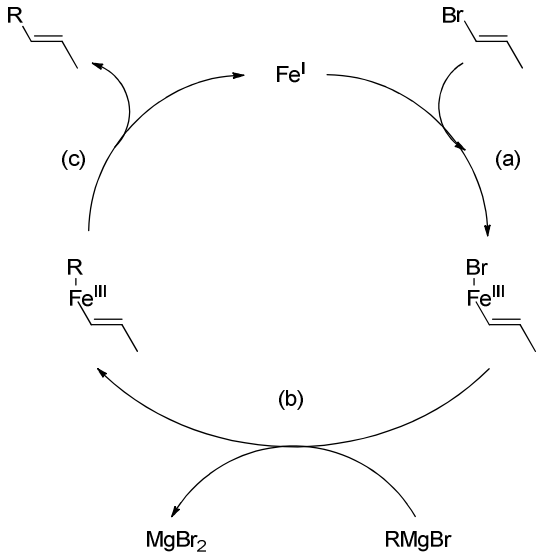


Scheme 3. Example of first iron-catalyzed cross-coupling of vinyl bromides with primary Grignard reagents by Kochi et al.

In the same year, the Kochi group extended this cross-coupling reaction to secondary and tertiary alkyl and aryl Grignard reagents and tested different iron complexes for the catalytic activity.[30] Furthermore, Kochi proposed the active iron catalyst as an iron(I) species formed by the facile reduction of the iron(III) by the Grignard reagent. These species are metastable and probably are deactivated by aggregation over a length of time. One can say that iron(I) species consist of a d^7 electron configuration, isoelectronic with manganese(0) and cobalt(II). Based on the kinetic studies and electron paramagnetic resonance investigations, Kochi suggested a mechanism of iron-catalyzed cross-coupling reaction of vinyl bromides with Grignard reagents. This mechanism, presented in Scheme 4, includes (a) an oxidative addition

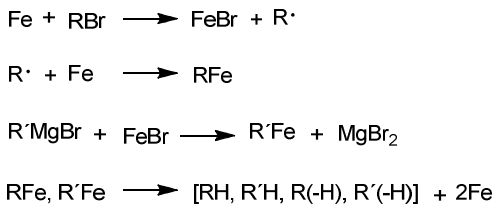
[29] Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 609.
[30] a) Kochi, J. K.; Tamura, M. *Synthesis* **1971**, 303; b) Tamura, M.; Kochi, J. K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3063.

of 1-bromopropene to iron(I) followed by (b) an exchange with ethylmagnesium bromide and (c) a reductive elimination.[31]



Scheme 4. Proposed mechanism for the iron-catalyzed cross-coupling reactions by Kochi et al.

Previously, Kochi and co-workers studied the mechanism of iron-catalyzed cross-coupling reactions of alkyl halides with alkyl Grignard reagents. Interestingly, the kinetic results show that this type of reaction is largely independent of the concentration of the alkylmagnesium halide and the rate is first-order in both alkyl halide and iron catalyst. A catalytic cycle with the following aspects was proposed, first - the oxidation of the iron species by alkyl halides takes place, second - regeneration of the catalyst by decomposition of alkyliron intermediates and the last aspect is the role of alkyl radicals in the chain process (see Scheme 5).



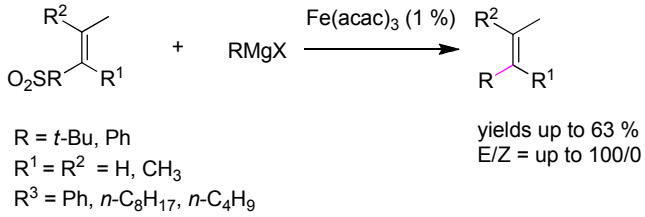
Scheme 5. Tentatively proposed mechanism for iron-catalyzed cross-coupling reactions of alkyl halides and alkyl Grignard reagents by Kochi et al.

[31] Smith, R. S.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502.

The kinetics support oxidative addition as the rate-limiting step in the catalytic process. The reaction proceeds most readily with mononuclear iron species and to a lesser degree with iron aggregates. Kochi proposed that the aggregation to a less active polynuclear iron species occurred with the liberation of Grignard reagents and ethereal ligands; he also observed the same deactivation effect for iron catalyst in the presence of high concentrations of triphenylphosphine.[32]

Scheme 6. Proposed aggregation of the iron species by Kochi et al.

Returning to cross-couplings with alkenyl electrophiles, in 1978 Felkin and Meunier published a stereoselective cross-coupling between alkenyl bromides and phenyl Grignard reagents using iron-phosphine catalysts.[33] The cross-coupling product is formed in 84 % yield in the presence of 5 % of the iron-catalyst. Julia and co-workers described that vinyl sulfones react with Grignard reagents, forming trisubstituted olefins of defined stereochemistry in good yields (see Scheme 7).[34]



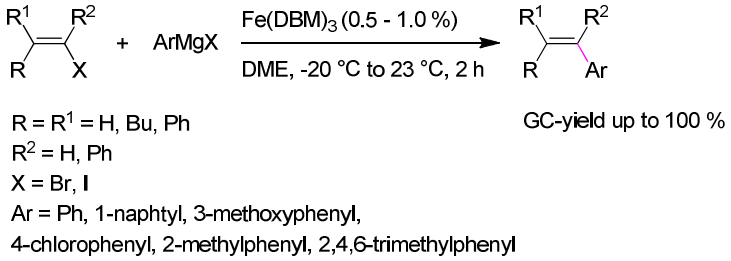
Scheme 7. Cross-coupling reaction of vinyl sulfones with Grignard reagents by Julia et al.

Later, the stereoselective synthesis of 2-isopropyl-1,4-dienes through the iron-catalyzed cross-coupling reaction of 2-benzenesulfonyl-1,4-dienes and isopropylmagnesium chloride was also published by the Julia group.[35]

Molander and co-workers further studied the cross-coupling reaction of alkenyl halides with aryl Grignard reagents, described first by Kochi.[36] The Molander group found that the use of

[32] Tamura, M.; Kochi, J. *J. Org. Chem.* **1971**, *31*, 289.
[33] Felkin, H.; Meunier, B. *J. Organomet. Chem.* **1978**, *146*, 169.
[34] Fabre, J.-L.; Julia, M.; Verpeaux, J.-N. *Tetrahedron Lett.* **1982**, *23*, 2469.
[35] a) Alvarez, E.; Cuvigny, T.; du Penhoat, C. H.; Julia, M. *Tetrahedron* **1988**, *44*, 111; b) Alvarez, E.; Cuvigny, T.; du Penhoat, C. H.; Julia, M. *Tetrahedron* **1988**, *44*, 119.
[36] Neumann, S. M.; Kochi, J. K. *J. Org. Chem.* **1975**, *40*, 599.

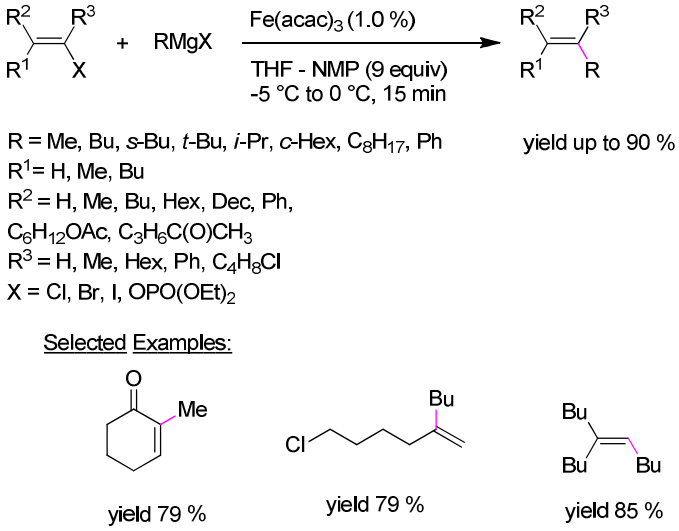
DME as a solvent and a lower reaction temperature (-20 °C) consistently provided highest yields and no excess of alkenyl halide was required (Scheme 8).[37]



Scheme 8. Cross-coupling reaction between alkenyl halides and Grignard reagents by Molander et al.

Naso and co-workers described a stereospecific cross-coupling reaction of secondary alkyl Grignard reagents with *Z* or *E*-1-bromo-2-phenylthioethene in the presence of an iron catalyst. Different iron compounds such as $FeCl_3$, $Fe(acac)_3$, $Fe(DBM)_3$, $Fe(DPM)_3$ were found to be effective catalysts and cross-coupling products were obtained in up to 80 % yield at -78 °C after 8 to 12 h with high chemo- and stereoselectivity.[38]

In 1998, Cahiez and co-workers reported, that in the presence of $Fe(acac)_3$, Grignard reagents react readily with alkenyl halides in a THF/NMP mixture to give the cross-coupling products in high yields with excellent stereoselectivity of up to 90 %.[39] Numerous functional groups were tolerated (Scheme 9).

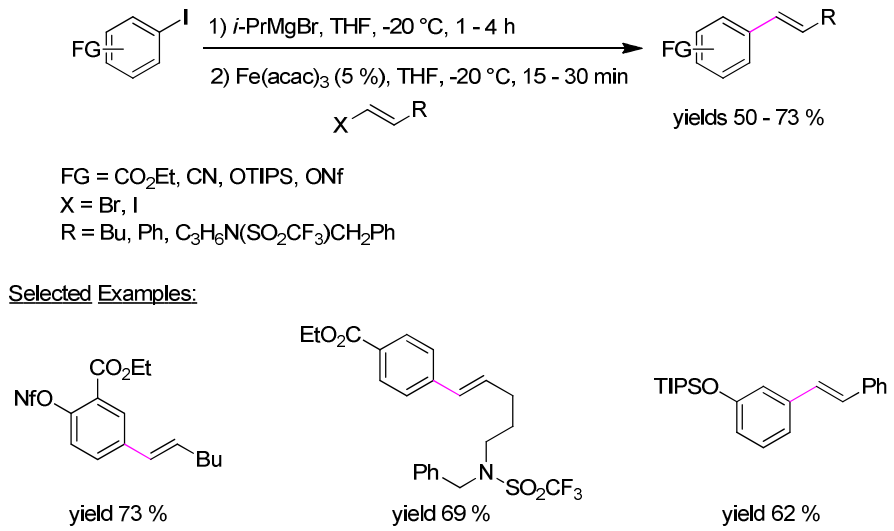


Scheme 9. Iron-catalyzed alkenylation of organomagnesium compounds by Cahiez et al.

[37] Molander, G. A.; Rahn, B. J.; Shubert, D. C. *Tetrahedron Lett.* **1983**, *24*, 5449.
[38] Fiandanese, V.; Miccoli, G.; Naso, F.; Ronzini, L. *J. Organomet. Chem.* **1986**, *312*, 343.
[39] Cahiez, G; Avedissian, H. *Synthesis* **1998**, 1199.

A solvent screening including DMPU, DMF, DMA, diethyl carbonate, sulfolane, tetramethylurea and DME, showed that 9 equivalents of DMF had the best co-solvent effect. The nature of iron salts was not essential as no difference was observed when $Fe(dpm)_3$, $Fe(dpb)_3$ or $FeCl_3$ was used instead of $Fe(acac)_3$. In some cases the catalyst amount could be lowered to 0.01 %. Enol phosphates could also be used as electrophile in the reaction with butylmagnesium chloride.

A collaboration work between the Knochel and the Cahiez groups in 2001 showed that alkenyl halides undergo cross-coupling reaction with functionalized arylmagnesium compounds, using 5 % of $Fe(acac)_3$ as catalyst at -20 °C. Functional groups such as ester, cyano, nonaflates and trialkylsiloxy could be tolerated and the cross-coupling products were formed in satisfactory yields. Excellent yields could be achieved by performing the cross-coupling reaction on the solid phase by generating the Grignard reagent on Wang resin (Scheme 10).[40]



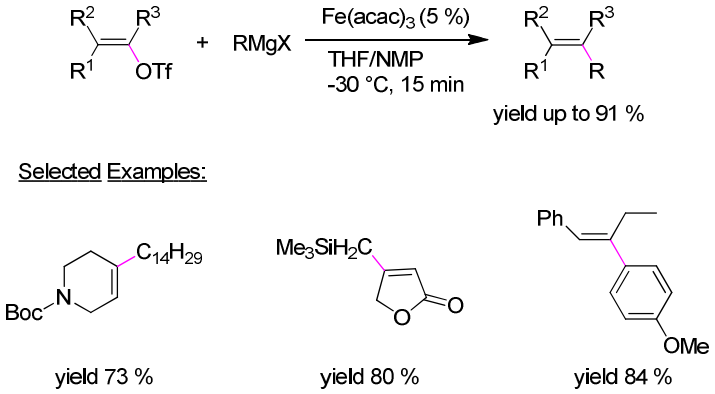
Scheme 10. Iron-catalyzed cross-coupling between functionalized arylmagnesium compounds by Cahiez and Knochel

Begtrup and co-workers applied the NMP-protocol described by Cahiez as one of the steps of the synthesis of 3-substituted pyrrolidines.[41] Hoffmann and co-workers published the Kumada-Corriu coupling of Grignard reagents with vinyl bromides, probed with a chiral Grignard reagent, using transition metals catalysts. Investigations showed that Ni(II)- and

[40] Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901.
[41] Østergaard, N.; Pedersen, B. T.; Skjærbæk, N.; Vedsø, P.; Begtrup, M. *Synlett* **2002**, 1889.

Pd(II)-catalyzed reactions proceed with essentially full retention of configuration, whereas when low-valent Fe or Co generated from $Fe(acac)_3$ or $Co(acac)_2$ were used, the enantiomeric excess of the coupling product was significantly reduced. The authors proposed that partial racemization could take place due to single electron transfer (SET) processes involved in the transmetallation step.[42] Itami and Yoshida described iron-catalyzed cross-couplings of alkenyl sulfides with Grignard reagents. Aryl and alkyl Grignard reagents are applicable and cross-coupling proceeds efficiently at alkenyl-S bonds, but almost no cross-coupling takes place at aryl-S bonds. An addition/elimination mechanism was proposed.[43]

In 2004, Fürstner and co-workers reported selective iron-catalyzed cross-coupling reactions of Grignard reagents with alkenyl triflates. A variety of alkenyl triflates derived from ketones, *β*-keto esters or cyclic 1,3-diketones could undergo a cross-coupling reactions in the presence of 5 % of $Fe(acac)_3$ in THF/NMP at -30 °C, yielding the desired products in good to excellent yields (Scheme 11).[44]



Scheme 11. Iron-catalyzed cross-coupling reaction of alkenyl triflates with Grignard reagents by Fürstner

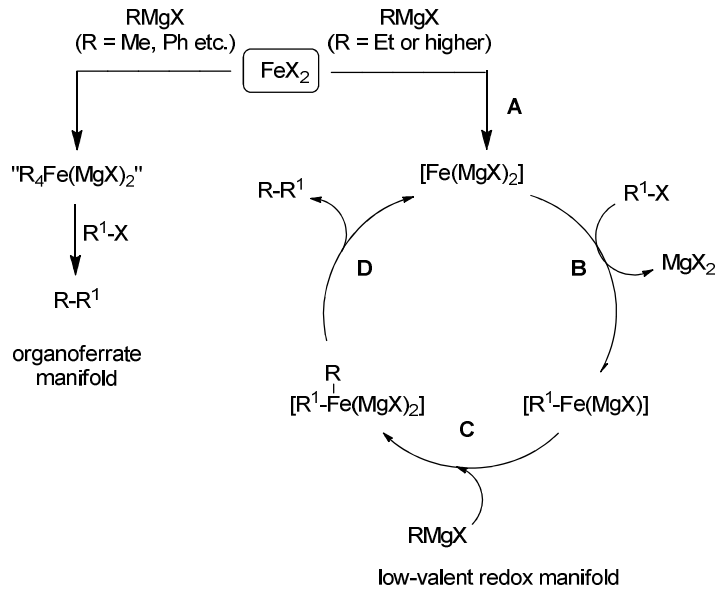
This methodology, which also works with enol triflates as electrophiles, was applied in a number of natural product syntheses.[45]

Fürstner and co-workers published the preparation, structure and reactivity of nonstabilized organoiron compounds and the implications for iron-catalyzed cross-coupling reactions.[46]

[42] Hölzer, B.; Hoffmann, R. W. *Chem. Commun.* **2003**, 732.
[43] Itami, K.; Higashi, S.; Mineno, M.; Yoshida, J.-I. *Org. Lett.* **2005**, *7*, 1220.
[44] Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943.
[45] a) Fürstner, A; De Souzy, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem. Int. Ed.* **2003**, *42*, 5358; b) Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006; c) Camacho-Dávilla, A. A. *Synth. Commun.* **2008**, *38*, 3823; d) Hamajima, A.; Isobe, M. *Org. Lett.* **2006**, *8*, 1205; e) Maulide, N.; Vanherck, J.-C.; Marrkó, I. E. *Eur. J. Org. Chem.* **2004**, 3962; f) Fürstner, A.; Schleker, A. *Chem. Eur. J.* **2008**, *14*, 9181.

Two distinctly different mechanisms were proposed, depending on the nature of the Grignard reagent. When MeMgX or PhMgX were used for cross-coupling, the reaction was proposed to proceed through the formation of discrete organoferrate complexes as reactive intermediates. EtMgCl and higher homologues generate a low-valent iron cluster species (step A of Scheme 12) that activates the electrophile. The authors assumed that the reaction of $[Fe(MgX)_2]_n$ with an organic halide (step B of Scheme 12) sets up a σ-bond metathesis rather than an oxidative insertion. Also, such a process does not generate an oraganoiron halide, which means that the reaction with RMgX must occure by alkylation rather than by transmetalation of the intermediate primarily produced (step C of Scheme 12). Finally, the formed diorganoiron species undergoes reductive elimination to generate the desired product and regenerates the catalyst (step D, see Scheme 12).

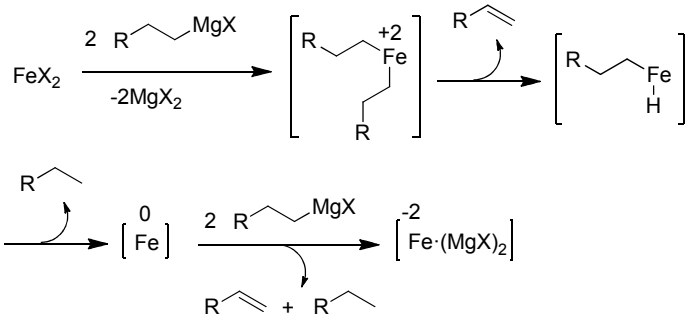
This hypothesis about such a difference in mechanism was based on conclusions made by Bogdanović and co-workers, who suggested that anhydrous FeX_2 reacts with RMgX to give bimetallic clusters $[Fe(MgX)_2]_n$, provided that the R group of the chosen Grignard reagent is able to undergo *β*-hydroelimination followed by formation of an "inorganic Grignard reagent" (Scheme 12).[47]



Scheme 12. Proposed basic scenarios for iron-catalyzed cross-coupling reactions by Fürstner et al.

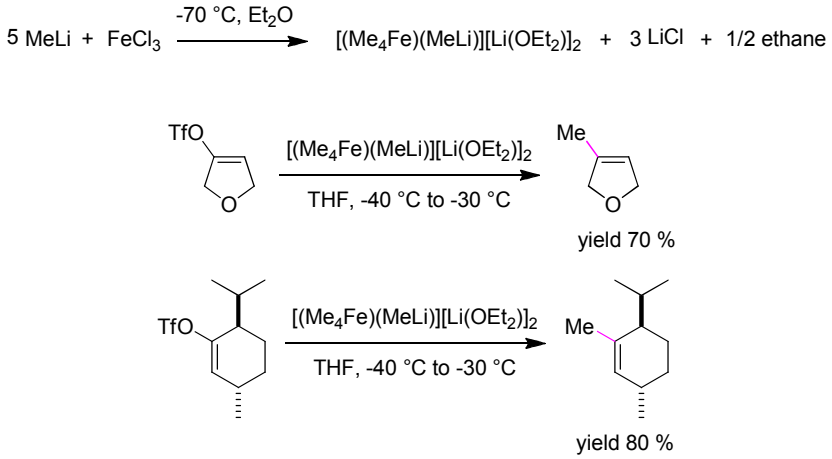
[46] Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773.
[47] Bogdanović, B.; Schwickardi, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4610.

The iron center in this intermediate is distinguished by a “formally negative” oxidation state - Fe(-2) (see Scheme 13). Since MeMgX or PhMgX cannot follow the Bogdanović activation pathway due to their inability to undergo *β*-hydroelimination, these compounds would generate metastable “iron-ate” complexes, which rapidly reduce Fe(3+) to Fe(2+) and then exhaustively alkylate or arylate the metal center (Scheme 13).



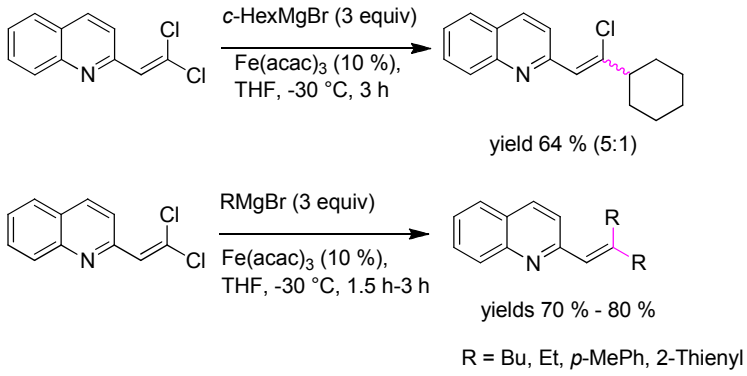
Scheme 13. Proposed elementary steps leading to the formation of an “inorganic Grignard reagent” of iron

In order to confirm these assumptions a number of iron complexes such as $[(Me_4Fe)(MeLi)][Li(OEt_2)]_2$, $[Ph_4Fe][Li(OEt_2)]_4$, $[Ph_4Fe][Li(OEt_2)]_4[Li(1,4\text{-dioxane})]$ were prepared, analyzed and tested for catalytic activity also with alkenyl electrophiles (Scheme 14).



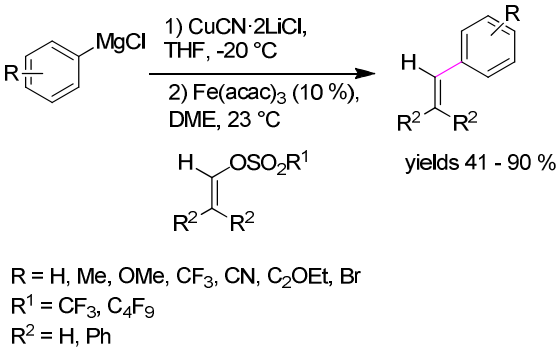
Scheme 14. $[(Me_4Fe)(MeLi)][Li(OEt_2)]_2$-catalyzed cross-coupling reactions with alkenyl elecrophiles by Fürstner et al.

Fürstner and co-workers also showed that the cyclobutenyl iodides could be further functionalized under iron catalysis.[48] Figadère and Alami published an iron-catalyzed coupling reaction between 1,1-dichloro-1-alkenes and Grignard reagents. This reaction led mainly to the coupled products in good to excellent yields. When *c*-hexyl Grignard reagent was used in reaction with quinoline derivatives, the mono-coupled adduct was obtained (Scheme 15).[49]



Scheme 15. Iron-catalyzed cross-coupling with 1,1-dichloro-1-alkenes by Figadère and Alami

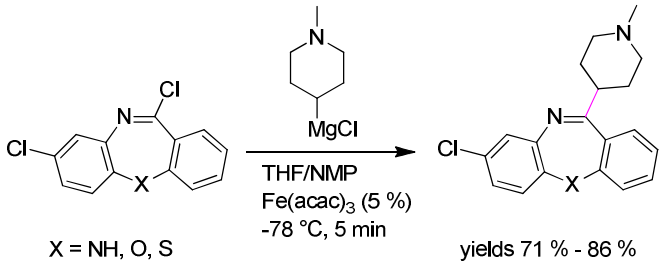
Knochel showed that arylcopper compounds prepared from Grignard reagents could also be applicable in iron-catalyzed cross-coupling reactions with alkenyl and dienyl sulfonates (Scheme 16).[50]



Scheme 16. Cross-coupling between alkenyl and dienyl sulfonates with arylcopper compounds prepared from Grignard reagents, by Knochel et al.

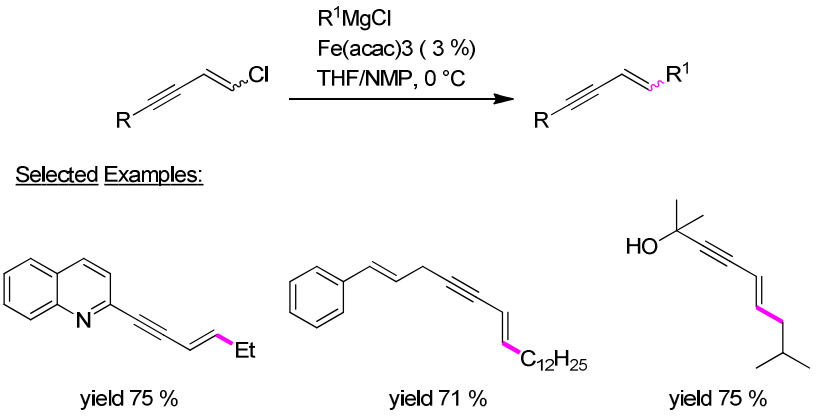
[48] Fürstner, A.; Schleker, A.; Lehmann, C. W. *Chem. Commun.* **2007**, 4277.
[49] Dos Santos, M.; Franck, X.; Hocquemiller, R.; Figadère, B.; Peyrat, J.-O., Provot, O.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2004**, *45*, 1881.
[50] Dunet, G.; Knochel, P. *Synlett* **2006**, 407.

Olsson and co-workers reported an iron catalyzed cross-coupling of imidoyl chlorides with Grignard reagents under mild conditions. Functionalities such as aryl chloride or ester were well tolerated. This protocol represents a good alternative for the synthesis of imines due to mild reaction conditions (Scheme 17).[51]



Scheme 17. Synthesis of Clozapine analogues by Olsson et al.

Syntheses of substituted quinolines by iron-catalyzed coupling reactions between chloroenynes and Grignard reagents were performed by Figadère and Alami in 2004.[52] Several functional groups such as propargyl acetate, ethyl benzoate, aryl bromide and hydroxyl were tolerated (Scheme 18).

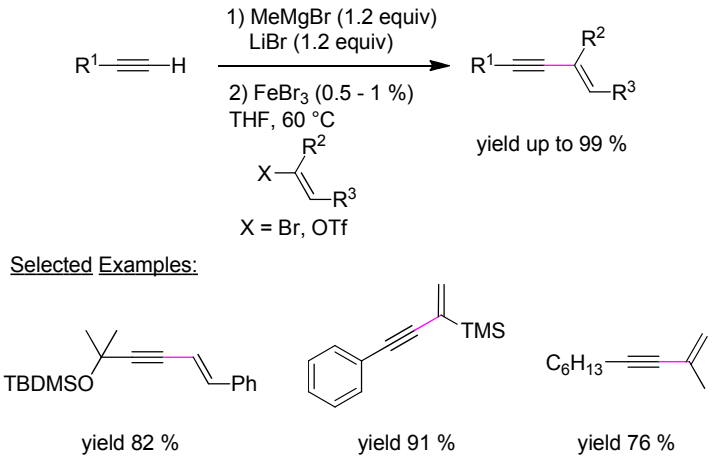


Scheme 18. Cross-coupling reactions with chloroenynes and Grignard reagents by Figadère and Alami

Nakamura and co-workers published an iron-catalyzed enyne cross-coupling reaction. This type of cross-coupling proceeds in the presence of 0.5-1 % of $FeCl_3$ and stoichiometric amounts of LiBr as a crucial additive in high to excellent yields.[53] Alkenyl Grignard reagents

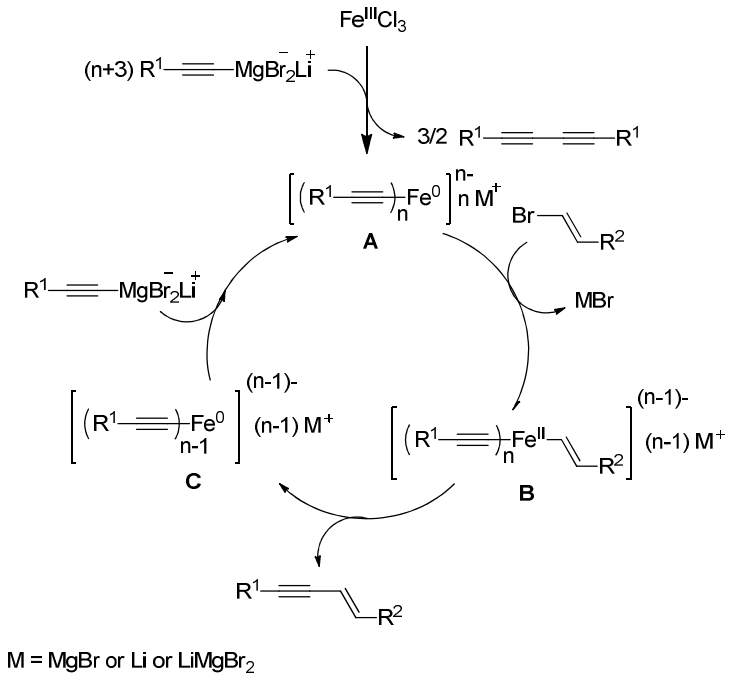
[51] Ottesen, L. K.; Ek, F.; Olsson, R. *Org. Lett.* **2006**, *8*, 1771.
[52] Seck, M.; Franck, X.; Hocquemiller, R.; Figadère, B.; Peyrat, J.-F.; Provot, O.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2004**, *45*, 1881.
[53] Hatakeyama, T.; Yoshimoto, Y.; Gabriel, T; Nakamura, Masaharu *Org. Lett.* **2008**, *10*, 5341.

were prepared from the corresponding alkynes and methylmagnesium bromide. Various terminal alkynes and alkenyl electrophiles were well tolerated (Scheme 19).



Scheme 19. Iron-catalyzed enyne cross-coupling reaction by Nakamura et al.

The mechanism proposed by the authors is shown in Scheme 20. It is based on initial formation of the diyne upon mixing the alkynyl organometalic species and the precatalyst $FeCl_3$. The authors assumed that the trivalent iron would possibly first be reduced to a low-valent state (**A**), such as Fe(0) or Fe(I), which probably possesses one or more alkynyl groups. The presence of LiBr is probably important due to the notable stability of Fe(II) alkenyl-ate complexes, which could make the initial reduction more difficult. The oxidative addition of an alkenyl bromide to a low-valent ferrat complex **A** provides the higher-valent complex **B**, which could undergo the reductive elimination to furnish the desired enyne. Ferrate complex **C** would react with alkenyl Grignard reagent to generate **A**. The authors also noticed that the particular loss of the stereochemical purity of *E*- and *Z*-propenylbromides indicates the likely involvement of an electron transfer process at the oxidative addition step.

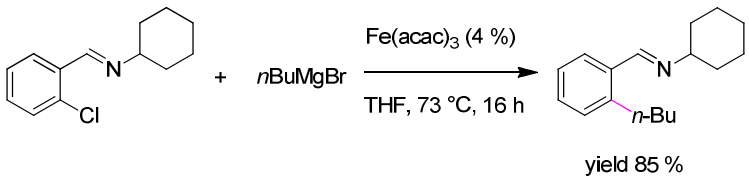


Scheme 20. Possible mechanism of iron-catalyzed enyne coupling by Nakamura et al.

2.2 Cross-Coupling of Aryl Electrophiles with Grignard Reagents

2.2.1 Alkyl Grignard Reagents

In 1989, Pridgen and co-workers described a transition metal catalyzed cross-coupling of ortho-halogenated aryl imines and Grignard reagents, where $Fe(acac)_3$ shows a better tolerance to the "reducing" Grignard reagents, containing β-hydrogen atoms, than $Ni(acac)_2$ (see Scheme 21).[54]

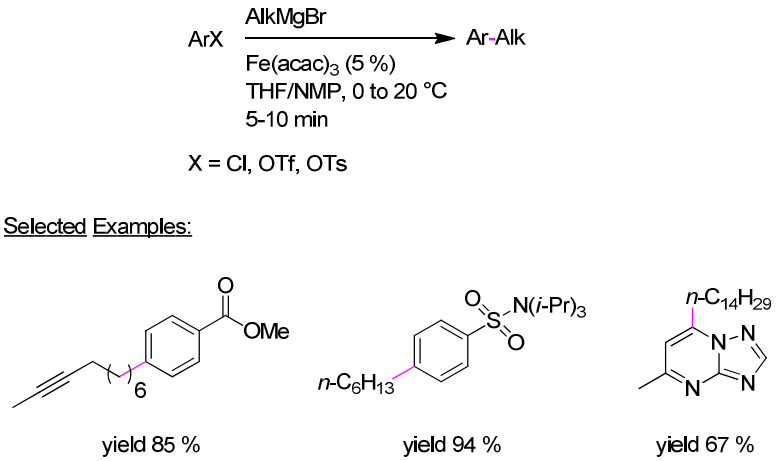


Scheme 21. Cross-coupling with ortho-halogenated aryl imines by Pridgen et al.

Fürstner et al deeply investigated iron-ctalyzed cross-coupling reactions with aryl or heteroaryl electrophiles and alkyl Grignard reagents.[55] High yields of the desired products

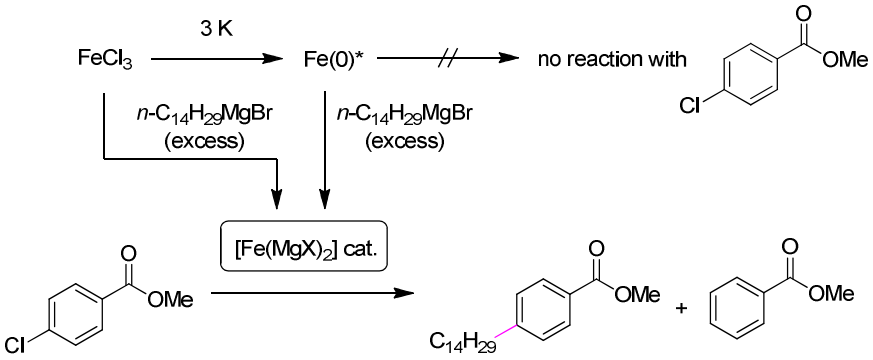
[54] Pridgen, L. N.; Snyder, L.; Prol, J. *J. Org. Chem.* **1989**, *54*, 1523.
[55] Fürstner, A.; Leitner, A; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856.

were obtained using $Fe(acac)_3$ or Fe(salen)Cl complex as a catalysts in THF/NMP solvent mixtures. A number of functional groups such as ether, sulfonate or nitrile were also tolerated.



Scheme 22. Cross-coupling of alkyl Grignard reagents with aryl and heteroaryl chlorides, tosylates and triflates by Fürstner et al.

In order to elucidate the mechanism of this iron-catalyzed process, the reaction between 4-chlorobenzoic acid methyl ester and *n*-tetradecylmagnesium bromide in the presence of 5 % of $FeCl_x$ (x = 2, 3) as a precatalyst was investigated. The cross-coupling product was obtained in a quantitative yield (>95 % GC-yield) within 5 min at ambient temperature, when $FeCl_3$ was used. In striking contrast, highly dispersed and nonpassivated iron metal Fe(0)* powder prepared by reduction of $FeCl_3$ with potassium does not insert at all into this substrate at 20 °C and reacts only after several hours under more harsh conditions. However the suspension of finely dispersed Fe(0)* particles in THF slowly dissolves on treatment with n-$C_{14}H_{29}MgBr$. The resulting mixture could catalyze this cross-coupling reaction. This fact means that during the cross-coupling reaction, the iron species get reduced by the Grignard reagent, but this process does not stop at Fe(0), it probably goes on generating a soluble complex, which likely contains iron in a formal oxidation state < 0, as postulated for the "inorganic Grignard reagent" $[Fe(MgX)_2]$ (see Scheme 23). This iron complex participates in the catalytic cycle for iron-catalyzed cross-coupling reactions with alkyl Grignard reagents, proposed by Fürstner (see Scheme 12).[46]

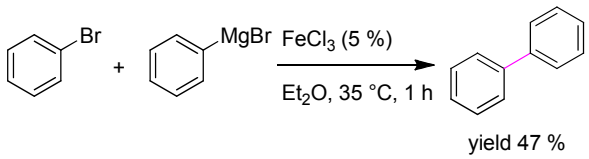


Scheme 23. Investigation of possible catalytically active iron species by Fürstner et al.

This procedure for iron-catalyzed aryl-alkyl cross-couplings could be applied in the synthesis of natural products, which was demonstrated by Fürstner in the total synthesis of (*R*)-(+)-Muscopyridine.[56] Nagano and Hayashi published the functionalization of aryl triflates using $Fe(acac)_3$ in Et_2O under reflux conditions.[57] The Hocek group examined the regioselectivity of iron-catalyzed cross-coupling reactions of 2,6-dichloropurines and 6,8-dichloropurines with the methyl Grignard reagent.[58] Fürstner and co-workers also reported the selective iron-catalyzed mono-substitution of dichloro-substituted arenes and heteroarenes.[44]

2.2.2 Aryl Grignard Reagents

The first aryl-aryl homo-coupling reaction was already described by Kharash and Fields in 1941 (Scheme 24).[27]

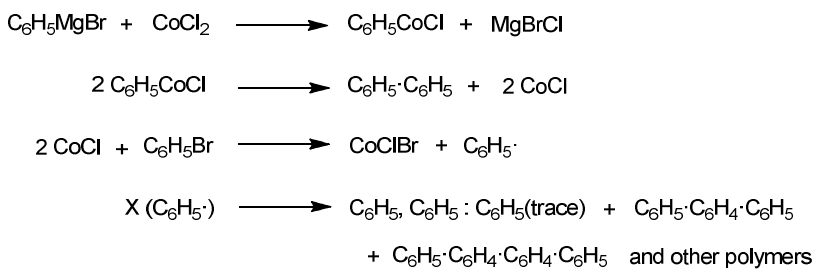


Scheme 24. Iron-catalyzed biaryl coupling by Kharash et al.

Bromobenzene was used as an oxidizing agent in converting the phenylmagnesium bromide to biphenyl as shown in Scheme 24. The authors proposed the following chain mechanism for cobalt chloride, but they admitted that iron could act in the same manner. The essential feature

[56] Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 308.
[57] Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297.
[58] a) Hocek,M.; Dvoŕáková, H. *J. Org. Chem.* **2003**, *68*, 5773; b) Hocek, M.; Hockova, D.; Dvoŕáková, H *Syntheis* **2004**, 889; c) Hocek, M.; Pohl, R. *Synthesis* **2004**, 2869.

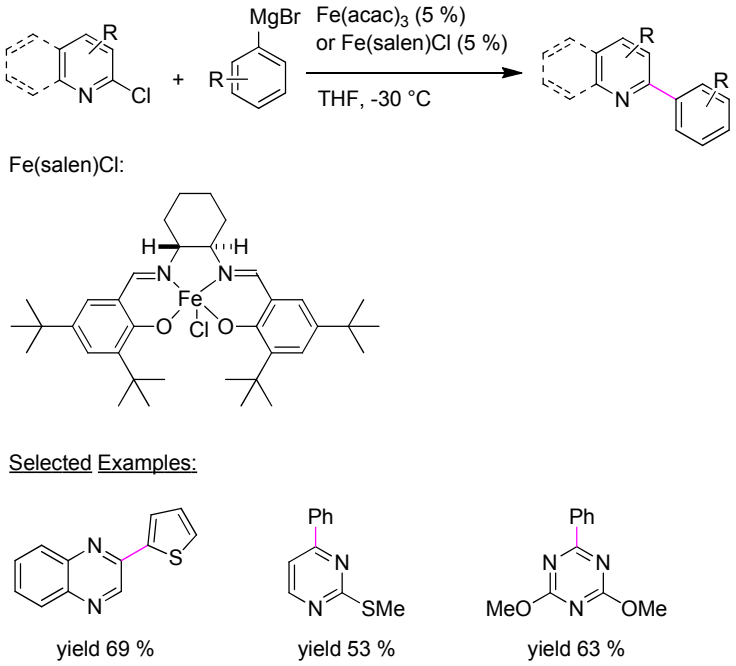
of this mechanism is that the reaction proceeds through the agency of a cobalt or iron subhalide, the active chain carrier. The biaryl is formed exclusively from the aryl Grignard reagent and the bromine atom of the phenyl bromide is converted into a bromide ion by the cobalt or iron subhalide (see Scheme 25).[59]



Scheme 25. Chain mechanism proposed by Kharash et al.[59]

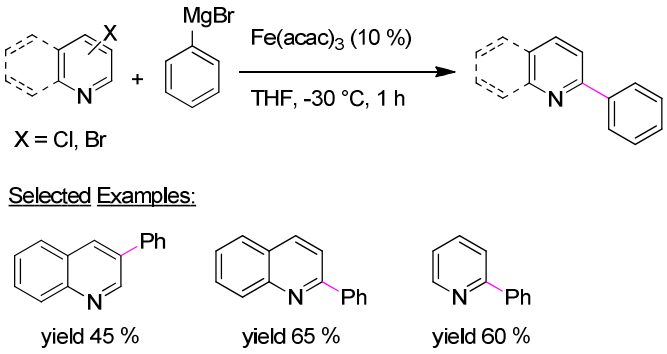
Fürstner and co-workers reported a cross-coupling reaction of aryl Grignard reagents and heteroaryl chlorides using 5 % of $Fe(acac)_3$ in THF. Electron-rich aryl halides tended to fail, giving only rise to the homo-coupling of the ArMgX, but various electron-deficient heterocycles could be used giving the desired cross-coupling products in good yields. However, the authors admitted that in all cases varying amounts of biphenyl were formed as byproducts. Sterically hindered Grignard reagents like mesitylmagnesium bromide failed in this cross-coupling, whereas 2-thienylmagnesium bromide and pyridine-3-magnesium bromide showed good results (see Scheme 26).[55]

[59] Scheme **25** represents a mechanism described for $CoCl_2$, like it was in the original paper from Kharash and Fields, but since authors suggested the same mechanism for $FeCl_3$, it makes sense to point it out here.



Scheme 26. Cross-coupling reactions using heteroaryl chlorides by Fürstner et al.

Figadère and co-workers studied iron-catalyzed arylations of heteroaryl halides by Grignard reagents. Iron salts such as $Fe(acac)_3$, $FeCl_3$ and $FeCl_2$ were tested for the catalytic activity in the reaction of 3-bromoquinoline with PhMgBr.[60] The effect of different additives like NMP, DMPU, CH_3CN, bipyridine, Ph_3P, $MnCl_2$, $ZnCl_2$ and CuCN was also investigated. The optimum conditions were determined to be $Fe(acac)_3$ in THF at -30 °C, 3-phenylquinoline could be achieved in 45 % yield. These conditions were applied to cross-coupling reactions with 2-chloroquinoline and 2-bromoquinoline with PhMgBr (see Scheme 27).

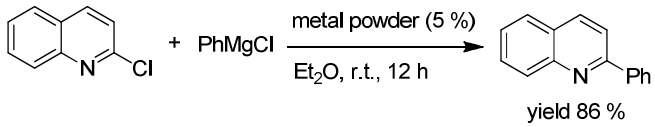


Scheme 27. Iron-catalyzed arylation of heteroaryl halides with PhMgBr by Figadère et al.

[60] Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère *Tetrahedron Lett.* **2002**, *43*, 3547.

Pie and co-workers described iron-catalyzed cross-coupling reactions of pyridine or diazine chlorides with aryl Grignard reagents. The synthesis of various unsymmetrical polyaryl or polyheteroaryl products was achieved.[61]

The Knochel group successfully used iron powder as a catalyst for the cross-coupling reaction of 2-chloroquinoline with PhMgCl, producing the desired product after 12 h in 86 % yield (see Scheme 28).[62]

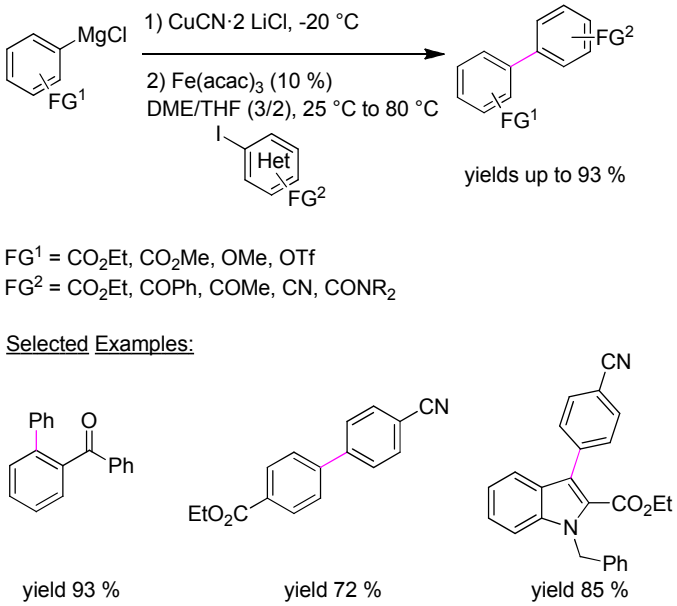


Scheme 28. Cross-coupling with catalytic iron powder by Knochel et al.

Several protocols for homo-coupling reactions of Grignard reagents under iron-catalysis were reported, using oxidizing agents such as 1,2-dichloroethane or oxygen.[63] The combination of the catalytic system of the $Fe(acac)_3$ or $Fe(DBM)_3$ with 2 equivalent of Mg in the absence of an oxidizing agent also furnishes homo-coupling products.[64]

Later, Knochel et al showed that the homo-coupling of the Grignard reagent could be suppressed if the arylmagnesium compound is transmetalated to the corresponding arylcopper reagent, using stoichiometric amounts of CuCN·2LiCl, prior to the iron-catalyzed cross-coupling reaction with aryl halides.[65]

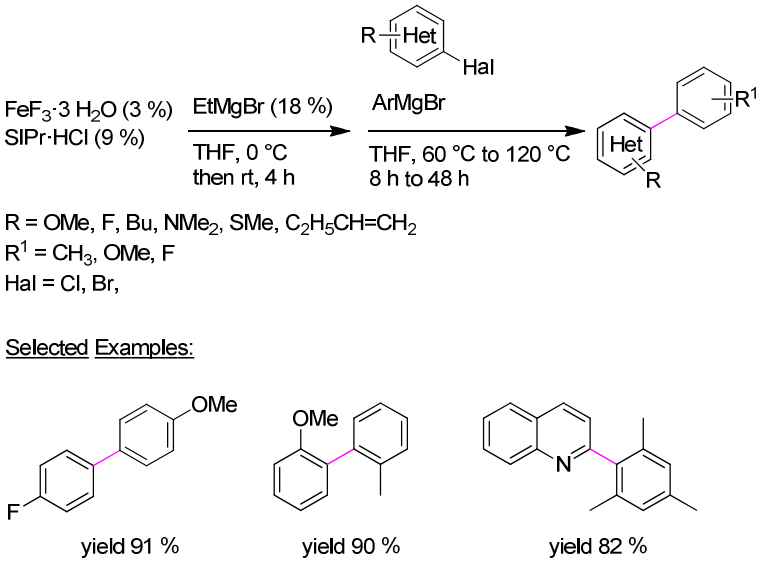
[61] Boully, L.; Darabantu, M.; Turck, A., Pié, N. *J. Heterocycl. Chem.* **2005**, *42*, 1423.
[62] Korn, T. J.; Cahiez, G.; Knochel, P. *Synlett* **2003**, 1892.
[63] a) Nagano, T; Hayashi, T. *Org. Lett.* **2005**, *7*, 491; b) Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788.
[64] Xu, X.; Cheng, D.; Pei, W. *J. Org. Chem.* **2006**, *71*, 6637.
[65] Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 1654.



Scheme 29. Iron-catalyzed aryl-aryl cross-coupling with magnesium-derived copper reagents by Knochel et al.

In 2007, Nakamura reported a novel combination of iron fluoride salts with a *N*-heterocyclic carbene (NHC) ligand, which specifically suppressed homo-coupling reactions. The optimum conditions include 3 % of $FeF_3 \cdot H_2O$ and 9 % of SIPr·HCl (NHC ligand). Ferrous fluoride ($FeF_2 \cdot 4H_2O$) showed comparable catalytic activity, indicating that the *in situ* reduction of $FeF_2 \cdot 4H_2O$ or $FeF_3 \cdot H_2O$ probably gives the same catalytically active iron species. The authors assumed that the water or hydroxide could react with the solid surface of FeF_3 and make it partially soluble in THF to promote the generation of catalytically active species to some extent.[66] In 2009, Nakamura continued the investigation of this "fluorine effect", expanded the scope of this methodology. They also proposed a mechanism for this cross-coupling reaction, based on DFT-calculations.[67] The authors found that EtMgBr could be used as a base in order to deprotonate the NHC precursors and hydrates of iron fluorides. Electron-rich arylhalides as well as electron-deficient ones could be tolerated in this cross-coupling reactions and gave the desired products in good yields. Heteroaromatic electrophiles undergo cross-coupling reactions using this catalytic system, although compared to other catalytic systems discussed before, a higher temperature (80 °C to 100 °C) and a longer reaction time (8 h to 24 h) was required.

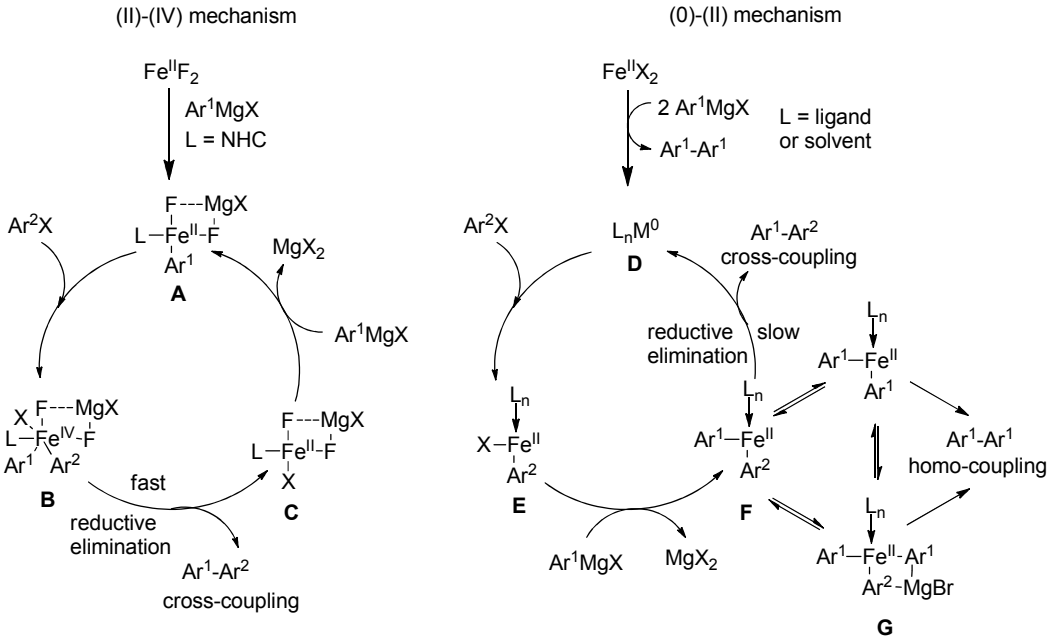
[66] Hatakayama, T; Nakamura, M *J. Am. Chem. Soc.* **2007**, *129*, 9844.
[67] Hatakeyama, T.; Hashimoto, S.; Ishizuka, K.; Nakamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 11949.



Scheme 30. Aryl-aryl cross-coupling using catalytic system of $FeF_3 \cdot H_2O$ with NHC ligand by Nakamura et al.

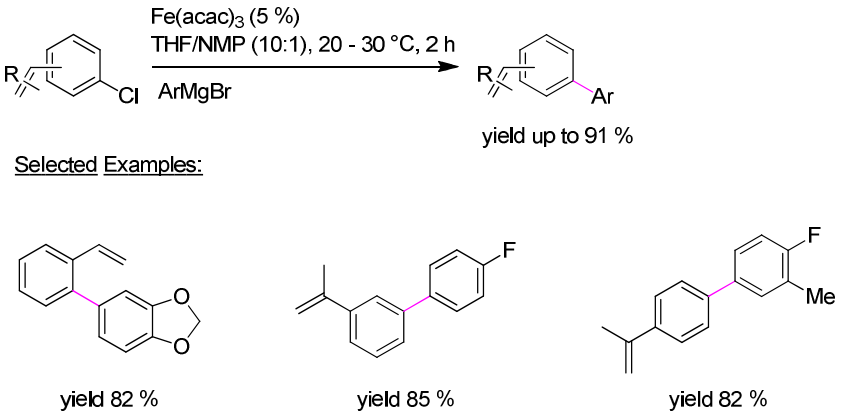
Two possible catalytic cycles, the "(II)-(IV)" and the "(0)-(II)", were proposed by Nakamura et al. The first cycle includes the formation of a heteroleptic metal (II)-ate complex **A** (Scheme 31) from a divalent fluoride and an arylmagnesium reagent (Ar^1MgX). The complex **A** undergoes oxidative addition with the aryl halide to generate an elusive higher-valent (formally IV oxidation state) species **B** having Ar^1 and Ar^2. Reductive elimination would give unsymmetrical biaryl Ar^1-Ar^2 and iron (II) complex **C** bearing two fluorides and one halogen ligand derived from Ar^2X on the metal center. Subsequent reaction of **C** with Ar^1MgX would regenerate species **A**.

The "(0)-(II) mechanism" involves oxidative addition of the aryl halide to the iron (0) intermediate **D**, transmetalation between aryliron halide **E** and Ar^1MgX and reductive elimination of Ar^1-Ar^2 from diaryliron(II) **F**. The authors assumed that the described cross-coupling reaction proceeds via the higher-valent iron intermediate of the first catalytic cycle "(II)-(IV)", this statement was supported by DFT calculations.



Scheme 31. Proposed mechanisms involving a metal-fluoride-ate complex as reactive intermediate by Nakamura et al.

Von Wangelin and co-workers recently described an iron-catalyzed hetero-biaryl coupling reaction using chlorostyrenes.[68] The authors assumed that the mechanism of this transformation involves the coordination of the vinyl substituent to the iron catalyst and the subsequent haptotropic migration to the site of C-Cl bond activation is decisive. The general procedure is quite practical (THF/NMP, 20-30 °C, 2 h) and based on $Fe(acac)_3$ (1-5 %) as a precatalyst (Scheme 32).



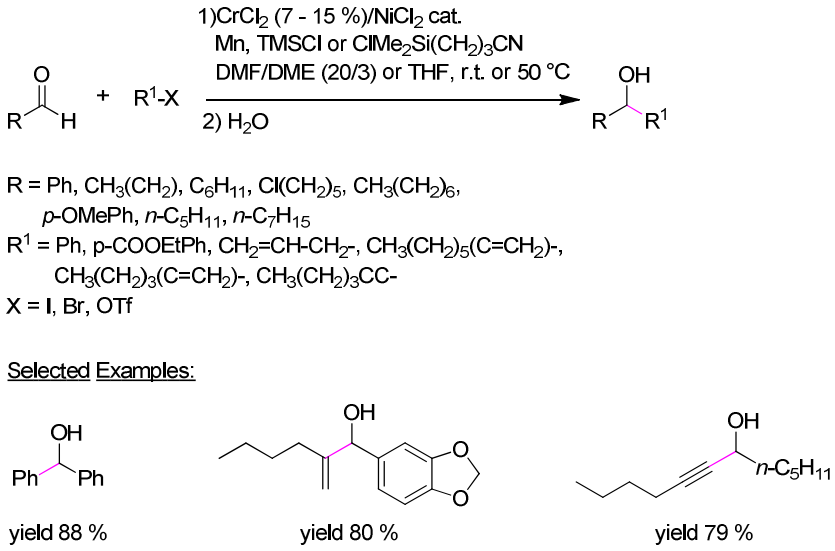
Scheme 32. Chlorostyrenes in iron-catalyzed biaryl coupling reactions by von Wangelin et al.

[68] Gülak, S.; von Wangelin, A. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 1357.

3. Chromium-Catalyzed Cross-Coupling Reactions

The first chromium reagent was prepared from the phenyl Grignard reagent with $CrCl_3$ in Et_2O by Hein as far back as 1919,[69] although the correct interpretation of the structure of this compound was described later.[70] In 1986, Kishi et al[71] and Nozaki et al[72] independently discovered that traces of nickel salts exert a catalytic effect on the formation of the C-Cr(III) bond. This finding became a standard tool when less reactive substrates such as alkenyl and aryl halides or triflates have to be used for Barbier type addition reactions. Many applications using stoichiometric amounts or excess of chromium salts for various coupling reactions were published.[73]

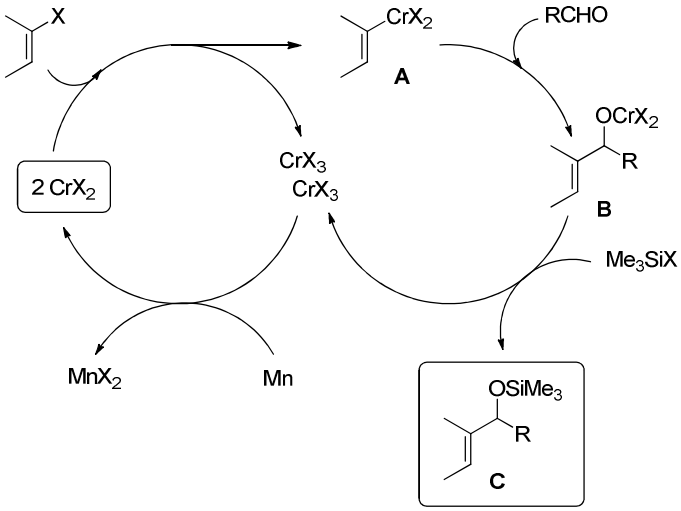
In 1996, Fürstner and co-workers reported a method, which allowed, the Nozaki-Hiyama-Kishi reaction to be performed with catalytic quantities of chromium. The catalytic system includes 7 – 15 % of $CrCl_2$ or $CrCl_3$ doped with $NiCl_2$, Mn powder as a stoichiometric reductive agent and chlorosilane as an additive for ligand exchange (see Scheme 33). Other chromium sources such as Cp_2Cr or $CpCrCl_2 \cdot THF$ also could be applied as a "pre-catalyst".



Scheme 33. Nozaki-Hiyama-Kishi reactions with a catalytic amount of $CrCl_2$ by Fürstner et al

[69] Hein, F. *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 195.
[70] Zeiss, H. H.; Tsutsui, M. *J. Am. Chem. Soc.* **1957**, *79*, 3062.
[71] Jin, H.; Uenishi, J.-i.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.
[72] Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.
[73] Selected publications for application of stehiometric amount of chromium salts: a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1976**, *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) Takai, K.; Matsukawa, N.; Takahashi, A.; Fujii, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 152; e) Takai, K.; Toshikawa, S.; Inoue, A.; Kokumai, R.; Hirano, M. *J. Organomet. Chem.* **2007**, *692*, 520; f) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.

A possible catalytic cycle for this transformation is shown in Scheme 34. It starts with the reaction of the organo halide with 2 $CrCl_2$. Since Cr^{+2} is a one-electron donor, 2 mol of this reagent/mol of halide are required for the formation of an oraganochromium nuchleophile **A** and CrX_3. Species **A** then adds to the aldehyde with formation of chromium alkoxide **B**. At this point, the higher stability of its O-Cr^{3+} bond impedes the ability of undertaking this reaction with a catalytic amount of chromium. Therefore, the addition of chlorosilane provides the ligand exchange with **B** and such an σ-bond metathesis would afford the silyl ether of the desired product **C** and liberate the second mol of CrX_3, which could be then reduced to CrX_2 with reductive agent (Mn powder) and participate again in the catalytic cycle.[74]

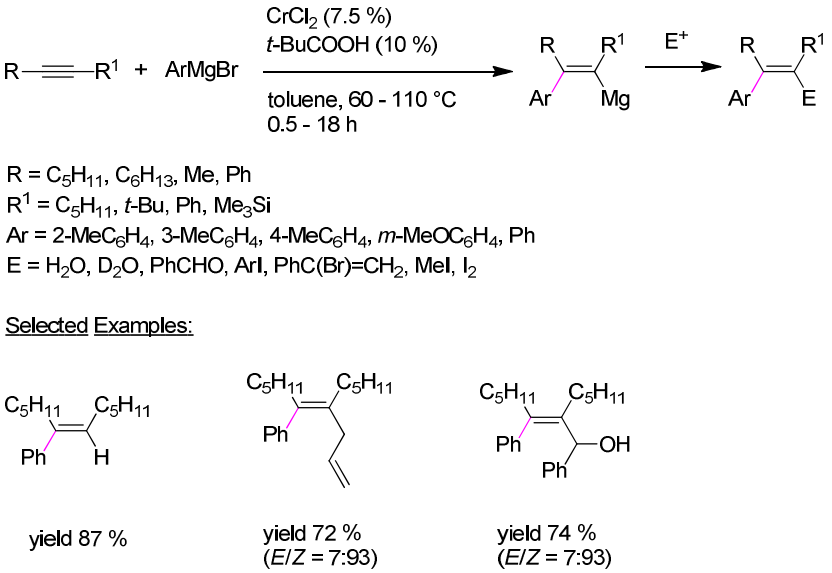


Scheme 34. Likely mechanism with a catalytic amount of $CrCl_2$ using chlorosilane as an additive by Fürstner et al.

However, one of the limiting features of this method is the incomplete ligand exchange between the chromium alkoxide and admixed chlorosilane.

In 2007, Yorimitsu, Oshima and co-workers reported the chromium-catalyzed arylmagnesiation of unfunctionalized alkynes in the presence of pivalic acid. The arylmagnesium intermediate reacted with various electrophiles to afford the corresponding tetrasubstituted olefins in good yields (Scheme 35).[75]

[74] Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349.
[75] Murakami, K.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, *9*, 1569.



Scheme 35. Chromium-catalyzed arylmagnesiation of alkynes by Yorimitsu et al.

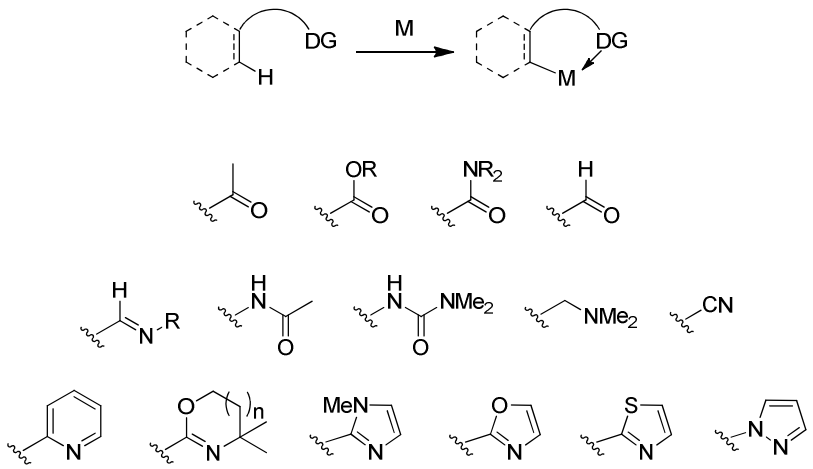
This procedure seems to be a highly effective manner to construct multisubstituted ethene units.

To our knowledge there are no protocols described for chromium-catalyzed cross-coupling reactions. Therefore, this field represents a new extension of the chromium chemistry and brings new features to the transition metal-catalyzed cross-coupling.

4. C-H Bond Activation Reactions Using Alternative Transition Metals

The direct transformation of C-H bonds into C-C bonds makes the prefunctionalization of starting materials unnecessary and therefore represents a more environmentally friendly way of performing the desirable molecular core then cross-coupling reactions.

However, in order to let a C-H bond activation occure selectively, one of the all C-H bonds in the organic molecule should be activated more than the others. The solution would be to have a directing group in the molecule. Some important directing groups are presented in Scheme 36.



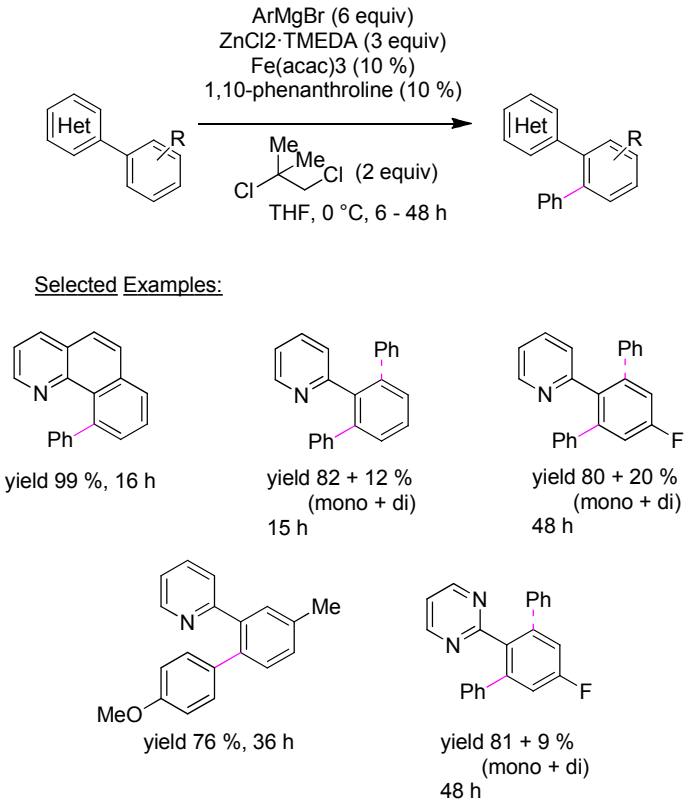
Scheme 36. Some important functional groups that act as directing group

Over the last decades C-H bond activation has widely been developed.[76] Transition metals such as Pd[77], Ru[78] and Rh[79] were extensively applied as catalysts for this type of reaction. But due to the high prices and toxicity the replacement of these salts is highly desired.

[76] For reviews about C-H bond activation see: a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731; b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174; c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; d) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087; e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; f) *Modern Arylation Methods*; Ackermann, L.; Woley-VCH: Weinheim, **2009**; g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147; h) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624; i) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; j) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726.

[77] For palladium-catalyzed C-H bond activation see: a) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302; b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. . *J. Am. Chem. Soc.* **2005**, *127*, 7330; c) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676; d) Zhou, W.; Li, H.; Wang, L. *Org. Lett.* **2012**, *14*, 4594.

In 2008 Nakamura et al published an iron-catalyzed arylation through directed C-H bond activation.[80] The authors showed that benzo[*h*]quinoline could be arylated at position 10 using 10 % of $Fe(acac)_3$ with 6 equivalents of PhMgBr in the presence of 3 equivalents $ZnCl_2 \cdot TMEDA$ and 2 equivalents of 1,2-dichloro-2-methylpropane (as an oxidant). 1,10-Phenantroline was used as a ligand. Other phenylsubstituted heterocycles such as 2-phenylpyridines gave mixtures of mono- and disubstituted products, except 2-(*o*-tolyl)pyridine, which was arylated exclusively on the side opposite to the methyl group, probably due to steric hindrance (Scheme 37). All the reactions were carried out at 0 °C with reaction times of 6 – 48 h.



Scheme 37. Iron-catalyzed direct arylation through directed C-H bond activation by Nakamura et al.

---

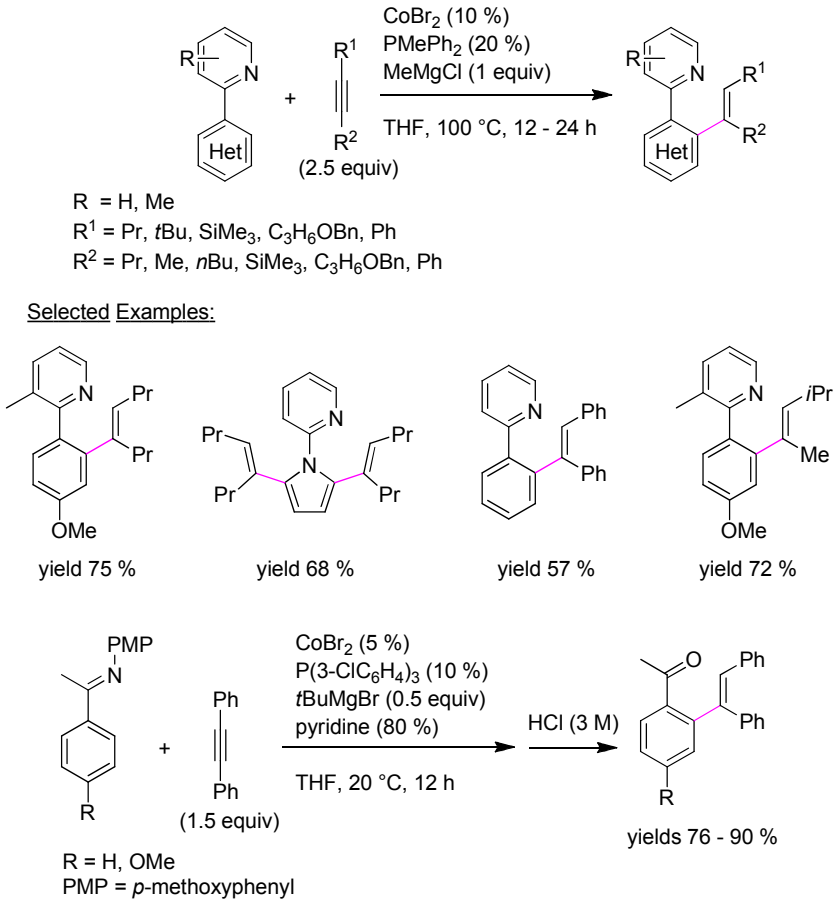
[78] For ruthenium-catalyzed C-H bond activation see: a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529; b) Harris, P. W. R.; Rickard, C. E. F.; Woodgate, P. D. *J. of Organom. Chem.*, **1999**, *589*, 168; c) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chantani, N. Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 9858; d) Muralirajan, K.; Parthasarathy, K; Cheng, C.-H. *Org. Lett.* **2012**, *14*, 4262; e) Ogiwara, Y.; Kochi, T.; Kakiuchi, F. *Chem. Lett.* **2014**, *43*, 667.

[79] For rhodium-catalyzed C-H bond activation see: a) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2011**, *50*, 4969; b) Patureau, F. W.; Nimphius, C.; Glorius, F. *Org. Lett.* **2011**, *13*, 6343; c) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2154.

[80] Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858.

Later, Nakamura et al extended this type of reaction to a C-H bond activation for the *ortho*-arylation of imines with Grignard reagents.[81]

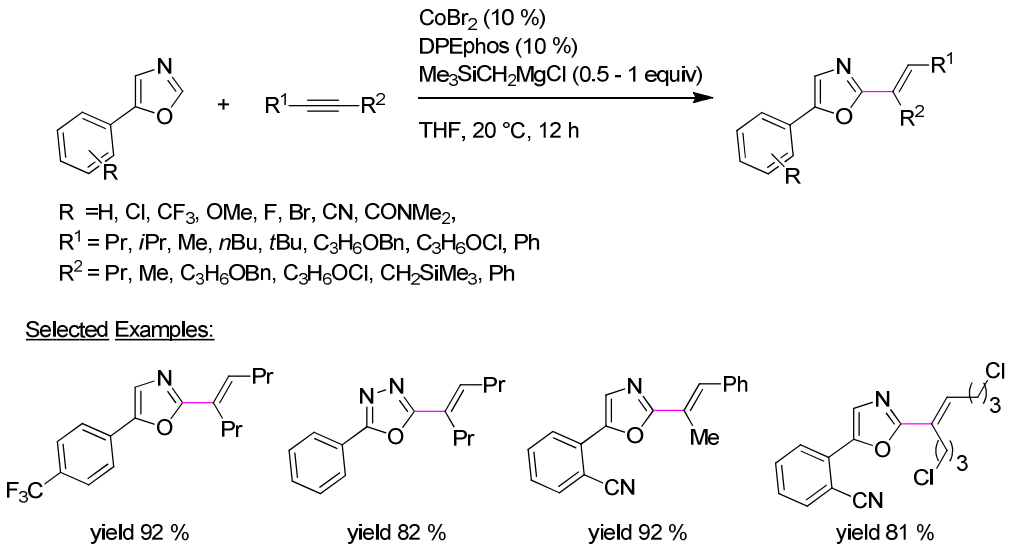
In 2011, the Yoshikai group described a cobalt-catalyzed hydroarylation of alkynes through chelation-assisted C-H bond activation (Scheme 38).[82] This addition reaction of arylpyridines and imines to internal alkynes gave olefins with high regio- and stereoselectivities using 10 % of $CoBr_2$ with 20 % of $PMePh_2$ (as a ligand) and 2.5 equivalent of an appropriate alkyne. MeMgCl (1.0 equiv) was used as a reducing agent. Reactions using arylpyridines were carried out at 100 °C for 12 – 24 h. Aryl imines were also amenable to hydroarylation reactions using a catalytic system which involved $CoBr_2$ (5 %), $P(3\text{-}ClC_6H_4)_3$ (10 %) as a ligand, *t*$BuCH_2MgBr$ (50 %) as a reducing agent and pyridine (80 %) as an additive.



Scheme 38. Cobalt-catalyzed hydroarylation of alkynes through chelation-assisted C-H bond activation by Yoshikai et al.

[81] Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem. Asian J.* **2011**, *6*, 3059.
[82] Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249.

In the same year, the Yoshikai group published a cobalt-catalyzed addition of azoles to alkynes.[83] The authors reported that the ternary catalytic system consisting of a cobalt salt, a diphosphine ligand, and the Grignard reagent promotes *syn*-addition of the azole C(2)-H bond across an unactivated internal alkyne with high chemo-, regio-, and stereoselectivities under mild conditions (Scheme 39). Mechanistic experiments suggest that the reaction involves oxidative addition of the oxazolyl C-H bond to the cobalt center, alkyne insertion into Co-H bond, and reductive elimination of the resulting diorganocobalt species.

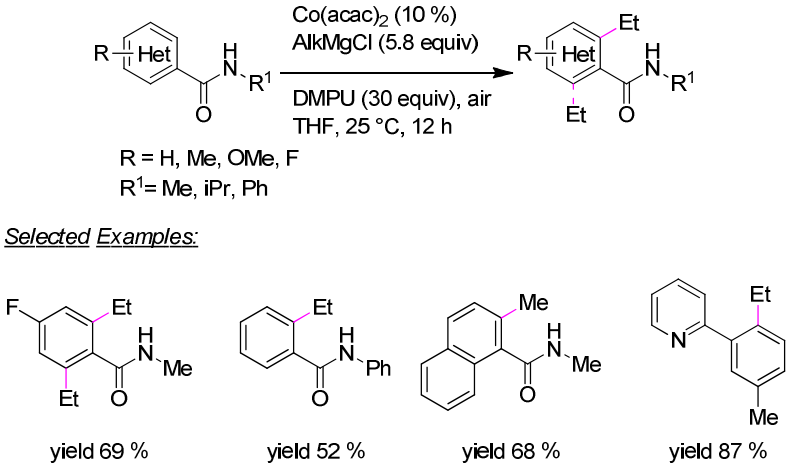


Scheme 39. Cobalt-catalyzed hydroarylation of alkynes through chelation-assisted C-H bond activation by Yoshikai et al.

The Yoshikai group also achieved a similar cobalt-catalyzed addition of aromatic imines to alkynes via directed C-H bond activation.[84]

Nakamura and Yoshikai described a cobalt-catalyzed coupling of alkyl Grignard reagents with benzamide and 2-phenylpyridine derivatives through directed C-H bond activation (Scheme 40). The authors showed that aromatic carboxamides and 2-phenylpyridine derivatives could be *ortho*-alkylated with Grignard reagents in the presence of a cobalt catalyst and DMPU as a ligand, using air as a sole oxidant at 25 °C in THF.[85]

[83] Ding, Z.; Yoshikai, N. *Org. Lett.* **2010**, *12*, 4180.
[84] Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283.
[85] Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2011**, *13*, 3232.

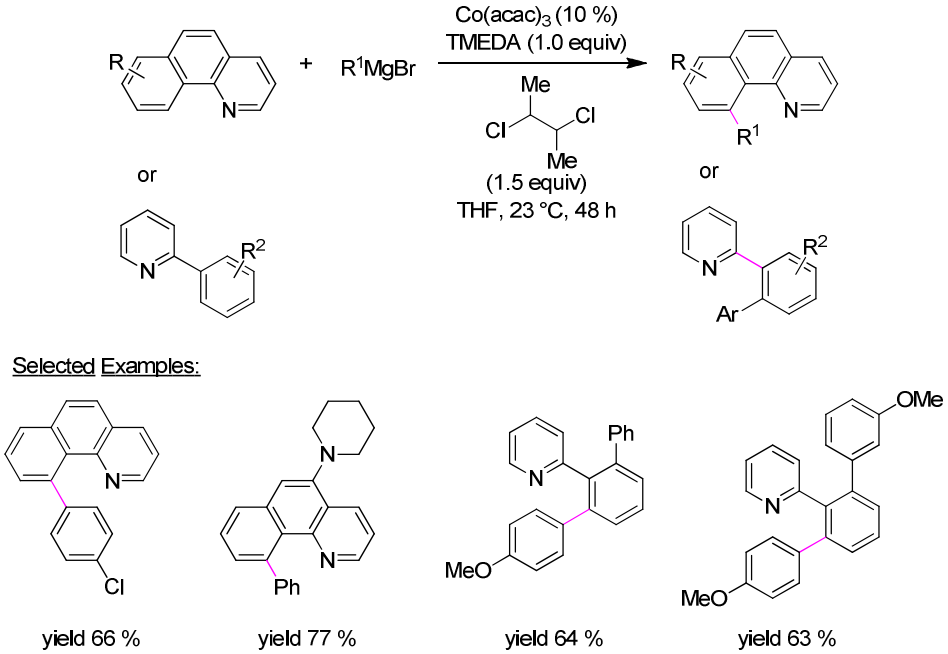


Scheme 40. Cobalt-catalyzed oxidative alkylation of aromatic carboxamides and arylpyridines with Grignard reagents by Nakamura and Yoshikai

In 2011, Nakamura described an iron-catalyzed stereospecific activation of olefinic C-H bonds with Grignard reagents for the synthesis of substituted olefins.[86] Arylated products were synthesized in good yields (up to 99 %), using 10 % of $Fe(acac)_3$, 15 % of dtbpy and 2 equivalents of 1,2-dichloro-2-methylpropane in PhCl with slow addition of 3.2 equivalents of ArMgBr in THF at 0 °C over 5 min.

Wang and Shi reported the direct cross-coupling of C-H bonds with Grignard reagents through cobalt catalysis (Scheme 41).[87] Various arylated benzo[*h*]quinolines could be produced in good yields (up to 92 %). Reaction conditions included 10 % of $Co(acac)_3$ with 1 equivalent of TMEDA and 1.5 equivalent of 2,3-dichlorobutane (as an oxidant).

[86] Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 7672.
[87] Li, B.; Wu, Z.-H.; Gu, Y.-F.; Sun, C.-L.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2011**, *50*, 1109.



Scheme 41. Directed cross-coupling of C-H bonds with Grignard reagents through cobalt catalysis by Wang and Shi

In 2013, the Yoshikai group described another example for cobalt-catalyzed *ortho*-alkylation reaction of aromatic imines with primary and secondary alkyl halides.[88,89] A cobalt-*N*-heterocyclic carbene (NHC) catalyst system allowed the authors to perform alkylations of aromatic imines at 23 °C with reaction times of 4 – 24 h.

The You group showed that the iron-catalyzed oxidative C-H/C-H cross-coupling could be an efficient route to α-amino acid derivatives.[90]

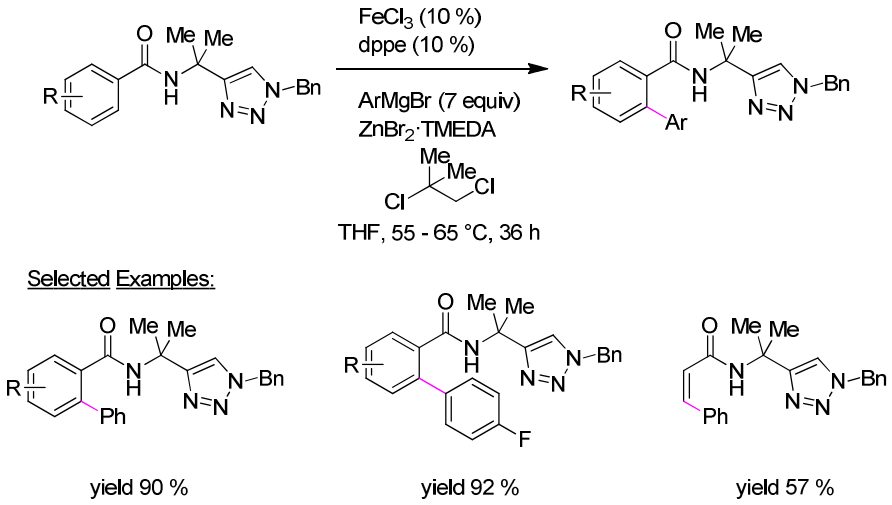
Nakamura and Ilies reported the iron-catalyzed *ortho*-allylation of aromatic carboxamides with allyl ethers.[91] They found that substrates bearing a bidentate directing group, *N*-(quinolin-8-yl)benzamide selectively afford the allylation products in good yields (up to 99 %).

In 2014, DeBoef et al found out that iron-catalyzed arylation of heterocycles *via* directed C-H bond activation could be successfully carried out on a variety of N-, S-, and O-containing

[88] Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279.
[89] Gao, K.; Yosikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208.
[90] Li, K., Tan, G.; Huang, J.; Song, F.; You, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12942.
[91] Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 17755.

heterocycles at 0 °C over 15 min.[92] A number of heterocyclic arylated imines or aldehydes were synthesized with yields up to 88 %.

The group of Ackermann showed that C(sp^2)-H and C(sp^3)-H arylation could be achieved by triazole assistance (Scheme 42).[93]



Scheme 42. Iron-catalyzed C(sp^2)-H and C(sp^3)-H arylation by triazole assistance by Ackermann and et al.

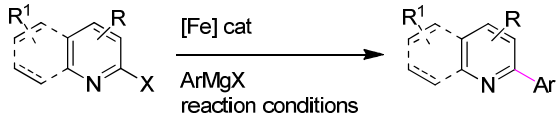
Among alternatives of the catalytic systems for the C-H bond activation reaction, iron and cobalt salts are predominant. To our knowledge, no chromium-catalyzed C-H bond activation has been described in the literature so far.

[92] Sirois, J. J.; Davis, R.; DeBoef, B. *Org. Lett.* **2014**, *16*, 868.
[93] Gu, Q.; Al Mamari, H.H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 3868.

5. Objectives

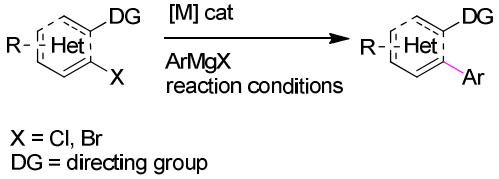
Transition-metal-catalyzed cross-coupling reactions are one of the most used C-C bond forming reactions, where palladium and nickel catalysts play a main role. However, the constantly increasing world market price of palladium, the toxicity of nickel salts, and the laborious synthesis of arylboronic acids are prompting the search for powerful alternatives, also for industrial process. Therefore, the development of alternative transition metal catalysts for cross-coupling reactions represents our general goal.

Iron-catalysts have received a lot of attention in the area of cross-coupling reactions due to environmentally friendly properties of iron salts combined with their moderate prices and absence of air-sensitive expensive ligands. Alkyl-aryl, alkyl-alkenyl, aryl-alkenyl, and alkynyl-coupling reactions are well documented. The corresponding aryl-aryl cross-couplings are much more challenging due to the formation of homo-coupling side-products. Therefore, our next aim would be to find simple and practical reaction conditions for sp^2-sp^2 type cross-coupling reactions using iron as a catalyst. Particularly, the cross-coupling between *N*-heterocyclic halides (chlorides or bromides) with arylmagnesium reagents should be investigated due to the potential biological activity of the resulting arylated heterocycles (Scheme 43).



Scheme 43. Iron-catalyzed cross-coupling reactions of *N*-heterocyclic halides with Grignard reagents

Other transition metals salts such as $CoCl_2$, $MnCl_2$, VCl_3, VCl_4 and eventually $CrCl_2$ should be tested for catalytic activity in cross-coupling reactions of aryl or alkenyl halides with arylmagnesium reagents (Scheme 44).

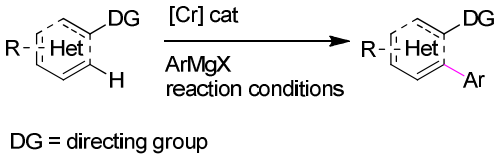


Scheme 44. Alternative metal-catalyzed cross-coupling reactions of aryl or alkenyl halides with Grignard reagents

In addition, mechanistic insights should not be neglected.

Over the last decades, the direct coupling of C-H bonds *via* C-H bond activation has developed from an exotic phenomenon to an indispensable tool for organic chemists. Pd-, Rh- and Ru-catalysts are the metals of choice, if one aims to perform direct coupling reactions. As discussed above, the replacement of these metals by readily available and less-toxic salts is highly desirable.

One further task of this work is to investigate the ability of Cr-salts to catalyze directed C-H bond activation reactions. Benzo[*h*]quinoline, 2-phenylpyridine, phenyloxazoline and imines should be tested in Cr-catalyzed C-H arylations with Grignard reagents (Scheme 45).



Scheme 45. Chromium-catalyzed C-H bond activation using arylmagnesium reagents

B. Results and Discussion

1. Iron-Catalyzed Cross-Coupling of *N*-Heterocyclic Halides with Grignard Reagents.

1.1 Introduction

In 1941, Kharash described the first iron-catalyzed reaction of PhMgCl, which provided the homo-coupling product biphenyl.[27] This discovery paved the way for the field of iron-catalyzed coupling reactions, but it also demonstrated the big challenge of performance of cross-coupling reactions between Csp^2-Csp^2 precursors due to the formation of the undesired homo-coupling side-products of the Grignard reagent such as biphenyl.

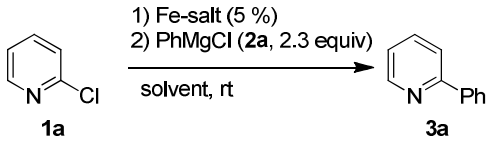
The use of iron fluorides in combination with carbene ligands improves such aryl-aryl cross-coupling dramatically as shown by Nakamura et al.[66] Although, long reaction time (8 - 48 h) and additional heat (60 – 100 °C) were required.

To our knowledge, only few examples of cross-coupling of *N*-heterocyclic halides with arylmagnesium reagents are described in the literature and no general methodology have been established.[55,56,61,62] The scope of Grignard reagents, which were used for this kind of transformation, also seems to be limited.

1.2 Results and Discussion

1.2.1 Optimization of reaction conditions

In preliminary experiments, we examined the cross-coupling between 2-chloropyridine (**1a**) and PhMgCl (**2a**) (see Sheme 46).



1a **3a**

Scheme 46. Cross-coupling of pyridyl chloride (**1a**) with PhMgCl (**2a**) in the presence of various Fe-salts

We investigated the effect of catalytic amounts (5 %) of various iron salts, which are represented in Table 1. Surprisingly, the common $Fe(acac)_2$ or $Fe(acac)_3$ in THF gave only 46 % and 55 % (GC-yield) of the desired 2-phenylpyridine (**3a**) respectively at room temperature (entries 1 and 2). The related iron salt $Fe(TMHD)_3$ (TMHD = 2,2,6,6-tetramethyl-3,5-heptanedionate) provided 53 % of the desired product **3a** after 2 h at room temperature (entry 3). Different 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 cross-coupling product **3a**. As expected, iron fluorides gave only traces of product apparently due to insolubility in THF (entry 9 and 10) as well as FeI_2 (entry 11). We have to admit that polar co-solvents such as NMP (*N*-methylpyrrolidone) hampered the cross-coupling, since the reaction of the Grignard reagent and NMP was dominant (entry 12).

Table 1. Optimization of the conditions for the reaction of pyridyl chloride (**1a**) with PhMgCl (**2a**) catalyzed by iron salts

Entry	Fe-salt[a]	Reaction time[b]	Yield (%)[c]
1	$Fe(acac)_2$	2 h	46
2	$Fe(acac)_3$	2 h	55
3	$Fe(TMHD)_3$	2 h	53
4	$FeCl_2$	5 h	56
5	$FeCl_3$	2 h	55
6	$FeBr_2$	2 h	62
7	$FeBr_3$	1.5 h	63
8	$Fe(OTf)_3$	5 h	60
9	FeF_2	20 h	traces[d]
10	FeF_3	20 h	traces[d]
11	FeI_2	20 h	traces[d]
12	$FeBr_3$	2 h	traces[e]
13	$FeBr_3 \cdot 3LiCl$	1.5 h	51
14	$FeBr_3 \cdot 3LiBr$	1.5 h	56
15	$Fe(acac)_3 \cdot 3LiCl$	1.5 h	50

(a) 5 % 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. (d) Starting

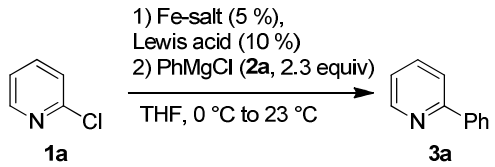
material was not consumed even after 20 h. (e) A mixture of THF/NMP (5:1) was used. The reaction of PhMgCl with NMP was dominant.

Solutions of iron salts in THF prepared in the presence of LiCl or LiBr such as $FeBr_3 \cdot 3LiCl$, $FeBr_3 \cdot 3LiBr$ or $Fe(acac)_3 \cdot 3LiCl$ were tested as well, but did not provide significant improvements (entries 13 – 15).

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 deactivated the catalytic system and hampered the coupling reaction.

We also investigated the influence of different Lewis acids, since they showed good results in the cross-coupling of pyridines with aryl bromides *via* metalation with TMPZnCl·LiCl base, reported by Knochel et al.[94] Results represented in Table 2 indicate that none of Lewis acids improved the yield of the cross-coupling product **3a**.

Table 2. Influence of various Lewis acids for cross-coupling reaction of 2-chloropyridine (**1a**) with PhMgCl (**2a**)



1a **3a**

Entry	Lewis acid	Fe-salt[a]	Yield (%)[b]
1	without	$Fe(acac)_3$	55
2	$BF_3 \cdot OEt_2$	$Fe(acac)_3$	37
3	$BF_3 \cdot OEt_2$	$FeBr_3$	3
4	$Sc(OTf)_3$	$Fe(acac)_3$	20
5	$Sc(OTf)_3$	$FeBr_3$	34
6	$(CF_3SO_3)_3Yb$	$Fe(acac)_3$	28
7	$(CF_3SO_3)_3Yb$	$FeBr_3$	31

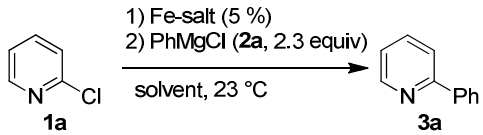
(a) The reaction was carried out using 5 % of Fe-salt, 2.3 equivalents of PhMgCl and THF as a solvent at 0 °C to 23 °C for 24 h. (b) Calibrated GC-yield using undecane ($C_{11}H_{24}$) as an internal standard.

[94] Duez, S.; Steib, A. K.; Manolikakes, S. M.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 7686.

Based on the screening of various iron salts we decided to use $FeBr_3$ in the subsequent reactions, since it showed the best result in THF (see Table 1) at 23 °C. We observed that carrying out the coupling reaction between 2-chloropyridine (**1a**) and 2.3 equivalents PhMgCl (**2a**) in the presence of 5 % $FeBr_3$ at -70 °C, -30 °C and 0 °C showed 4 %, 21 % and 30 % GC-yield of the desired product respectively after 1.5 h. The amount of the Grignard reagent was also screened. The use of 2.3 equivalents of **2a** have shown to be reasonable, since the employment of 1.2 equivalent of the Grignard reagent **2a** gave less good results; on the other hand 3 equivalents of the reagent **2a** did not improve the yield significantly.

Next, we screened different solvents in order to examine solvent effects for this kind of transformation. Nonpolar solvents like *n*-hexane or toluene, did not display any considerable improvements in comparison to THF (entries 1-3, Table 3). The use of acetonitril led to only 14 % yield of the desired product due to a side reaction of this solvent and PhMgCl (**2a**; entry 4). However, the usage of ethereal solvents such as diethylether or *t*BuOMe allowed us to dramatically improve the yield and reach full conversion of the starting material. Thus, we isolated the desired product **3a** using Et_2O or *t*-BuOMe in 84 % and 82 % yield respectively (entries 7 - 8). Dibutylether also showed good results (entry 9) in contrast with dimethylether, which provided only 28 % of 2-phenylpyridine (**3a**, entry 6). A reasonable GC-yield was achieved using MCPE (methoxycyclopentane) as a solvent. Only 58 % yield of the cross-coupling product **3a** was determined using 2-Me-THF (2-methyltetrohydrofurane) (entry 11). Since comparably good yields were obtained using *t*BuOMe or Et_2O, we have pursued our investigations using the industry-friendly solvent *t*BuOMe.

Table 3. Solvent screening for the cross-coupling reaction of 2-chloropyridine (**1a**) with PhMgCl (**2a**)



Entry[a]	Solvent	Reaction time[b]	Yield (%)[c]
1	THF	1.5 h	63
2	*n*-hexane	2 h	53
3	toluene	1.5 h	14
4	CH_3CN	1.5 h	18
5	1,2-dioxane	3 h	49

6	DME	2 h	48
7	Et_2O	1.5 h	73, 87,[d] (84)[d]
8	*t*-BuOMe	1.5 h	75, 87,[d] (82)[d]
9	Bu_2O	1.5 h	72
10	CPME	5 h	80[d]
11	2-Me-THF	1.5 h	58[d]

(a) 5 % of Fe-salt was used. (b) The 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) 3 % of $FeBr_3$ was used.

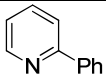
Based on the results obtained after optimization of the reaction conditions, we went on with our investigations using 3 % of $FeBr_3$, 2.3 equivalent of the Grignard reagent and *t*BuOMe as solvent at 23 °C.

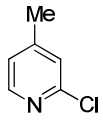
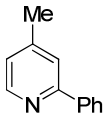
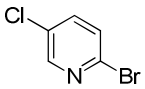
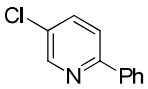
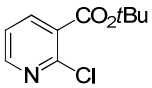
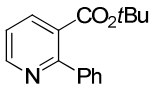
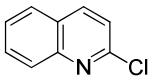
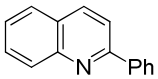
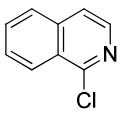
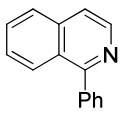
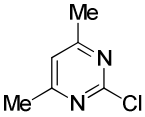
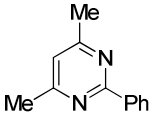
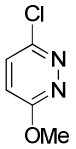
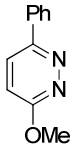
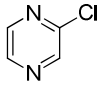
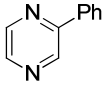
1.2.2 Investigation of the reaction scope

The use of 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 investigated their reactions with PhMgCl (**2a**) in *t*BuOMe at 23 °C. Since PhMgCl as well as all Grignard reagents, which we used, were prepared in THF, the cross-coupling reactions in fact performed in a mixture of THF and *t*BuOMe (ca 2:5).

Therefore, we observed that 2-bromopyridine (**1b**) reacted with PhMgCl (**2a**) at a faster rate for completion than 2-chloropyridine (**1a**) (70 min instead of 90 min) and produced **3a** in the same yield (83 %, entry 2 of Table 4). Substituted bromo- or chloro-pyridines such as 2-chloro-4-picoline (**1c**) and 2-bromo-5-chloropyridine (**1d**) reacted smoothly with similar reaction times leading to the pyridines **3b** and **3c** in 78 – 84 % yield (entries 3 and 4).

Table 4. Scope of iron-catalyzed cross-coupling of *N*-heteroarylchlorides/-bromides (**1a** – **j**) with PhMgCl (**2a**)

Entry[a]	**Substrate**	**Reaction time**	**Product**	**Yield (%)**[b]
				
1	**1a**: X = Cl	1.5 h	**3a**	82

2	**1b**: X = Br	70 min	**3a**	83
				
3	**1c**	2 h	**3b**	84
				
4	**1d**	70 min	**3c**	78
				
5	**1e**	5 min	**3d**	60
				
6	**1f**	5 min	**3e**	88
				
7	**1g**	5 min	**3f**	90
				
8	**1h**	2 h	**3g**	76
				
9	**1i**	5 h	**3h**	22[c]
				
10	**1j**	3 h	**3i**	24[c]

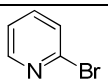
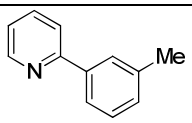
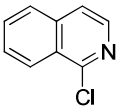
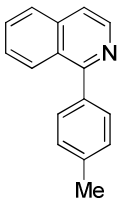
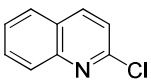
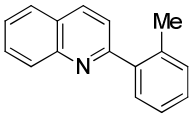
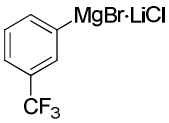
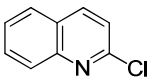
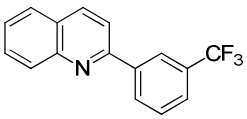
(a) The reaction was performed on a 1 mmol scale with 3 mol% of $FeBr_3$ in THF:*t*BuOMe (ca. 2:5) at room temperature. (b) Isolated yield. (c) GC-yield.

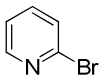
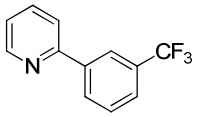
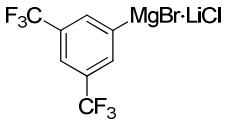
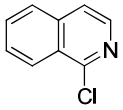
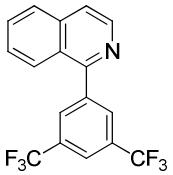
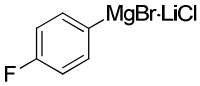
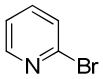
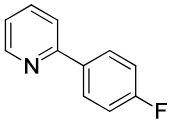
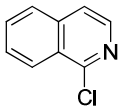
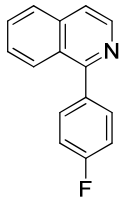
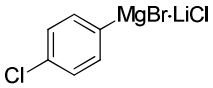
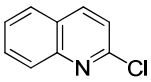
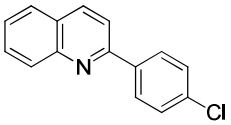
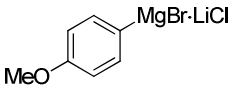
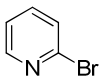
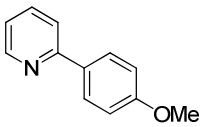
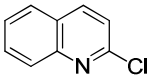
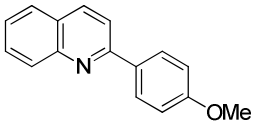
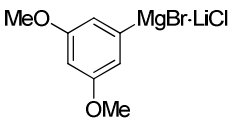
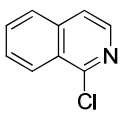
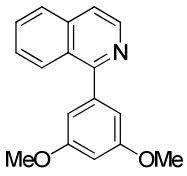
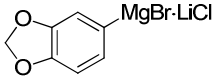
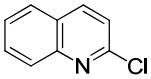
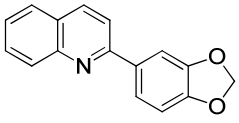
Interestingly, the presence of a *tert*-butoxycarbonyl group in position 3 (**1e**) dramatically increased the reaction rate leading to full conversion within 5 min (entry 5). The cross-coupling product **3d** was isolated in 60 % yield. No starting chloride **1e** was detected, and the relatively moderate yield may be due to a polymerization of **1e**. The annulation of the pyridine ring with a benzene moiety also accelerated the reaction rate, and the cross-coupling

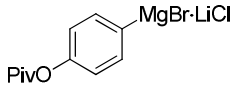
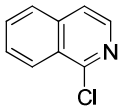
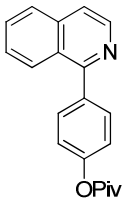
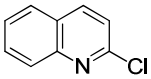
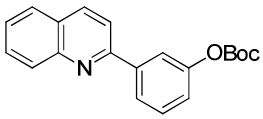
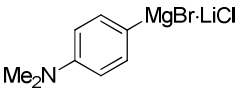
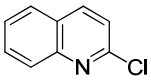
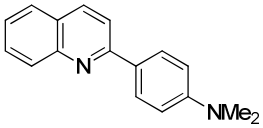
of PhMgCl (**2a**) with 2-chloroquinoline (**1f**) or 1-chloroisoquinoline (**1g**) were completed in 5 min and gave the expected phenylated *N*-heterocycles **3e** and **3f** in 88 – 90 % yield (entries 6 and 7). Diazines were also tested for cross-coupling reactions. For instance, 2-chloropyrimidine derivative **1h** reacted with PhMgCl (**2a**) within 2 h providing the arylated pyrimidine **3g** in 76 % yield (entry 8). The more sensitive chloropyridazine **1i** and –pyrazine **1j** required 3 - 5 h for the full conversion of starting material, but led to the phenylated products **3h - i** in only 22 – 24 % yields (entries 9 and 10). Unfortunately, the use of other heterocyclic halides, such as 3- and 4-chloropyridine, 2-chlorothiophene, or 2-bromofuran, as well as standard haloarenes resulted in only low yields.

Thereafter, we have varied the nature of the Grignard reagent, using typical *N*-heterocyclic chlorides and bromides (**1b**, **1f** and **1g**) as electrophiles (Table 5).

Table 5. Iron-catalyzed cross-coupling of *N*-heteroarylchlorides/-bromides **1b**, **1g** and **1f** with various Grignard reagents

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

			
5	**2e**	**1b**; 2 h	**3n**; 66%
			
6	**2f**	**1g**; 5 h	**3o**; 75%
			
7	**2g**	**1b**; 5 min	**3p**; 68%
			
8	**2g**	**1g**; 5 min	**3q**; 90%
			
9	**2h**	**1f**; 5 min	**3r**; 84%
			
10	**2i**	**1b**; 10 min	**3s**; 82%
			
11	**2i**	**1f**; 5 min	**3t**; 87%
			
12	**2j**	**1g**; 5 min	**3u**; 71%
			

13	**2k**	**1f**; 5min	**3v**; 81%
			
14	**2l**	**1g**; 15 min	**3w**; 80%
			
15	**2m**	**1f**; 15 min	**3x**; 84%
			
16	**2n**	**1f**; 5 min	**3y**; 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.

In all cases presented in Table 5, the Fe-catalyzed cross-couplings were relatively fast and led to full conversion of the starting material. Both electron-rich and -poor Grignard reagents could be tolerated. For steric hindrance reasons, we first examined the substitution pattern of the arylmagnesium reagent. We have found that *ortho*-, *meta*-, and *para*-substituted Grignard reagents can be applied. Whereas *m*-TolMgBr·LiCl (**2b**) and *p*-TolMgBr·LiCl (**2c**) react at similar rates as the unsubstituted magnesium reagent, the presence of an *ortho*-methyl substituents in *o*-TolMgBr·LiCl (**2d**) reduced the reaction rate (compare entry 3 of Table 5 with entry 6 of Table 4). However, in all cases excellent yields (80 – 93 %; entries 1 – 3 of Table 5) were obtained.

Various electron-poor substituted Grignard reagents were examined and proved to be applicable in this kind of transformation. Therefore, substituents such as a trifluoromethyl group (as in 3-trifluoromethyl-magnesium bromide **2e** and in 3,5-ditrifluoromethyl-magnesium bromide **2f**; entries 4-6), a fluorine group (as in 4-fluorophenylmagnesium bromide **2g**; entries 7 and 8), and a chlorine group (as in **2h**; entry 9) were well tolerated in the cross-coupling providing the desired products **3m** – **r** in 66 – 92 % yields (entries 4 – 9). Remarkably, electron-rich substituents were also compatible with rapid iron-catalyzed cross-couplings. Thus, methoxy-, methylenedioxy- as well as pivalate-functionalized Grignard reagents **2i** – **l** undergo cross-coupling reactions giving 71 – 87 % yields of the expected

products **3s - w** (entries 10 – 14 of Table 5). More sensitive Boc-protected Grignard reagent **2m** also smoothly underwent cross-coupling with 2-chloroquinoline (**1f**) leading to the 2-arylated quinoline **3x** in 84 % yield (entry 15).

We were interested to test the amino-substituted Grignard reagent due to its potential importance in the drug´s structures. We observed that a di-alkylated amino substituent did not disturb the cross-coupling, and the Grignard reagent **2n** reacted with **1f** within 5 min providing the product **3y** in 82 % yield (entry 16).

2. Ligand-Accelerated Iron- and Cobalt-Catalyzed Cross-Coupling between *N*-Heterocyclic Halides and Aryl Magnesium Reagents.

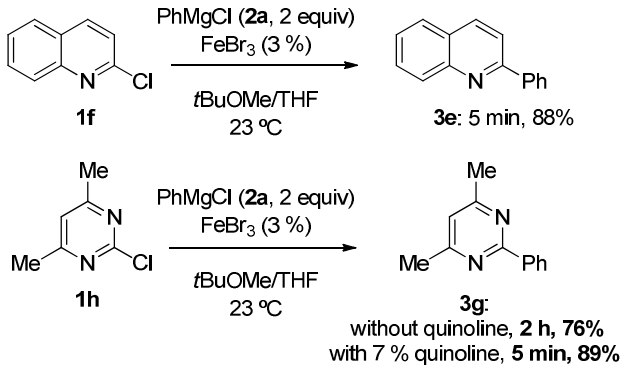
2.1 Introduction

In order to further optimize our reaction conditions, we looked more close at possible additives or ligands for iron-catalyzed cross-coupling between Csp^2-Csp^2 centers.

Nakamura and co-workers have shown that *N*-heterocyclic carbene (NHC) ligands can suppress the homo-coupling reaction to less than 5 %.[67] Although this is a large improvement, NHC ligands are expensive, and even optimized conditions, elevated temperatures and long reaction times are often required to complete the coupling reaction. Clearly, there is a need to discover new classes of ligands for Fe catalysis.

During the course of our work, we have made the serendipitous discovery that quinoline or isoquinoline could be used as ligands to promote Fe-catalyzed cross-coupling, improving both the yield and reaction rate. Moreover, these new ligand-accelerated cross-coupling reactions could be extended to Co catalysts.

Thus, cross-coupling of 2-chloroquinoline (**1f**) with PhMgCl (**2a**) in the presence of 3 % $FeBr_3$ in *t*BuOMe/THF was completed at 25 °C in 5 min (producing the phenylated product **3e** in 90 % yield; Scheme 47). Cross-coupling of the 2-chloropyrimidine **1h** under the same reaction conditions requires 2 h for completion and provides the arylated pyrimidine **3g** in 76 % yield.



Scheme 47. Rate acceleration and improved yield of Fe-catalyzed cross-coupling in the presence of quinoline

However, carrying out the same reaction in the presence of 7 % of quinoline leads to a reaction completion within 5 min (about 50 times faster) and an increased yield of **3g** (89 % yield of isolated product; Scheme 47).

2.2 Results and Discussion

Prompted by the rate acceleration effect observed with quinoline, we screened other ligands. We observed that NMP and TMEDA, which have been traditionally used for iron catalysis, had a detrimental effect under our conditions (compare entries 1-4 of Table 6).[29] 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 observed when a methyl group is placed at position 6 (entry 7)

Benzo[*h*]quinoline and acridine led even to a decrease in yield (entries 8 and 9). Remarkably, 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 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).

In 2002, Knochel and coworkers have shown that 4-fluorostyrene promotes Co-catalyzed coupling reactions.[95]

However, styrene had no effect (entry 20), and various substituted styrene derivatives caused only a moderate rate enhancement (entries 21-23).

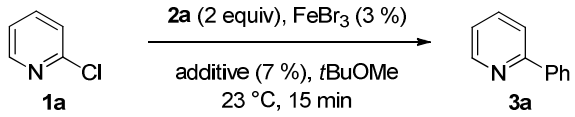
Additionally, the amount of isoquinoline was varied from 1-100% and it was found that 10% of the ligand was optimum. Pleasingly, isoquinoline (or quinoline) was not consumed during the cross-coupling according to the GC-analysis.

Using isoquinoline, we tested the ability of other metallic salts to undergo rate-enhanced cross-coupling reactions. In response to the current debate as to whether trace impurities of

[95] 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*, 18.

Cu in commercial samples of Fe salts can be the cause of catalytic activity,[96] $CuBr_2$ was tested and none to minimal activity was found (compare entries 1-2 with 3-4 of Table 7).

Table 6. Screening different additives for the Fe-catalyzed cross-coupling reaction of 2-chloropyridine (**1a**) with PhMgCl (**2a**)



Entry	Additive	Yield of 3a (%)[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

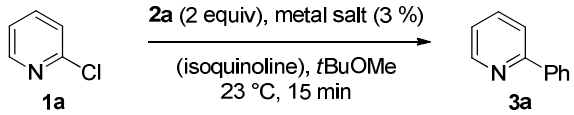
[96] For the role of metal contaminants in iron catalysis, see: a) Buchwald, S. L.; Bolm, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5586. (b) Larsson, P.-F.; Correa, A.; Carril, M.; Norrby, P.-O.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5691. (c) Thomé, I.; Nijs, A.; Bolm, C. *Chem. Soc. Rev.*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

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

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). Finally, we were pleased to find that isoquinoline can also be used as a ligand to accelerate Co-catalyzed reactions (entries 12 and 13 of Table 7).

Table 7. Performance of different transition metals with isoquinoline-promoted cross-coupling



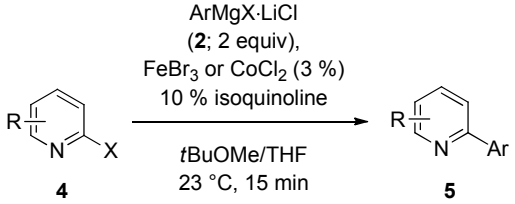
Entry	Metal salt	Isoquinoline (mol%)	Yield of 3a (%)[a]
1	$FeBr_3$	0	40
2	**$FeBr_3$**	**10**	**92 (89)[b]**
3	$CuBr_2$[c]	0	0
4	$CuBr_2$	10	2
5	$FeBr_3$ + $CuBr_2$	10	89
6	VCl_3	0	0
7	VCl_3	10	2
8	VCl_4	0	5
9	VCl_4	10	9
10	$MnCl_2$	0	28
11	$MnCl_2$	10	14
12	$CoCl_2$	0	46
13	**$CoCl_2$**	**10**	**90**

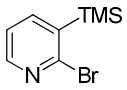
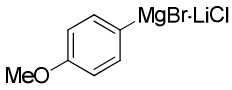
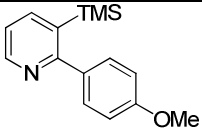
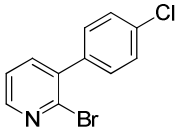
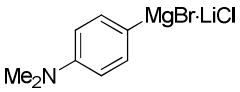
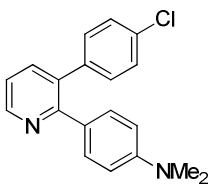
(a) Yield determined after 15 min by integration of a GC-chromatogram and comparison against undecane as a calibrated internal standard. (b) Isolated yield after purification by flash column chromatography. (c) Cu_2O was also used and gave the same results.

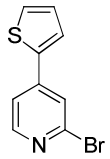
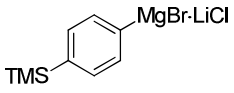
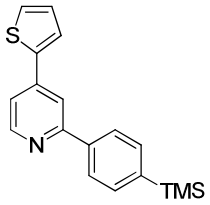
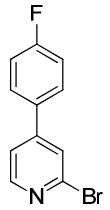
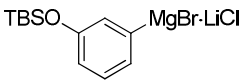
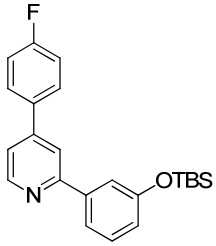
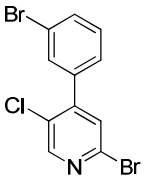
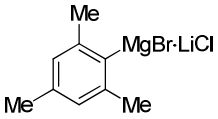
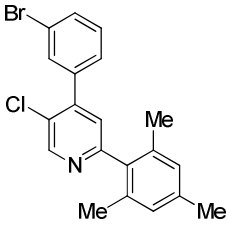
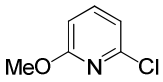
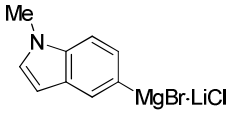
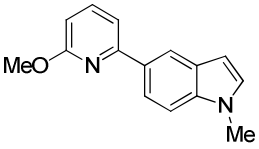
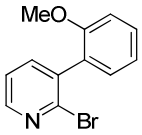
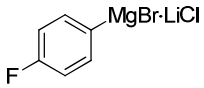
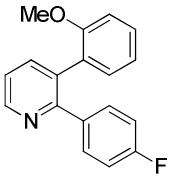
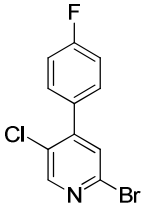
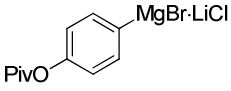
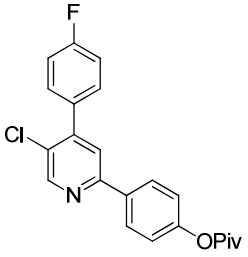
Since both Fe and Co had a similar activity, both of these transition metals were used, while exploring the scope of this new catalytic system.

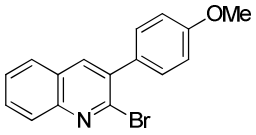
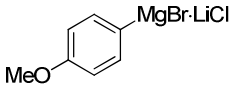
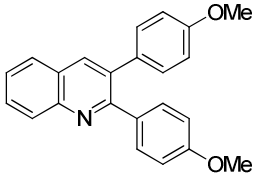
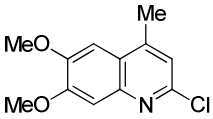
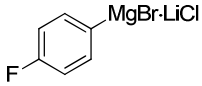
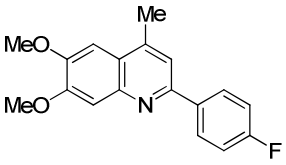
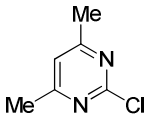
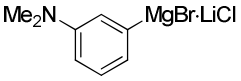
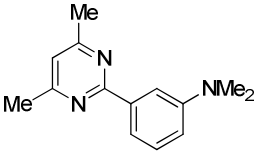
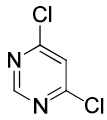
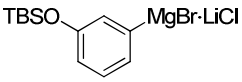
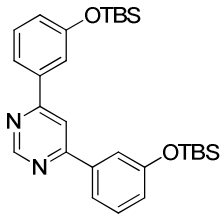
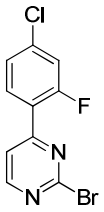
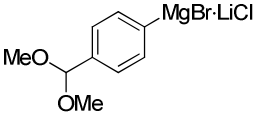
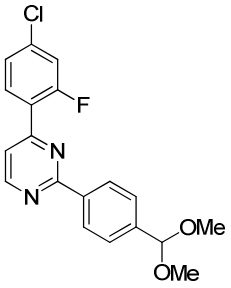
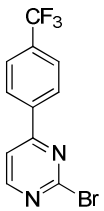
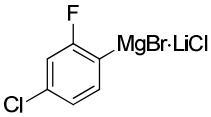
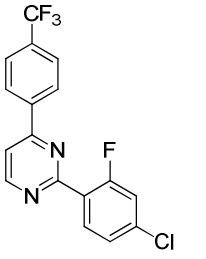
Using isoquinoline as a ligand (10 %), it is possible to obtain the expected cross-coupled products with a variety of chloro- or bromo-substituted pyridines as well as with a fair range of Grignard reagents. Good yields of the substituted pyridines **5a - f** (65 - 91 %) were obtained especially with electron-rich Grignard reagents (entries 1 - 6 of Table 8) as well as with electron-poor 4-fluorophenylmagnesium bromide **2g** to give pyridine **54g** (77 - 79 % yield, entry 7). It is possible to couple the polyfunctional pyridine **4h** with the sensitive ester-substituted Grignard compound **2l** to produce pyridine **5h** in 65 % yield (entry 8). Often both Co- and Fe-catalyzed couplings proceed with comparable yield, and it is difficult to propose that one metallic salt is a superior catalyst for all substrates. Pyrimidines, which are common motifs in pharmaceuticals, can be obtained from the same set of Grignard reagents to yield functionalized *N*-heterocycles **5k - n** 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 (**5o - r**) in 61 - 84 % yield (entries 15 - 18).

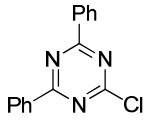
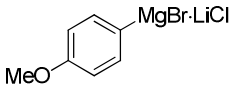
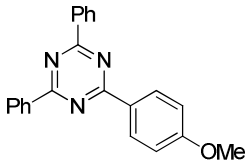
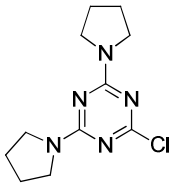
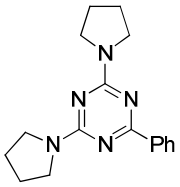
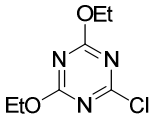
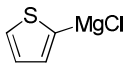
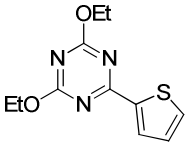
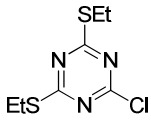
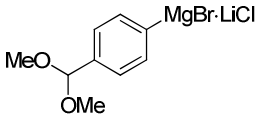
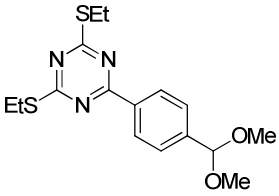
Table 8. Scope of Co- and Fe-catalyzed cross-coupling reactions utilizing isoquinoline as a ligand



Entry	Starting material	Grignard reagent	Product[a]
1	 **4a**	 **2i**	 **5a**; Fe: 91 % Co: 85 %
2	 **4b**	 **2n**	 **5b**; Fe: 82 %

				Co: 77 %
3		**4c**		**2o**		**5c**; Fe: 65 %
				Co: 70 %
4		**4d**		**2p**		**5d**; Fe: 71 %
				Co: 79 %
5[b]		**4e**		**2q**		**5e**; Co: 82 %
6[c]		**4f**		**2r**		**5f**; Co: 65 %
7		**4g**		**2g**		**5g**; Fe: 77 %
				Co: 79 %
						

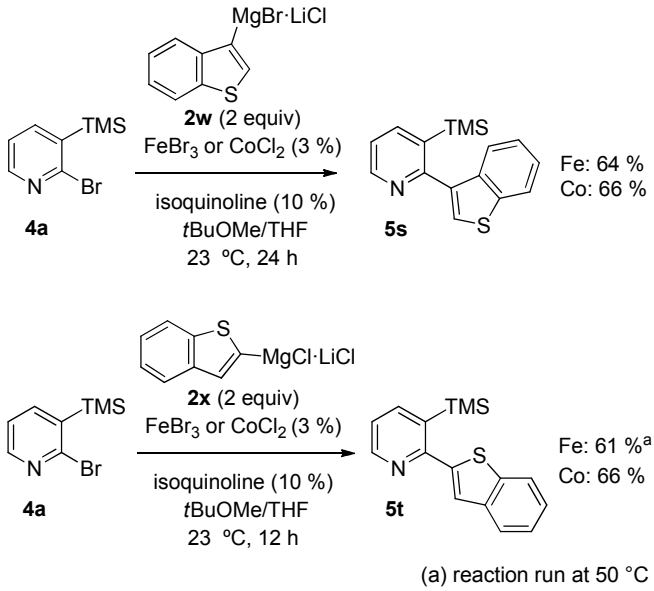
8	**4h**	**2l**	**5h**; Fe: 65 %
			
9	**4i**	**2i**	**5i**; Co: 78 %
			
10	**4j**	**2g**	**5j**; Fe: 82 % Co: 67 %
			
11[d]	**1h**	**2s**	**5k**; Fe: 78 % Co: 63 %
			
12[e]	**4k**	**2p**	**5l**; Fe: 95 %
			
13	**4l**	**2t**	**5m**; Co: 68 %
			
14	**4m**	**2u**	**5n**; Fe: 61% Co: 60 %

15	 **4n**	 **2i**	 **5o**; Fe: 81 % Co: 79 %
16[f]	 **4o**	**2a**	 **5p**; Fe: 76 %
17[g]	 **4p**	 **2v**	 **5q;** Fe: 84 % Co: 79 %
18	 **4q**	 **2t**	 **5r;** Fe: 61 %

(a) Isolated yield after purification by flash column chromatography. (b) Reaction run at 23 °C for 5 h. (c) Reaction run at 23 °C for 1 h. d) Reaction run at 23 °C for 30 min. (e) 4 equivalent of **2p** were used. (f) Reaction run at 50 °C for 12 h. (g) Reaction run at 23 °C for 12 h.

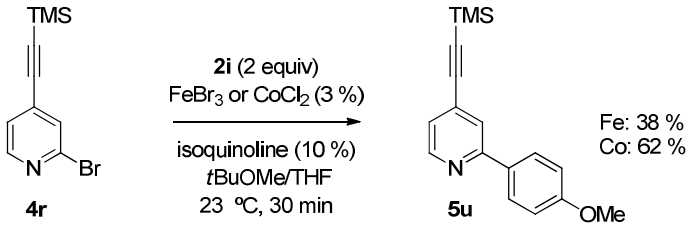
The synthesis of heteroaryl-heteroaryl coupling products is often challenging. In the case of Pd- or Ni-catalysis, deactivation of the catalyst is observed due to chelation of the product with the catalyst.[97] However, it was noted that both Fe- and Co-catalysts promoted by 10 % isoquinoline allow smooth cross-couplings with either the 3-magnesiated benzothiophene **2w** or the 2-magnesiated heterocycle **2x** to afford heterobyaryls **5s** and **5t** in 61 - 66 % isolated yield (Scheme 48).

[97] 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 48. Heteroaryl-heteroaryl cross-coupling reactions between bromopyridine **4a** and benzothiophenes **2w** and **2x**

Delicate functional groups, such as alkynes, which could undergo carbometallation under iron catalysis,[98] provide poor yields of the desired product. Nevertheless, we observed that the use of 3 % $CoCl_2$ and 10 % isoquinoline improved the yield and allows the isolation of pyridine **5u** in 62 % yield (Scheme 49).



Scheme 49. Cross-coupling reactions of acetylene-containing pyridines

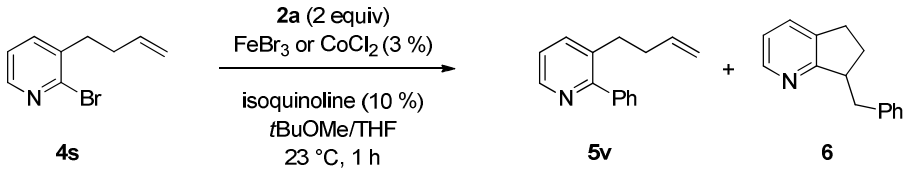
To probe the mechanism of Fe- and Co-catalyzed cross-coupling reactions, we prepared the radical clock **4s**.[99] Treatment of this unsaturated pyridine **4s** with PhMgCl (**2a**), using either

[98] 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.

[99] 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.*

$FeBr_3$ or $CoCl_2$, produces a 4:1 mixture of the expected cross-coupling product **5v** and the cyclized pyridine **6** indicative of a radical intermediate. The addition of isoquinoline did not change the product ratio, but as expected, it improved the yields (compare entries 1-4 of Table 9). 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 the cyclized product.

Table 9. Scope of Co- and Fe-catalyzed cross-coupling reactions utilizing isoquinoline as a ligand



4s **5v** **6**

Entry	Catalyst	5v:6	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.

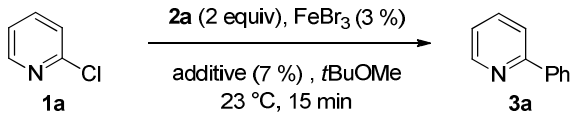
In spite of remarkable results, which we obtained using isoquinoline in Fe- and Co-catalyzed coupling reactions, we aimed to further optimize the reaction conditions. Therefore, we went on with our hunt for appropriate ligands using coupling between 2-chloropyridine (**1a**) and PhMgCl (**2a**) as a standard reaction.

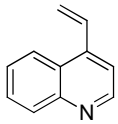
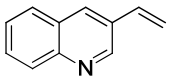
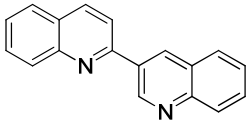
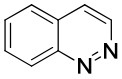
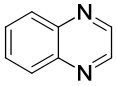
First of all, we tested various quinoline derivatives. Vinyl-substituted quinolines did not have any effect (entries 2 and 3 of Table 10). 2,3´-Biquinoline (**7c**) provided no improvement and even slowed down the reaction (17 % yield after 15 min; entry 4). Polycyclic compounds

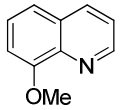
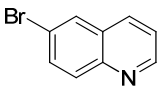
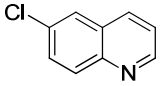
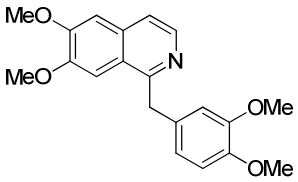
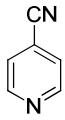
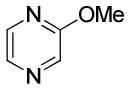
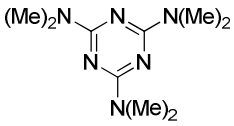
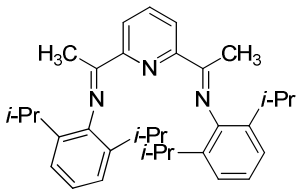
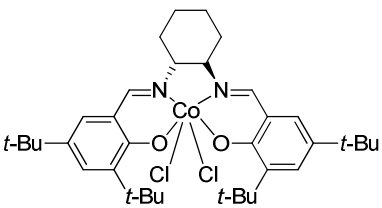
Int. Ed. **2009**, *48*, 205; d) Guisán-Ceinos, M.; Tato, F.; Bunuel, E.; Calle, P.; Cárdenas, D. J. *Chem. Sci.* **2013**, *4*, 109

contained two nitrogens, such as cinnoline (**7d**) and quinoxaline (**7e**) hampered the reaction (entries 5 and 6). The quinoline derivative having a methoxy group in position eight (**7f**) demonstrated no acceleration effect (entry 7). 6-Chloroquinoline (**7g**) slightly promoted the reaction (58 % yield; entry 9), whereas 6-bromoquinoline (**7h**) gave a good yield already after 15 min (73 % yield; entries 8). Previously we observed that quinoline having a methoxy group in position six resulted in a positive effect. However, papaverin (**7i**) led to only 59 % GC-Yield of cross-coupling product **3a** (entry 10). Various six-membered ring *N*-heterocycles **7j – l** demonstrated moderate activity (entries 11 – 13).

Table 10. Screening different additives for the Fe-catalyzed cross-coupling reaction of 2-chloropyridine (**1a**) with PhMgCl (**2a**)

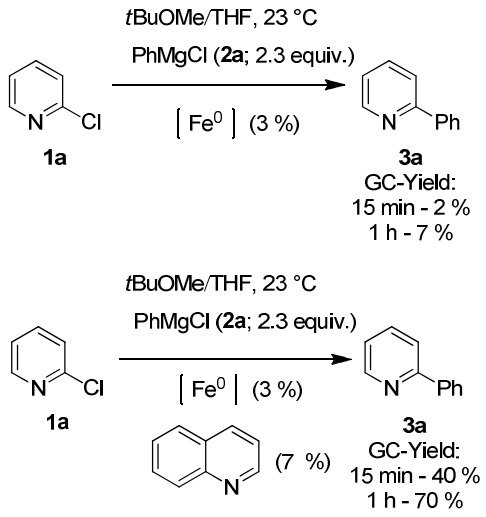


Entry	Additive	Additive Number	Time, h	GC-Yield of 3a (%)
1	without additive		15 min	40
			1.5 h	78
2		**7a**	15 min	43
			1.5 h	70
3		**7b**	15 min	38
			1.5 h	63
4		**7c**	15 min	17
			1.5 h	61
5		**7d**	15 min	18
			1.5 h	33
6		**7e**	15 min	14
			1.5 h	35

7		**7f**	15 min 1.5 h	40 69
8		**7h**	15 min 1.5 h	73 74
9		**7g**	15 min 1.5 h	58 76
10		**7i**	15 min 1.5 h	59 62
11		**7j**	15 min 1.5 h	66 67
12		**7k**	15 min 1.5 h	22 61
13		**7l**	15 min 1.5 h	60 71
14		**7m**	15 min 1.5 h	35 62
15		**7n**	15 min 1.5 h	19 40

Bis(imino)pyridine ligand **7m** is often used for iron-catalyzed polymerization[100] reactions or as hydrogenation and hydrosilylation catalyst.[101] Recently, it has been also used in regioselective syntheses of α-aryl carboxylic acids. [102] Nevertheless, in our cross-coupling reaction this ligand **7m** did not show any activity (entry 14). The tetradentate amine complex with Co **7n**, hampered the reaction between 2-chloropyridine (**1a**) and PhMgCl (**2a**) (entry 15).[103]

Based on this small screenshot of all tested ligands, the following trend could be highlighted. The quinoline or isoquinoline core seemed to be the most reactive in this kind of coupling reactions. Electron-donating substituents of quinoline showed better results than electron-withdrawing ones. The second positions of quinoline should not have any residues besides hydrogen. A positive trend was observed when the electron-rich groups were placed in the sixth position of quinoline. Finally, chelating ligands disprove their activity in this kind of coupling reactions, probably due to aggregation and therefore deactivation of the iron catalyst.



Scheme 50. Positive effect of quinoline for reduced iron-species

[100] a) Britovsek, G. J. P.; Gibson, V. C.; Kimberley, B. S.; Maddox, P. J.; McTavish, S. J.; Solan, G. A.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1998**, 849; b) Small, B. L.; Brookhart, M.; Bennett, A. M. A. *J. Am. Chem. Soc.* **1998**, *120*, 4049.
[101] a) Bart, S. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13794. b) Tondreau, A. M.; Atienza, C. C. H.; Weller, K. J.; Nye, S. A.; Lewis, K. M.; Delis, J. G. P.; Chirik, P. J. *Science* **2012**, *335*, 567.
[102] Greenhalgh, M. D.; Thomas, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 11900.
[103] This salen ligand was previously used for the reductive cross-coupling of vinyl halides and Grignard reagents Le Bailly, B. A. F.; Greenhalgh, M. D.; Thomas, S. P. *Chem. Commun.* **2012**, *48*, 1580.

Bedford and coworkers described the catalytic activity of iron nano-particles in cross-coupling reactions. Therefore, we aimed to investigate reduced iron(0)-species in the coupling reaction between *N*-heterocyclic halides and aromatic Grignard reagents. Iron(0)-species, produced via *in situ* reduction of $FeBr_3$ with *n*BuLi showed no catalytic activity in reaction between 2-chloropyridine (**1a**) and PhMgCl (**2a**). The addition of 7 % of quinoline to this reaction significantly improved this reaction, yielding the desired product **3a** in 70 % (GC-Yield) after 1 h reaction time. It can be concluded that quinoline forms catalytically active species with *in situ* reduced iron(0) (Scheme 50).

3. Efficient Chromium(II)-Catalyzed Cross-Coupling Reactions

3.1 Introduction

On the way of our search for alternative metal catalysts having an acceptably low toxicity, we have examined the potential use of chromium salts.[104]

Palladium and nickel-catalyzed cross-coupling reactions between aromatic and heteroaromatic groups are well established and have many applications.[105] 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 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.[106]

3.2 Results and Discussion

Preliminary experiments showed that chromium-catalyzed cross-couplings between Csp^2-centers proceed quite smoothly and lead to significantly lower amounts of homo-coupled side-products compared to iron or cobalt. Thus, the reaction of 2-chloropyridine (**1a**, 1.0 equiv) with PhMgCl (**2a**, 2.3 equiv) in THF in the presence of 3 % $CrCl_2$ (purity 99.99 %) is complete within 15 min at 23 °C, affording the desired cross-coupled product **3a** in 90% yield. GC-analysis of the crude reaction mixture indicated that less than 1 % of the homo-coupling product (biphenyl) is obtained (Scheme 51). Performing the same reaction with 3 % $FeBr_3$ or 3 % $CoCl_2$ under optimized conditions leads to about 15 % of the homo-coupled

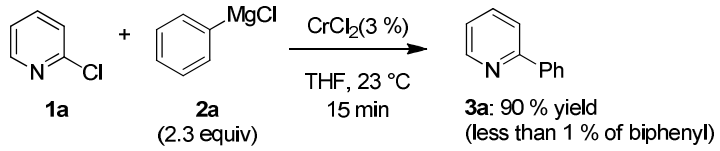
[104] For key coupling reactions using chromium(II) salts, see: a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179; b) Okude, Y.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1977**, 3829; c) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron 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.

[105] a) *Cross-Coupling Reactions. A Practical Guide*; Miyara, N., Ed.; Springer: Berlin, **2002**; b) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**; c) *Organotrasition Metal Chemistry*; Harwig, J. F., Ed.; University Scienca Books: Sausalito, CA, **2010**.

[106] according to IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung; July 2013).

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 **3a**[107] compared to 90 % yield obtained with 3 % $CrCl_2$.

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 11). PhMgCl (**2a**) also undergoes a smooth cross-coupling with 2-bromo-3-(but-3-en-1-yl)pyridine (**4s**; 23 °C 15 min), leading to the 2,3-disubstituted pyridine **5v** in 95 % yield (entry 1). Interestingly, no radical cyclization product is observed in this cross-coupling (similar iron and cobalt cross-couplings produce 20 % of the radical cyclization product). Both electron-rich and electron-poor Grignard reagents can be used for such cross-couplings. Thus, the sterically hindered bromo-pyridine **4b** reacts with 4-*N*,*N*-dimethyl-aminophenylmagnesium bromide (**2n**) within 1.5 h at 23 °C, producing the 2,3-diarylated pyridine **5b** (80 % yield; entry 2).



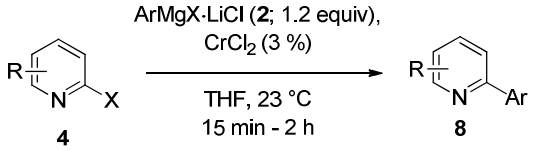
Scheme 51. Chromium-catalyzed cross-coupling between 2-chloropyridine (**1a**) and PhMgCl (**2a**)

Also, the electron-poor Grignard reagent **2y** reacts with 2-bromo-3-chloropyridine (**4t**) in 15 min at 23 °C, leading to the pyridine **8a** in 76 % yield (entry 3). A similar cross-coupling performed with 3 % of $FeBr_3$ gives only traces of product and significant amounts of homo-coupling. 2-Chloro-5-fluoropyridine (**4u**) also undergoes the cross-coupling reaction with the sensitive ester-substituted Grignard reagent **2l** to give the pyridine **8b** in 66 % yield (entry 4). Further *N*-heterocyclic halides such as the 2-chloroquinoline **4j** and the 4-chloroquinoline **4v**, react well with Grignard reagents **2k** and **2n**, affording the expected products **8c** and **8d** (74 - 78 %; entries 5 and 6). In contrast, the corresponding iron-catalyzed cross-coupling with the 4-chloroquinoline **4v** fails, indicating that this Cr(II)-catalyzed cross-coupling may have a

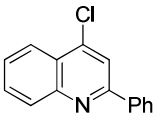
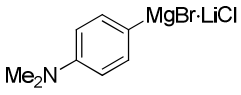
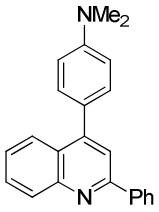
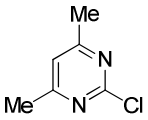
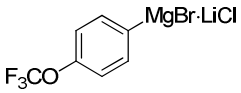
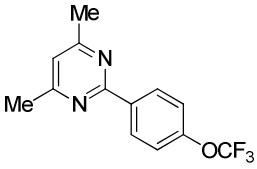
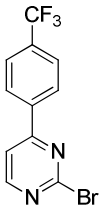
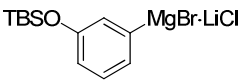
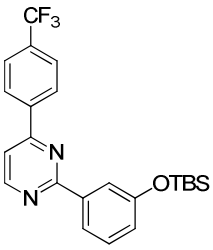
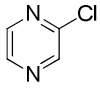
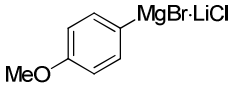
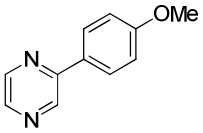
[107] Rueping, M.; Ieawsuwan, W. *Synlett* **2007**, 247.

broader reaction scope than the corresponding Fe- and Co-catalyzed cross-couplings. Halogenated diazenes, such as the 2-chloropyrimidines **1h** and **4m** as well as the 2-chloropyrazine **1j**, rapidly react with the magnesium organometallics **2z**, **2p** and **2i** to provide the substituted diazenes **8e**-**g** (71 - 85 %; entries 7 - 9).

Table 11. Room-temperature Cr-catalyzed cross-coupling reactions between *N*-heterocyclic halides and arylmagnesium reagents

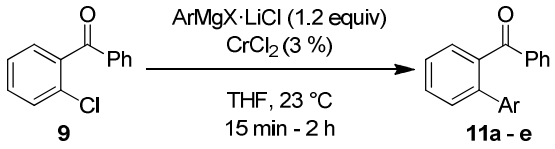


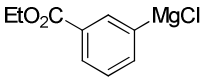
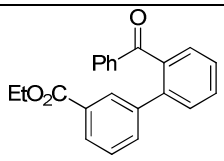
Entry	Starting material	Grignard reagent	Product[a]
1	**4s**	**2a**	**5v**; 95 %; 15 min
2	**4b**	**2n**	**5b**; 80 %; 90 min
3	**4t**	**2y**	**8a**; 76 %; 15 min
4	**4u**	**2l**	**8b**; 66 %; 15 min
5	**4j**	**2k**	**8c**; 74 %; 1 h

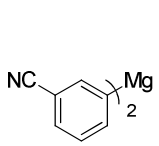
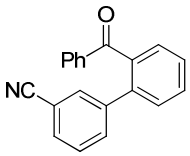
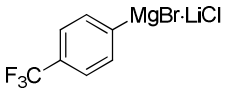
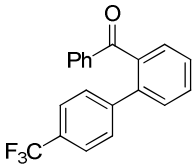
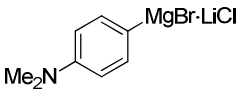
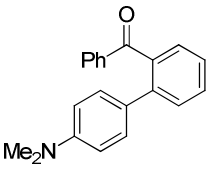
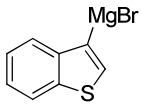
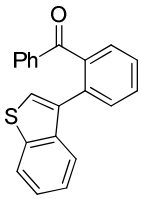
			
6	**4v**	**2n**	**8d**; 78 %; 15 min
			
7	**1h**	**2z**	**8e**; 71 %; 2 h
			
8	**4m**	**2p**	**8f**; 85 %; 15 min
			
9	**1j**	**2i**	**8g**; 72 %; 30 min

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

Table 12. Cr-catalyzed cross-coupling reactions between 2-chlorobenzophenone (**9**) and phenylmagnesium reagents



Entry	Grignard reagent	Product	Yield[a]
			
1	**10a**	**11a**	79 %; 15 min

2[b]	 **10b**	 **11b**	71 %; 2 h
3	 **2y**	 **11c**	93 %; 15 min
4	 **2n**	 **11d**	94 %; 15 min
5[c]	 **2w**	 **11e**	89 %; 2 h

(a) Isolated yields after purification by flash column chromatography. (b) 0.7 equiv of **10b** were used. (c) Reaction run at 50 °C for 2 h.

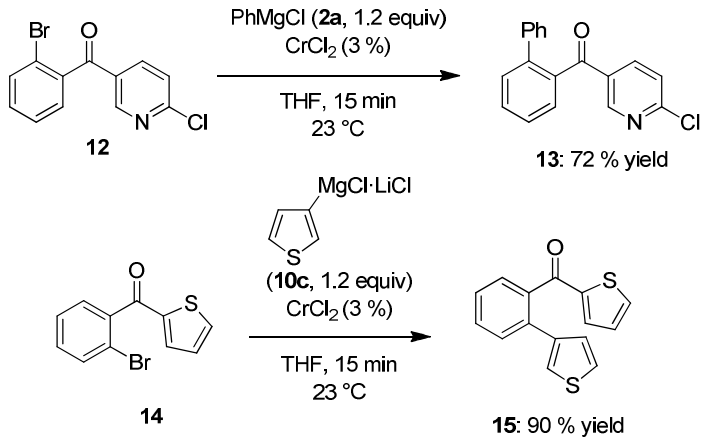
Remarkably, 2-halogenated aromatic ketones also undergo the chromium-catalyzed cross-coupling at room temperature within 15 min to 2 h (Table 12).[108] Thus, 2-chlorobenzophenone (**9**) reacts with a range of aryl- and heteroaryl-magnesium reagents (**2n**, **2w**, **2y**, **10a**, **10b**) yielding the corresponding polyfunctional ketones **11a-e** (71-94%; entries 1-5 of Table 12).

Interestingly, the (2-bromophenyl)(6-chloropyridin-3-yl)-methanone (**12**) reacts with the Grignard reagent **2a** with complete regioselectivity (no chloride-substitution occurs) and gives the pyridyl ketone **13** in 72% yield (Scheme 52). Heterocyclic ketones, such as **14**, also couple well with 3-thienylmagnesium chloride **10b** affording the new ketone **15** in 90% yield (Scheme 52). These reactions show a remarkable functional group tolerance, since ester,

[108] 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.

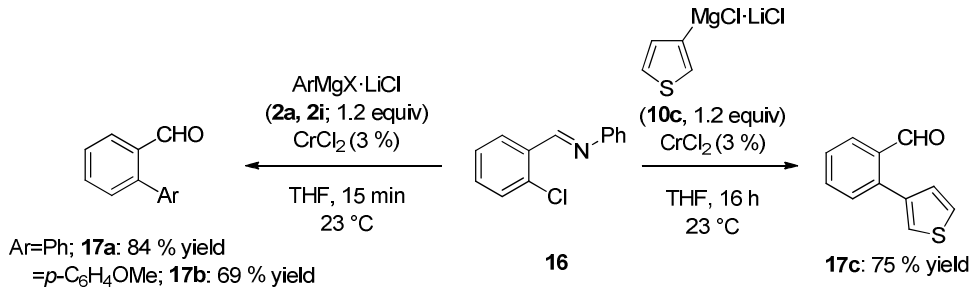
nitriles and ketones are compatible with this Cr-catalyzed cross-coupling. Interestingly, the imine-protected 2-chlorobenzaldehyde **16** reacts readily with various Grignard reagents (**2a**, **2i**, **10c**) at 23 °C, which after acidic work-up provides the aldehydes **17a-c** in 69-84% yield (Scheme 53).

The presence of the sulfur-containing Grignard reagent **10c** considerably extends the reaction-rate and a 16 h reaction time is required to complete the cross-coupling leading to **17c**.



Scheme 52. Cr-catalyzed cross-coupling reactions between heteroaryl-substituted ketones and Grignard reagents

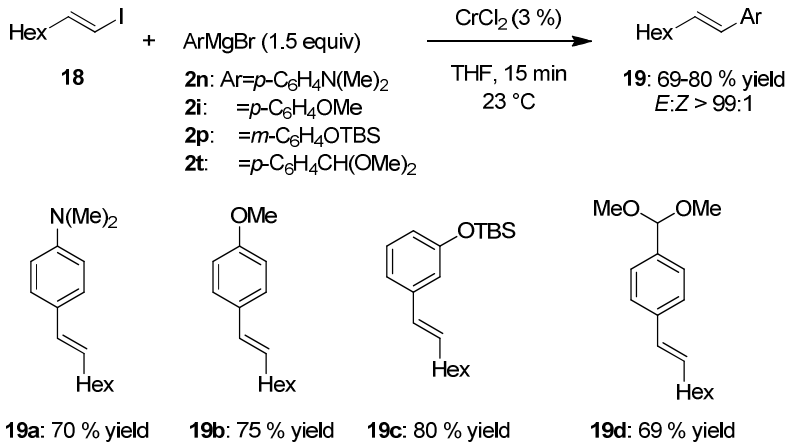
Thus, this cross-coupling constitutes a simple way for functionalizing aromatic aldehydes in the *ortho*-position.



Scheme 53. Cr-catalyzed cross-coupling reactions between imine-protected aldehyde **16** and Grignard reagent

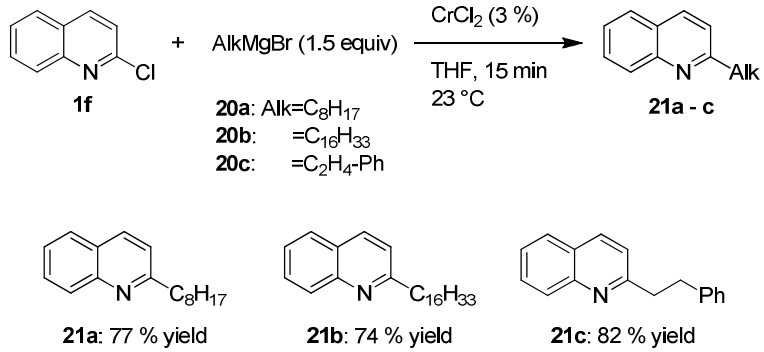
Alkenyl iodides, such as **18**, also undergo a fast stereoselective chromium-catalyzed arylation with a range of Grignard reagents (**2i, 2n, 2p, 2t**), affording in all cases the functionalized

styrenes **19a-d** in 69 - 80% yield with an *E*:*Z* ratio better than 99:1. Remarkably, all reactions were performed at 23 °C and were completed within 15 min (Scheme 54).



Scheme 54. Cr-catalyzed cross-coupling reactions between alkenyl iodide **18** and Grignard reagents

Furthermore, such chromium(II)-catalyzed cross-coupling reactions could be performed using alkyl Grignard reagents (Scheme 55). 2-Chloroquinoline (**1f**) reacts with alkylmagnesium reagents **20a** – **c** affording after 15 min at 23 °C alkylated heterocycles **21a** – **c** in 74 – 82 % yield.



Scheme 55. Cr-catalyzed cross-coupling reactions of 2-chloroquinoline (**1f**) with alkyl Grignard reagents

4. Room-Temperature Chromium(II)-Catalyzed Direct Arylation of Pyridines, Aryl Oxazolines and Imines

4.1 Introduction

The formation of C-C bond involving a transition-metal catalyzed C-H activation has been widely developed in recent years.[76] A range of transition metals such as Pd, Ru, Rh,[77-79] Co and Fe catalyze these cross-couplings. Iron-catalysts and to some extend cobalt-catalysts are of special interest due to the moderate price of these metals. Iron salts are furthermore of low toxicity and the pioneering work of Nakamura and Yoshikai has attracted much attention.[80-86] Although very attractive, the large amounts of Grignard reagents required to reach full conversion, long reaction times[87,93] and the addition of appropriate ligands (such as *cis*-1,2-bis(diphenylphosphino)ethylene, 1,10-phenantroline, 4,4´-di-*tert*-2,2´-bipyridiyl or *N*-heterocyclic carbenes)[80,87-89,91] are drawbacks and improvements are still desirable. Preliminary experiments showed that $CrCl_2$ is an excellent catalyst for performing cross-couplings between aryl or heteroaryl halides and Grignard reagents.[109]

The key feature of this cross-coupling is the very small amount of the homo-coupling product formed, implying that almost no excess of Grignard reagent is required. Furthermore, these chromium(II)-catalyzed cross-couplings are very fast reactions. In this context it was of interest to examine directed C-H bond activation reactions involving $CrCl_2$. This Cr-catalyzed directed arylation could be performed with *N*-heterocyles, [77b,77d,78c,78e,80,82,85,87] aryl oxazolines[78c,78e] and aryl imines.[84,86,88-89,92]

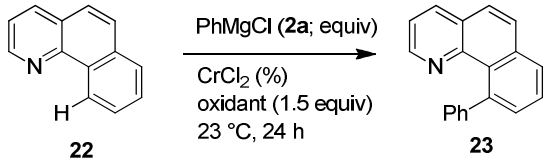
4.2 Results and Discussion

The optimization of the reaction conditions was done using the reaction of the benzo[*h*]quinoline (**22**) with PhMgBr (**2a**, 1.5 – 4 equiv.) with catalytic amounts of $CrCl_2$ and an oxidant at 23 °C for 24 h (Table 13). In the absence of the $CrCl_2$-catalyst, no 10-phenylbenzo[*h*]quinoline (**23**) is formed (entry 1). The use of 5 mol % of $CrCl_2$ (99.99 %

[109] Steib, A. K.; Kuzmina, O. M.; Fernandez, S.; Flubacher, D.; Knochel P. *J. Am. Chem. Soc.* **2013**, *135*, 15346-15349.

pure) led to the desired phenylated product **23** in 57 % yield, using 2,3-dichlorobutane (DCB) (entry 2). Using 10 mol % of $CrCl_2$ increased the yield of **23** to 98 % (calibrated GC-yield) (entry 3). Lowering the amount of Grignard reagent to 1.5 equiv or 2.5 equiv (instead of 4 equiv) decreased the yield to 19 % and 63 %, respectively (entries 4 and 5). Changing the nature of the oxidant (from DCB to 1,2-dichloroethane or 1,2-dichloro-2-methylpropane) led to lower yields (45 – 87 %; entries 6 and 7). In the absence of an oxidant, only 10 % of product **23** was observed (entry 8 of Table 13).

Table 13. Optimization of the conditions for reaction of benzo[*h*]quinoline (**22**) with PhMgBr (**2a**) catalyzed by $CrCl_2$



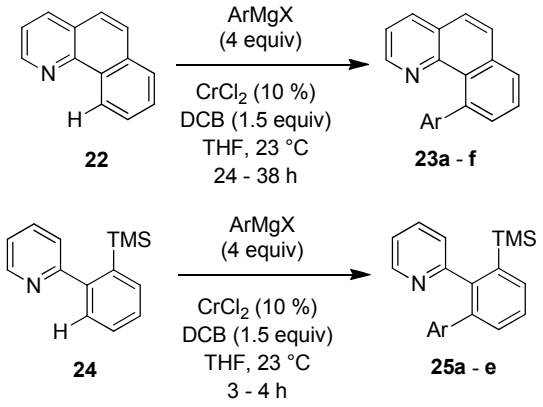
Entry	$CrCl_2$ (%)	PhMgBr (2a) (equiv)	Oxidant (1.5 equiv)	Yield of 23 (%)[a]
1	0	4	DCB	0
2	5	4	DCB	57
3	10	4	DCB	98 (95) [b]
4	10	1.5	DCB	19
5	10	2.5	DCB	63
6	10	4	1,2-dichloroethane	45
7	10	4	1,2-dichloro-2-methylpropane	87
8	10	4	without	10

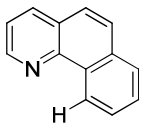
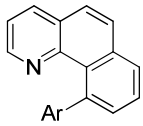
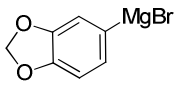
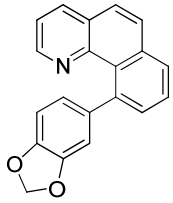
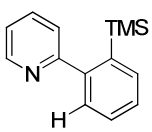
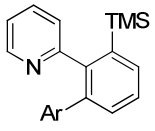
(a) Yield determined after 24 h by integration of a GC-chromatogram and comparison against undecane as a calibrated internal standard. (b) Yield of isolated product after purification by flash column chromatography.

Treatment of benzo[*h*]quinoline (**22**) with PhMgBr (**2a**; 4 equiv) with the optimized conditions provides the arylated heterocycle **23** in 95 % isolated yield (entry 3 of Table 13). Similarly other arylmagnesium reagents either donor or acceptor undergo a high yield arylation at position 10 furnishing the arylated benzo[*h*]quinolines **23b** - **f** in 66 - 90 % yield

(Table 14). Using the same conditions, it was also possible to arylate the 2-(2-trimethylsilylphenyl)pyridine (**24**) with various arylmagnesium reagents affording the expected pyridines **25a-e** in 79 - 92 % yield. Interestingly, these chromium(II)-catalyzed arylations proceed within a few hours at 23 ºC (Table 14).

Table 14. Chromium-catalyzed arylation of benzo[*h*]quinoline (**22**) and 2-(2-trimethylsilylphenyl)pyridine (**24**)

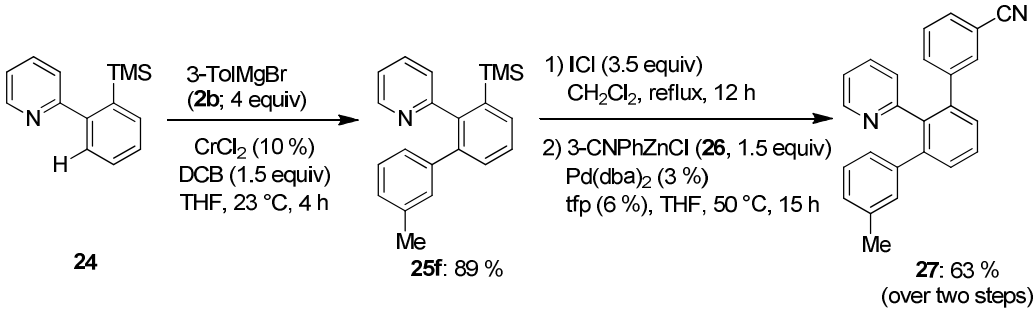


Entry	Substrate	ArMgX	Reaction Time (h)	Product; Yield (%)[a]
				
1	**22**	PhMgBr (**2a**)	24	**23a**: Ar = Ph; 95 %
2	**22**	3-MeO-C_6H_4MgBr (**10d**)	24	**23b**: Ar = 3-MeO-C_6H_4; 90 %
3	**22**	4- Me_2N-C_6H_4MgBr (**2n**)	24	**23c**: Ar = 4-Me_2N-C_6H_4; 87 %
				
4	**22**	**2k**	24	**23d**: 67 %
5	**22**	4- F_3C-C_6H_4MgBr (**2y**)	38	**23e**: Ar = 4-F_3C-C_6H_4; 66 %
6	**22**	4-F-C_6H_4MgBr (**2g**)	24	**23f**: Ar = 4-F-C_6H_4; 86 %
				

7	**24**	PhMgBr (**2a**)	3	**25a**: Ar = Ph; 92 %
8	**24**	3-MeO-C_6H_4MgBr (**10d**)	3	**25b**: Ar = 3-MeO-C_6H_4; 79 %
9	**24**	4- Me_2N-C_6H_4MgBr (**2u**)	4	**25c**: Ar = 4-Me_2N-C_6H_4; 85 %
11	**24**	3-OTBS-C_6H_4MgBr (**2p**)	3	**25d**: Ar = 3-OTBS-C_6H_4; 83 %
12	**24**	4-F-C_6H_4MgBr (**2g**)	3	**25e**: Ar = 4-F-C_6H_4; 84 %

(a) Yield of the isolated product after purification by flash column chromatography.

The role of the TMS-group (TMS = trimethylsilyl) at position 2 is to avoid double arylation. Interestingly, this group can be further used to introduce a second different aryl substituent as shown in Scheme 49. Thus, the treatment of **24** with 3-tolylmagnesium bromide (**2b**) in the presence of 10 % $CrCl_2$ and DCB (1.5 equiv) afforded the arylated product **25f** in 89 % yield. Treatment with ICl in refluxing CH_2Cl_2 (12 h), followed by Negishi cross-coupling[110] with the cyano-substituted phenylzinc derivative **26** in the presence of 3 % $Pd(dba)_2$ (dba = dibenzylideneacetone) and 6 % tfp (tri(2-furyl)phosphine) at 50 ºC for 15 h furnishes the bis-arylated pyridine **27** in 63 % yield over two steps (Scheme 56).

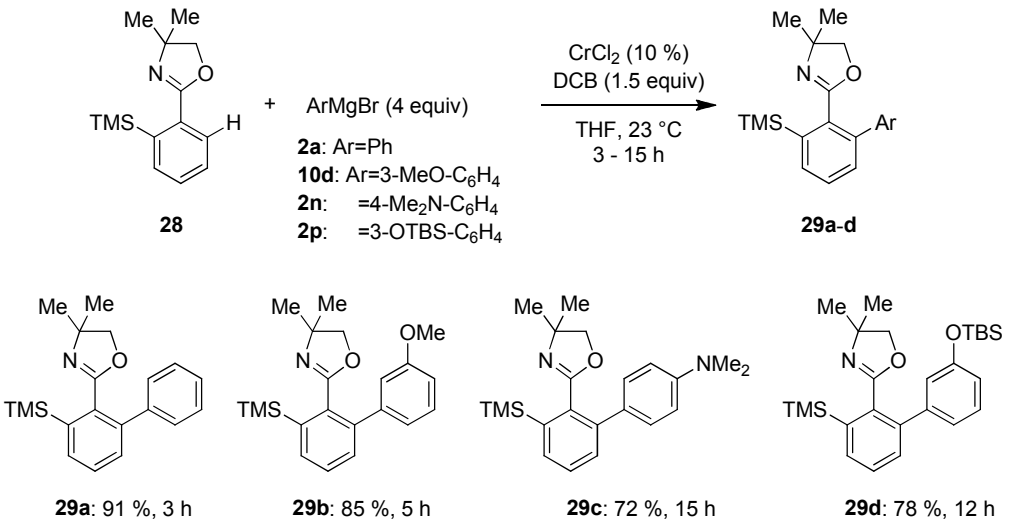


Scheme 56. Selective bis-arylation of the phenylpyridine **24** using chromium and palladium catalysts

The oxazoline directing group is a very popular group for directed C-H bond activation. Using the 2-TMS-phenyl oxazoline **28**, we have achieved an efficient C-H activation and arylation with various Grignard reagents as shown in Scheme 57. Functional groups such as methoxy,

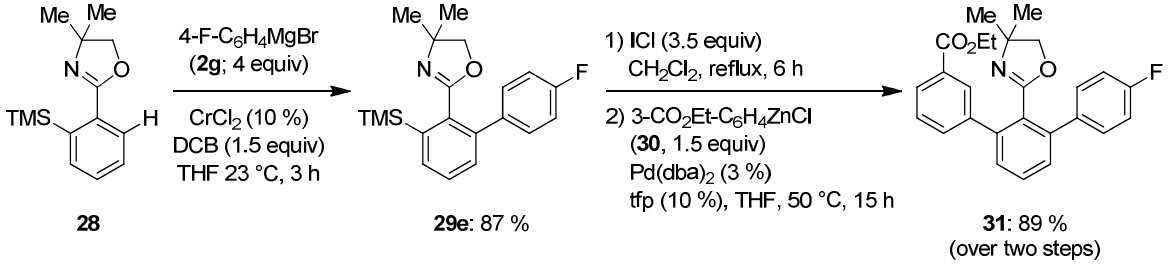
[110] (a) Negishi, E.-I. Metal-Catalyzed Cross-Coupling Reactions (Eds.: Diederich, F.; Stang, P. J.) Woley, New York, 1998, chap. 1; (b) Negishi, E.-i.; Valente, L. F.; Kobayashi, M. *Am. Chem. Soc.* **1980**, *102*, 3298; (c) Negishi, E.-I. *Acc. Chem. Res.* **1982**, *15*, 340.

dimethylamino or TBS-protected alcohol could be tolerated well and the arylated oxazolines **29a** – **d** were synthesized in 72 – 91 % yield.



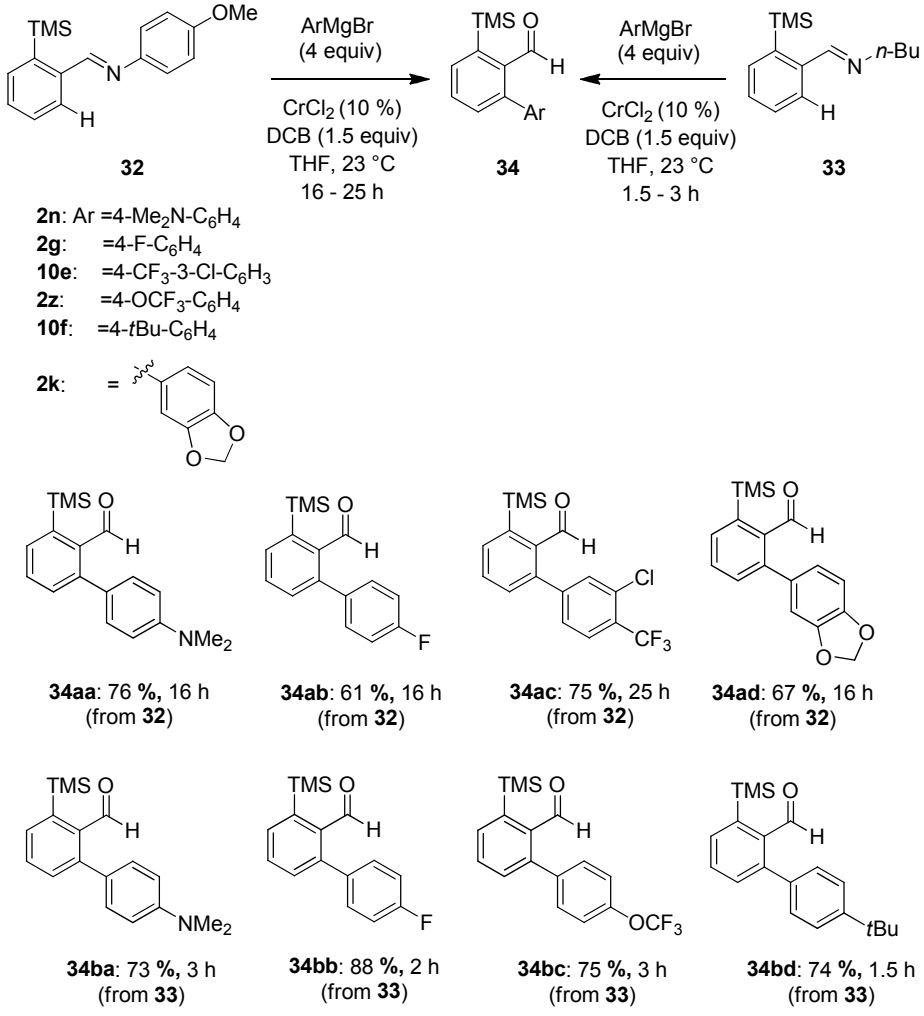
Scheme 57. Chromium-catalyzed arylation of 2-(2-(trimethylsilyl)phenyl)oxazoline **28** with Grignard reagents

In order to transform the TMS-group into a second aryl substituent, the oxazoline **29e** was synthesized using 10 % of the $CrCl_2$ and DCB (1.5 equiv) in 87 % yield. Treatment with ICl in refluxing CH_2Cl_2 (6 h), and subsequent Negishi cross-coupling reaction with the ester-substituted phenylzinc derivative **30** in the presence of 3 % $Pd(dba)_2$ and 6 % tfp at 50 ºC for 15 h furnishes the bis-arylated pyridine **31** in 89 % yield over two steps (Scheme 58).



Scheme 58. Selective bis-arylation of the 2-(2-(trimethylsilyl)phenyl)oxazoline **28** using chromium and palladium catalysts

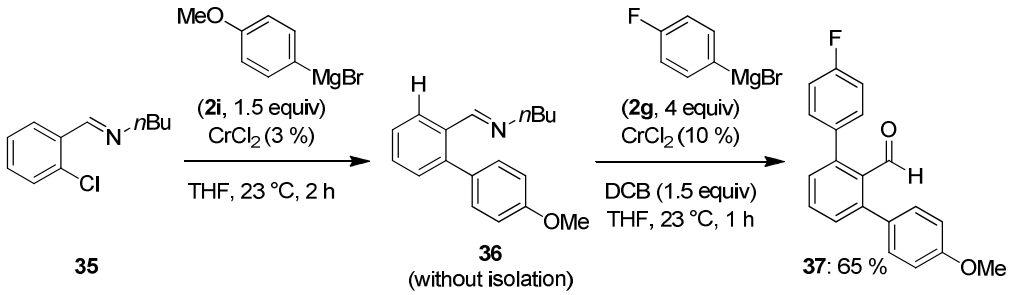
Imine-protected aldehydes undergo chromium-catalyzed C-H bond activation reaction, furnishing compounds **34aa - ad** and **34ba - bd** in 61 – 88 % yield (Scheme 59). Interestingly, the reaction time was strongly dependent on the nature of the imine protection group. When *p*-methoxyphenyl imine **32** was used, chromium-catalyzed arylation reactions proceeded with reaction times of 16 – 25 h (**34aa - ad**). *N*-Butyl imine **33** reacted with the Grignard reagents **2n**, **2g**, **2z** and **10f** at faster rates (1.5 h – 3h) giving after acidic work up the arylated aldehydes **34ba - bd** in 73 – 88 % yield.



Scheme 59. Chromium-Catalyzed Arylation of Imines **32** and **33** with Grignard Reagents

In order to show the practicability of our chromium-methodology, we aimed to perform bi-arylation of the imine-protected 2-chloro-benzaldehyde **35** *via* a one-pot Cr-catalyzed cross-coupling with subsequent Cr-catalyzed C-H bond activation (Scheme 60). In the first step, **35** undergoes a Cr-catalyzed coupling reaction with the Grignard reagent **2i** to yield the arylated

product **36**, which undergoes subsequent Cr-catalyzed direct C-H arylation with the Grignard reagent **2g** to produce, after acetic work-up, bis-arylated aldehyde **37** in a one-pot fashion in 65% yield.



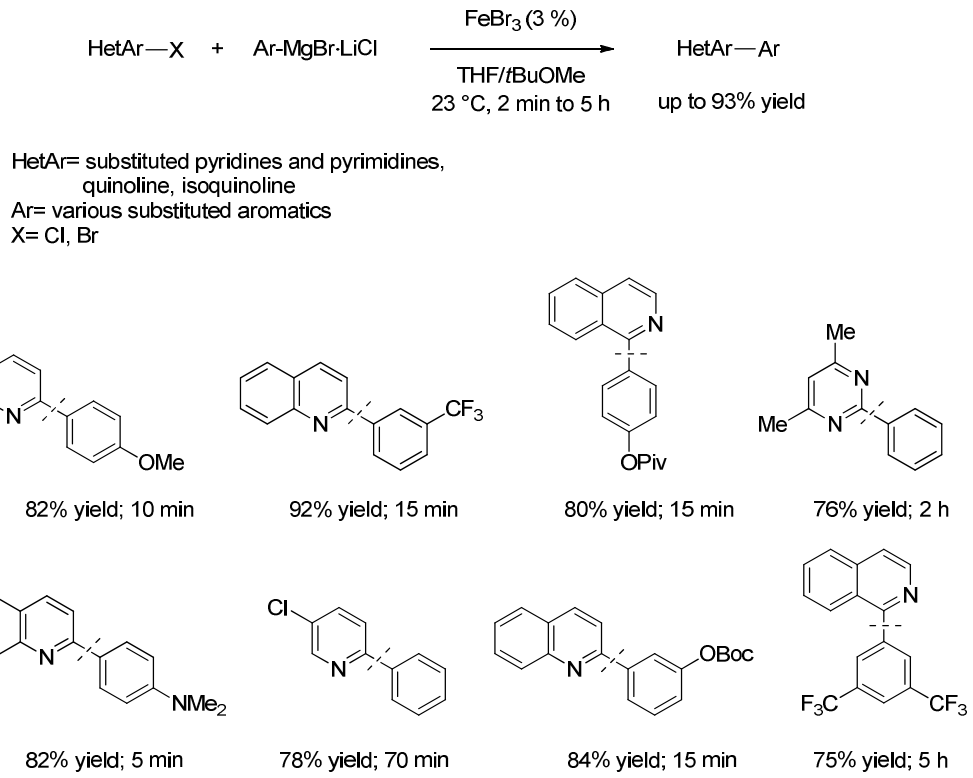
Scheme 60. One pot bis-arylation of aldehyde **37** using chromium catalyzed cross-coupling reaction and C-H bond activation reaction

5. Summary

5.1 Iron-Catalyzed Cross-Coupling of *N*-Heterocyclic Halides with Grignard Reagents

A simple and practical iron-catalyzed cross-coupling of *N*-heterocyclic chlorides and bromides with arylmagnesium reagents was developed. The reactions were performed at room temperature and proceeded at fast rates. The desired substituted *N*-heterocyclic products were obtained in high yields and various functional groups like electron-withdrawing groups such as trifluoromethyl-, fluoro- and pivalate-functions, as well as electron-donating groups like methoxy-, methylenedioxy- and dimethylamino-moieties were well tolerated.

The addition of an ethereal co-solvent like diethyl ether or *tert*-butyl methyl ether was found to be essential to prevent homocoupling and to obtain high yields (Scheme 61).



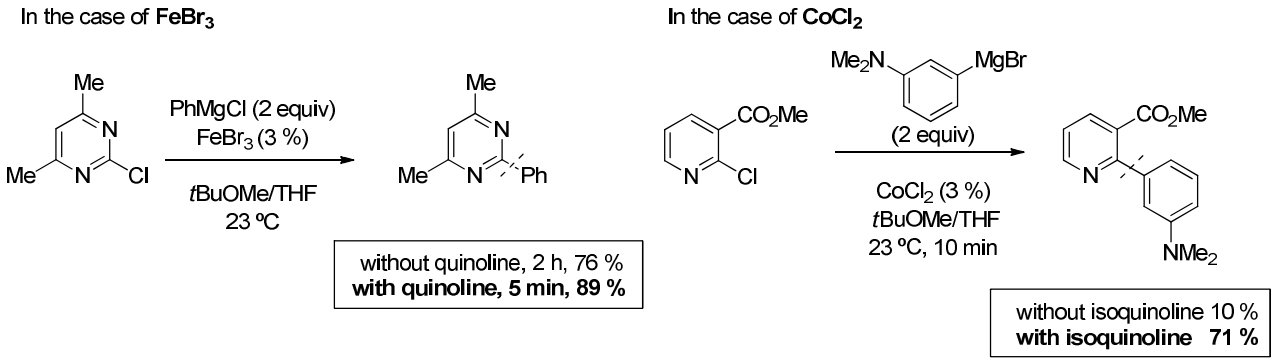
Scheme 61. Iron-catalyzed cross-coupling reactions between *N*-hetrocyclic halides and aryl Grignard reagents

5.2 Ligand-Accelerated Iron- and Cobalt-Catalyzed Cross-Coupling between *N*-Heterocyclic Halides and Aryl Magnesium Reagents

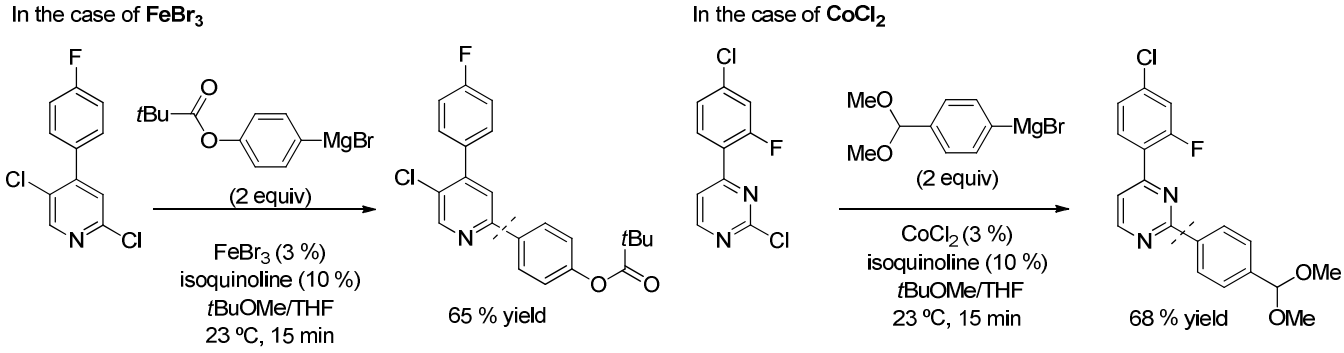
The cross-coupling of *N*-heterocyclic halides and Grignard reagents was further investigated. It was found that isoquinoline (and quinoline) has an ability to act as a new ligand for iron- but also for cobalt-catalyzed cross-coupling reactions. The rate and yield of iron- or cobalt-catalyzed cross-coupling reactions were dramatically increased while simultaneously decreasing the amount of homocoupling. With this new method, it was possible to widen the scope of these reactions considerably to couple a variety of functionalized Grignard reagents with an assortment of *N*-heterocycles.

Most important advances:

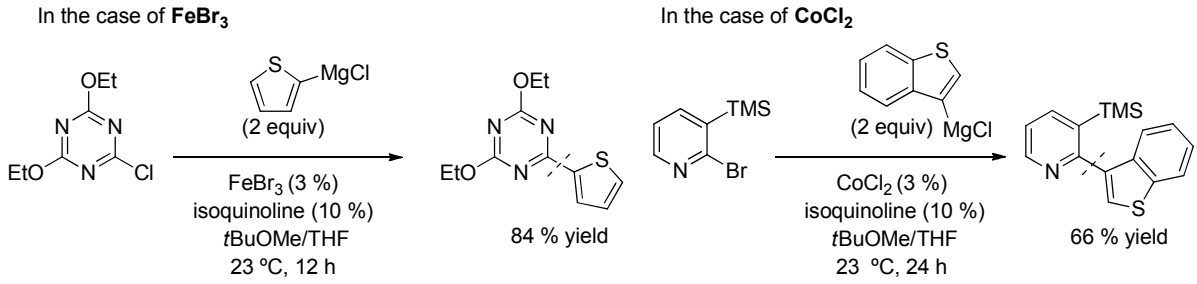
- Increased reaction rate and yield



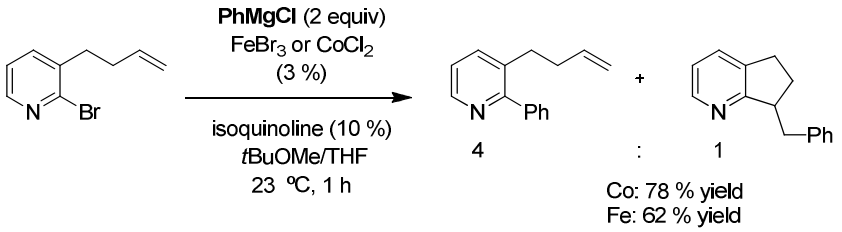
- Functionalized Grignard reagents could be used



- An extension to the formation of heteroaryl-heteroaryl bonds was performed



- A mechanistic study indicates that radical intermediates are involved

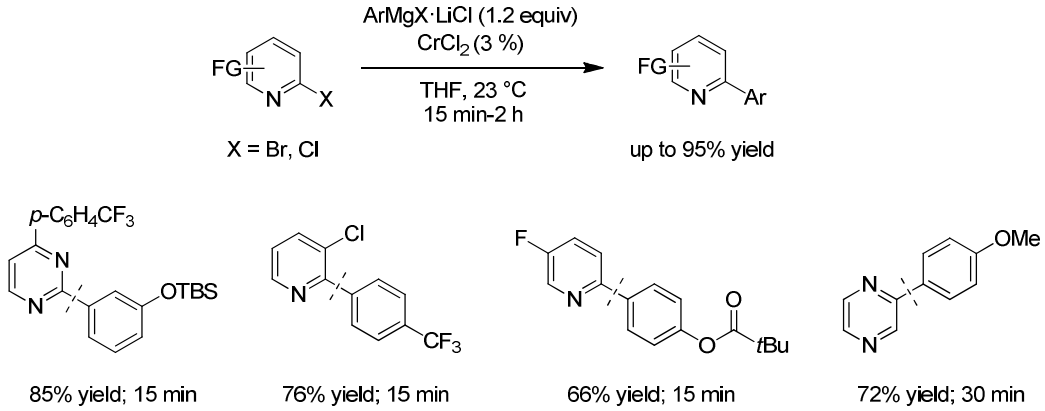


5.3 Efficient Chromium(II)-Catalyzed Cross-Coupling Reactions

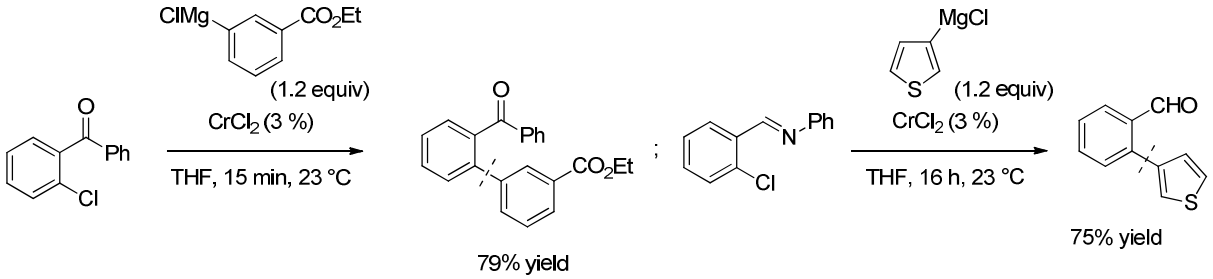
An efficient chromium(II)-catalyzed cross-coupling reaction between heterocyclic and aromatic Grignard reagents and various aromatic and *N*-heterocyclic halides was investigated. This new cross-coupling reaction does not require additional ligands, proceeds at 25 °C within 15 min to 2 h and produces the desired cross-coupled products in good yields. Homo-coupling side-products were produced in much lower amounts compared to Fe-, Co- or even Mn-cross-couplings. As electrophiles, various halogenated *N*-heterocycles (chlorides and bromides), aromatic halogenated ketones or imines and alkenyl iodides could be used. Against common wisdom, toxicological data indicate that $CrCl_2$ is a chromium-salt of low toxicity, as it is sold as a low-toxic chemical by major international suppliers (compare LD_{50} values of $CrCl_2$ (1870 mg/kg), $FeCl_2$ (450 mg/kg) and $CoCl_2$ (766 mg/kg)).

Features of the method:

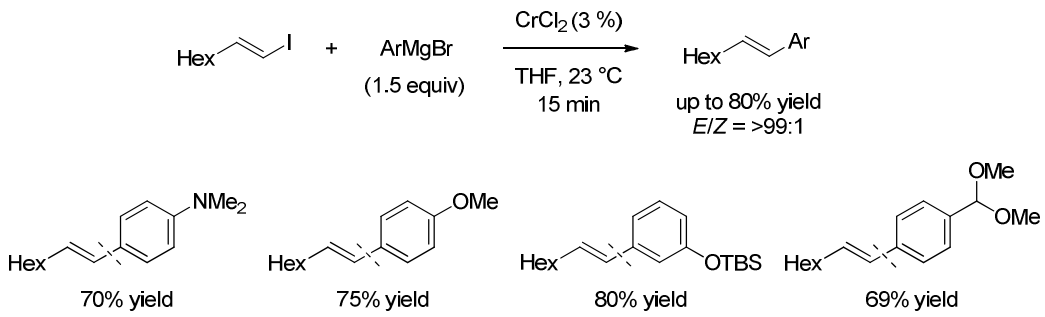
- *N*-Heterocyclic bromides and chlorides undergo $CrCl_2$-catalyzed cross-couplings without the formation of homo-coupling side-products



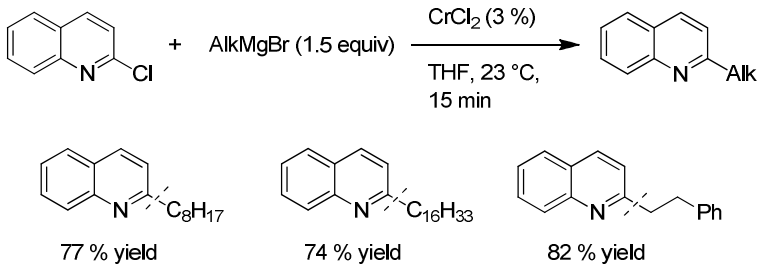
- Aromatic chloro-and bromo-ketones as well as chloro-imines react smoothly



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



- Cr(II)-catalyzed cross-coupling between Csp^2-Csp^3 centers also could be achieved



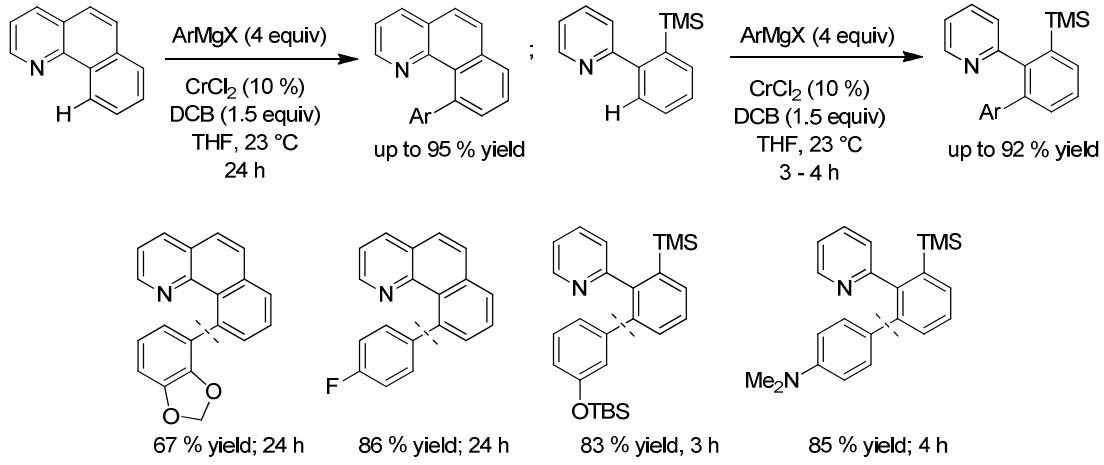
5.4 Room-Temperature Chromium(II)-Catalyzed Direct Arylation of Pyridines, Aryl Oxazolines and Imines

Direct C-H bond activation reactions with aromatic Grignard reagents catalyzed by $CrCl_2$ were examined. This type of reaction proceeds usually rapidly at 23 °C and does not require any additional ligands. Different compounds such as benzo[*h*]quinoline, 2-phenylpyridine, phenyloxazoline and imines were successfully arylated in good yields.

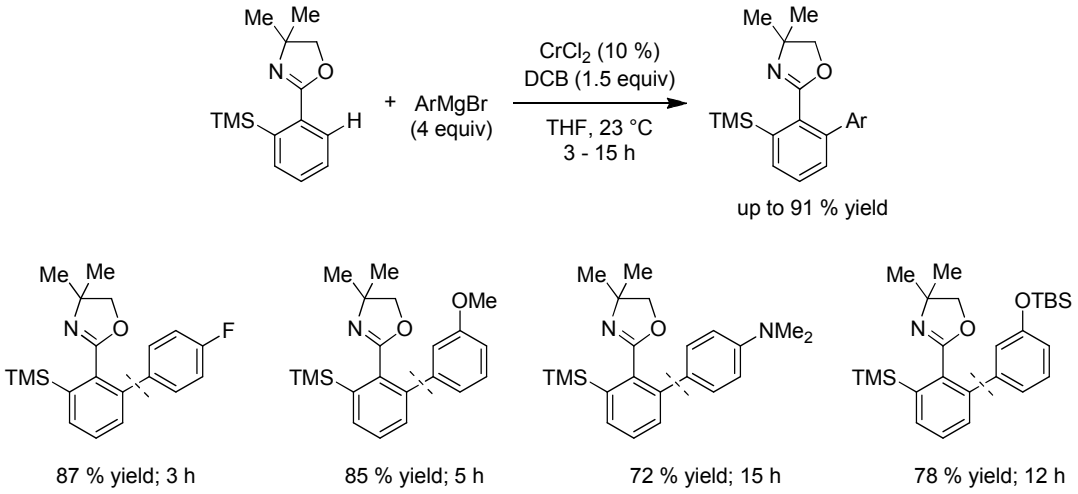
A TMS-group was used to avoid double arylation, which after treatment with ICl was further used to introduce a second aryl substituent.

Most important advances:

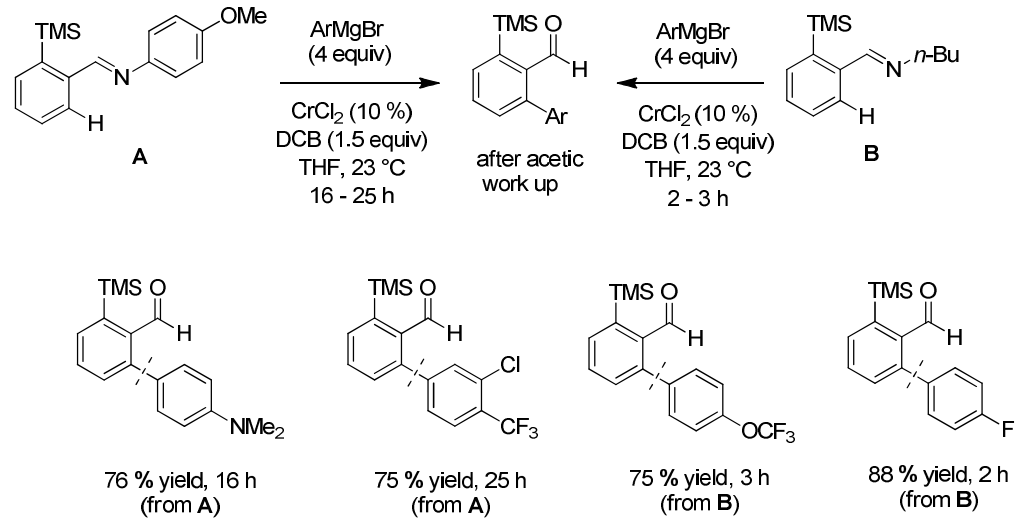
- Benzo[*h*]quinoline and 2-(2-trimethylsilylphenyl)pyridine could be arylated



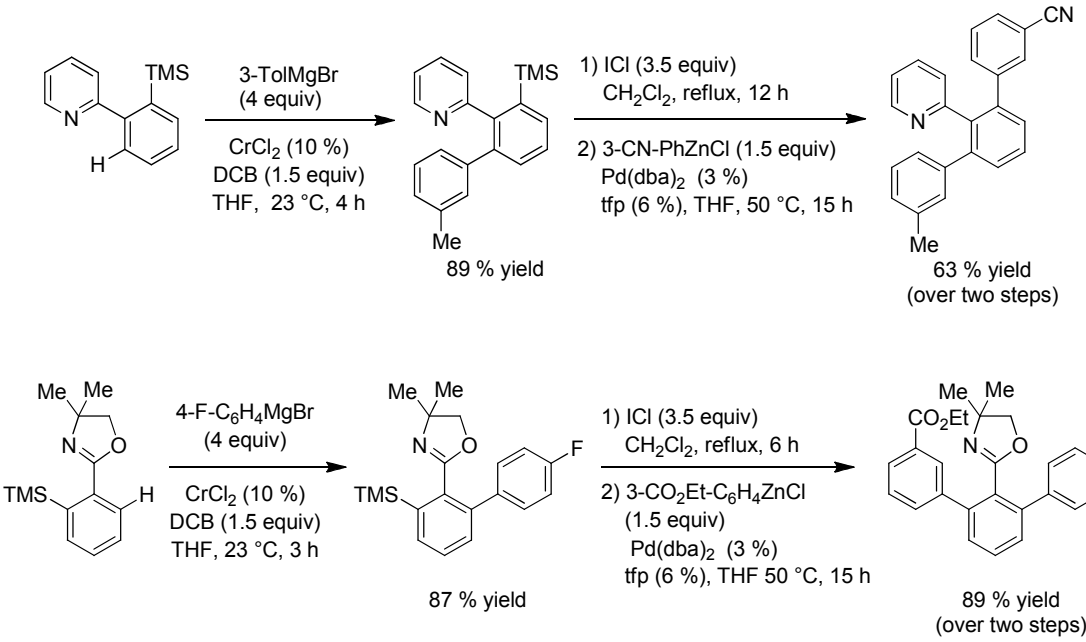
- 2-(2-(Trimethylsilyl)phenyl)oxazoline underwent mild chromium(II)-catalyzed C-H bond activations in relatively fast rates.



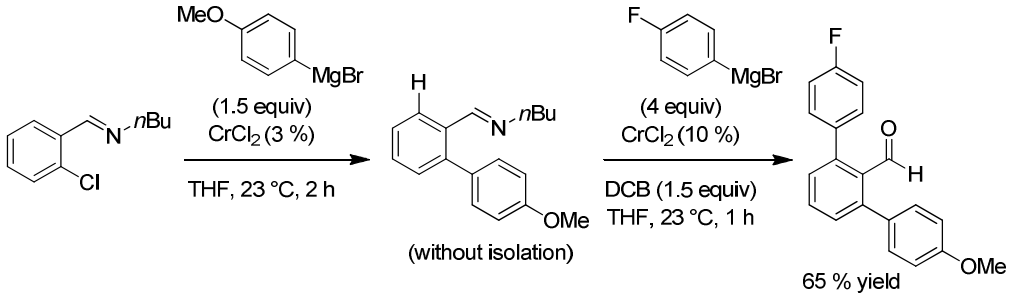
- Arylated aldehydes could be furnished in good yields, wherein imine **B** reacted in faster rates than imine **A**.



- The TMS-group could be further transformed to iodide and used in Negishi cross-coupling reactions.



- The One pot bis-arylation of aldehydes could be achieved using a chromium catalyzed cross-coupling reaction and a C-H bond activation reaction



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

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

Et_2O was predried over CaH_2 and dried with the solvent purification system SPS-400-2 from INNOVATIVE TECHNOLOGIES INC.

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

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.

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

CH_3CN was heated to reflux for 14 h over CaH_2 and distilled from CaH_2.

1,2-dioxane was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

Bu_2O was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

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

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.

$CoCl_2$ was dried under high vacuum at 150 °C for 2 min prior reactions (until the colour turned blue).

$CrCl_2$ was dried under high vacuum at 150 °C for 2 min prior reactions (until the colour turned white-grey).

$BF_3 \cdot OEt_2$ 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.

TMSCl was distilled under Ar prior to use.

$ZnCl_2$ 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.

TMPH was distilled under Ar prior to use.

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.

Grignard reagents 2b - u, **2w**, **2y - z**, **10d - f**, **21a - c** were prepared *via* LiCl-assisted Mg-insertion into the corresponding aromatic halides.[111]

Grignard reagents 2v, **2x**, **10a - c** were prepared *via* halogen-magnesium exchange reaction.[112]

Aryl Zn-compounds 26 and **30** were prepared via LiCl-assisted Zn-insertion into the corresponding aromatic halides[113] or *via* Mg/Zn transmetalation reaction using $ZnCl_2$ (1.0 M in THF).

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[111] Piller, F. M.; Metzger, A. ; Schade, M. A.; Haag, B. A.; Gavryushin, A.; Knochel, P. *Chem. Eur. J.*, **2009**, *15*, 7192.

[112] a) A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 3333; b) A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 159.

[113] Krasovskiy, A.; Malakhov, V.; Gavryushin; A. Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6040.

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.

1.4 Chromotography

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 abbreviations 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 Fe-Catalyzed Cross-Coupling Reactions of *N*-Heterocyclic Chlorides and Bromides with Arylmagnesium Reagents (TP1)

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 (4.4 mg, 0.015 mmol, 0.03 equiv) 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.

2.2 Typical Procedure for Ligand-Accelerated Iron- and Cobalt-Catalyzed Cross-Coupling Reactions between *N*-Heteroaryl Halides and Aryl Magnesium Reagents (TP2)

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 23 °C. The suspension was stirred at 23 °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 23 °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.

2.3 Typical Procedure for Efficient Chromium(II)-Catalyzed Cross-Coupling Reactions between Aryl Halides and Aryl or Alkyl Grignard Reagents (TP3)

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 23 °C. The suspension was stirred at 23 °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.

2.4 Typical Procedure for Efficient Chromium(II)-Catalyzed Cross-Coupling Reactions between Imine Halide **16** and Aryl 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 imine **16** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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.

2.5 Typical Procedure for Efficient Chromium(II)-Catalyzed Cross-Coupling Reactions between Alkenyl Iodide **18** and Aryl Grignard Reagents (TP5)

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 **18** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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.

2.6 Typical Procedure for Room-Temperature Chromium(II)-Catalyzed Direct Arylation of Pyridines and Aryl Oxazolines (TP6)

A solution of the appropriate Grignard reagent (concentration in THF varying depending on the nature of the Grignard reagent, 2 mmol, 4 equiv) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv; 97% purity) and the appropriate aryl compound (0.5 mmol, 1.0 equiv) at 23 °C. 2,3-Dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The suspension was stirred at 23 °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.

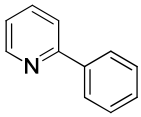
2.7 Typical Procedure for Room-Temperature Chromium(II)-Catalyzed Direct Arylation of Imines (TP7)

A solution of the appropriate Grignard reagent (concentration in THF varying depending on the nature of the Grignard reagent, 2 mmol, 4 equiv) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv; 97% purity) and the appropriate aryl imine (0.5 mmol, 1.0 equiv) at 23 °C. 2,3-Dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv.) was added dropwise at 23 °C. The suspension was stirred at 23 °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.

3. Fe-Catalyzed Cross-Coupling Reactions of *N*-heterocyclic Chlorides and Bromides with Arylmagnesium Reagents

3.1 Preparation of Cross-Coupling Products Using TP1

Synthesis of 2-phenylpyridine (3a):



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 (**1a** or **1b**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, phenylmagnesium chloride (**2a**; 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).

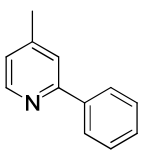
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.60, 122.10, 126.92, 128.74, 128.99, 136.84, 139.24, 149.53, 157.39.

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.

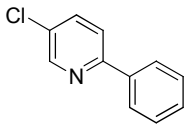
Synthesis of 4-methyl-2-phenylpyridine (3b):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloro-4-methylpyridine (**1c**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, phenylmagnesium chloride (**2a**; 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, 121.59, 123.14, 126.94, 128.68, 128.88, 139.26, 147.99, 149.18, 157.21.
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 (3c):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-bromo-5-chloropyridine (**1d**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, phenylmagnesium chloride (**2a**; 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).

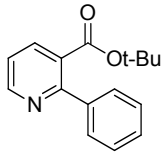
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 121.17, 126.82, 128.85, 129.33, 130.63, 136.60, 138.00, 148.34, 155.48.

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 (3d):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, *tert*-butyl 2-chloronicotinate (**1e**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, phenylmagnesium chloride (**2a**; 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).

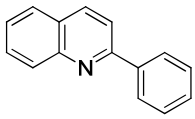
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.51, 82.17, 121.54, 128.03, 128.38, 128.67, 128.93, 137.73, 140.64, 150.68, 158.75, 167.20.

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 (3e):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**1f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, phenylmagnesium chloride (**2a**; 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).

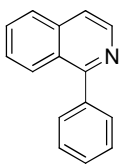
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 119.04, 126.38, 127.18, 127.45, 127.65, 128.85, 129.44, 129.52, 129.81, 137.03, 139.35, 147.98, 157.27.

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 (3f):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**1g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were

dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, phenylmagnesium chloride (**2a**; 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).

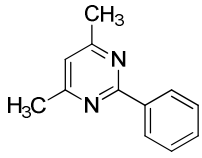
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.01, 126.68, 126.99, 127.26, 127.64, 128.36, 128.69, 129.93, 130.16, 136.93, 139.23, 141.86, 160.60.

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 (3g):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloro-4,6-dimethylpyrimidine (**1h**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol%) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, phenylmagnesium chloride (**2a**; 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).

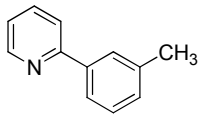
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 24.11, 117.97, 128.24, 128.42, 130.31, 137.94, 164.06, 166.77.

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 (3j):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-bromopyridine (**1b**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, *m*-tolyl-magnesium bromide (**2b**; 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).

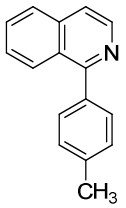
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 21.51, 120.61, 121.61, 123.99, 127.64, 128.62, 129.70, 136.67, 138.39, 139.35, 149.58, 157.63.

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.

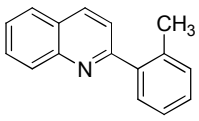
Synthesis of 1-(*p*-tolyl)isoquinoline (3k):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**1g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, *p*-tolyl-magnesium bromide (**2b**; 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, 119.77, 126.72, 126.96, 127.13, 127.74, 129.04, 129.87, 130.07, 136.37, 136.94, 138.58, 141.86, 160.66.
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 (3l):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**1f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, *o*-tolyl-magnesium bromide (**2b**; 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).

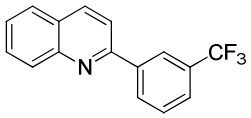
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 20.34, 122.37, 126.01, 126.44, 126.73, 127.49, 128.54, 129.50, 129.68, 129.70, 130.86, 136.00, 136.18, 140.56, 147.75, 160.22.

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 (3m):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**1f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, (3-(trifluoromethyl)phenyl)magnesium bromide (**2e**; 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).

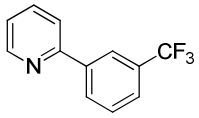
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 118.52, 124.16 (q, *J*=272.65 Hz), 124.39 (q, *J*=3.92 Hz), 125.84 (q, *J*=3.93 Hz), 126.74, 127.37, 127.48, 129.27, 129.81, 129.94, 130.66, 131.23 (q, *J*=32.26 Hz), 137.11, 140.35, 148.24, 155.52.

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 (3n):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-bromopyridine (**1b**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, (3-(trifluoromethyl)phenyl)magnesium bromide (**2e**; 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).

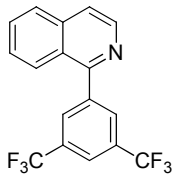
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.55, 122.79, 123.76 (q, *J*=3.93 Hz), 124.16 (q, *J*=272.36 Hz), 125.50 (q, *J*=3.93 Hz), 129.18, 130.01, 131.20 (q, *J*=32.54 Hz), 136.95, 140.10, 149.86, 155.81.

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) $[M]^+$: 223.0609.

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



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**1g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, (3,5-bis(trifluoromethyl)phenyl)magnesium bromide (**2f**; 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).

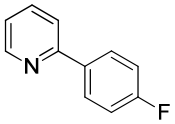
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 121.17, 122.38, 123.27 (q, *J*=272.72 Hz), 126.07, 126.32, 127.44, 128.19, 130.14, 130.52, 131.83 (q, *J*=37.59 Hz), 136.95, 141.56, 142.29, 157.22.

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 (3p):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-bromopyridine (**1b**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, (4-fluorophenyl)magnesium bromide

(**2g**; 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).

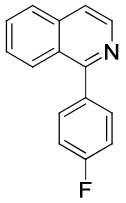
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 115.62 (d, *J*=21.63 Hz), 120.17, 122.00, 128.65 (d, *J*=8.26 Hz), 135.54 (d, *J*=4.4 Hz), 136.77, 149.66, 156.44, 163.47 (d, *J*=248.25 Hz).

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 (3q):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**1g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, ((4-fluorophenyl)magnesium bromide (**2g**; 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).

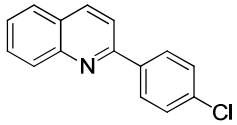
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 115.37 (d, *J*=21.64 Hz), 120.00, 126.64, 127.06, 127.24, 127.30, 130.06, 131.70 (d, *J*=8.26 Hz), 135.65 (d, *J*=3.41 Hz), 136.88, 142.17, 159.59, 163.08 (d, *J*=247.96 Hz).

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 (3r):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**1f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, (4-chlorophenyl)magnesium bromide (**2h**; 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).

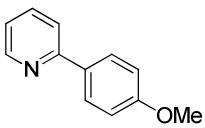
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 118.49, 126.47, 127.20, 127.47, 128.79, 129.99, 129.70, 129.81, 135.53, 136.91, 138.02, 148.22, 155.93.

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 (3s):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-bromopyridine (**1b**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, (4-methoxyphenyl)magnesium bromide (**2i**; 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).

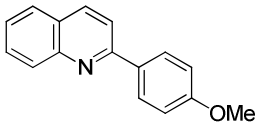
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.34, 114.14, 119.91, 121.42, 128.21, 131.71, 136.87, 149.28, 156.98, 160.53.

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 (3t):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**1f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, (4-methoxyphenyl)magnesium bromide (**2i**; 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).

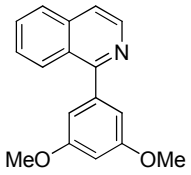
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.37, 114.23, 118.51, 125.90, 126.90, 127.43, 128.89, 129.49, 129.57, 132.18, 136.63, 148.24, 156.85, 160.84.

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 (3u):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**1g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, (3,5-dimethoxyphenyl)magnesium bromide (**2j**; 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).

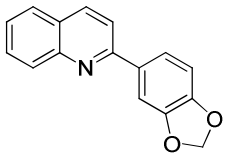
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.48, 101.04, 107.98, 120.08, 126.66, 126.91, 127.18, 127.57, 130.05, 136.80, 141.39, 141.99, 160.55, 160.66.

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 $\mathbf{C_{17}H_{15}NO_2}$ (265.1103) $[M]^+$: 265.1090.

Synthesis of 2-(benzo[*d*][1,3]dioxol-5-yl)quinoline (3v):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**1f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, benzo[*d*][1,3]dioxol-5-ylmagnesium bromide (**2k**; 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 °C.

^{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).

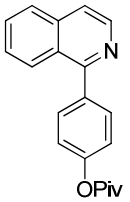
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 101.35, 107.91, 108.45, 118.56, 121.73, 126.03, 126.98, 127.39, 129.54, 129.62, 134.11, 136.64, 148.17, 148.38, 148.82, 156.62.

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 $\mathbf{C_{16}H_{11}NO_2}$ (249. 0790) $[M]^+$: 249.0782.

Synthesis of 4-(isoquinolin-1-yl)phenyl pivalate (3w):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 1-chloroisoquinoline (**1g**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, (4-(pivaloyloxy)phenyl)magnesium bromide (**2l**; 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).

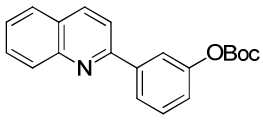
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.16, 39.17, 120.19, 121.50, 126.71, 127.01, 127.39, 127.52, 130.23, 131.01, 136.59, 136.93, 141.80, 151.58, 159.77, 177.00.

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 (3x):



In a dry and argon flushed 10 mL *Schlenk*-tube, equipped with a magnetic stirring bar and a septum, 2-chloroquinoline (**1f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, (3-(*tert*-butoxycarbonyloxy)phenyl)magnesium bromide (**2m**; 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).

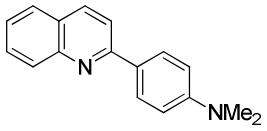
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.75, 83.58, 118.80, 120.43, 122.23, 124.80, 126.50, 127.30, 127.45, 129.71, 129.77, 136.93, 141.13, 148.12, 151.67, 151.83, 156.03.

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 (**1f**; 1.0 mmol, 1.0 equiv) and iron (III) bromide (3 mol %) were dissolved in dry *t*-BuOMe (5 mL) following **TP1**. Then, (4-(dimethylamino)phenyl)magnesium bromide (**2n**; 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, 112.24, 118.26, 125.33, 126.69, 127.33, 127.37, 128.46, 129.33, 136.26, 148.41, 151.35, 157.33.

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.

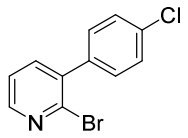
HRMS (EI) for $\mathbf{C_{17}H_{16}N_2}$ (248. 1313) $[M]^+$: 248.1309.

4. Ligand-Accelerated Iron- and Cobalt-Catalyzed Cross-Coupling Reactions between *N*-Heterocyclic Halides and Aryl Magnesium Reagents

4.1 Preparation of Starting Materials

Substance **7a** was prepared according to the procedure described in the literature.[114]
Substance **7b** was prepared according to the procedure described in the literature.[115]

Synthesis of 2-bromo-3-(4-chlorophenyl)pyridine (4b):



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 (1.0 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 23 °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).

[114] Rodriguez, J. G., Benito, Y. *J. Heterocycl. Chem.* **1988**, *25*, 819.
[115] Joucla, L.; Cusati, G.; Pinel, C.; Djakovitch, L. *Applied Catalysis* **2009**, *360*, 145.

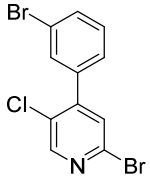
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 122.74, 128.56, 130.62, 134.56, 137.24, 138.60, 138.90, 142.21, 149.01.

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 (4e):



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 (1.0 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 23 °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).

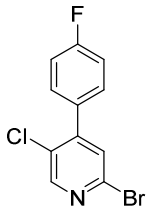
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 122.60, 127.47, 129.13, 129.74, 130.11, 131.68, 132.45, 137.09, 140.03, 148.61, 150.05.

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 (4h):



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 (1.0 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 23 °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).

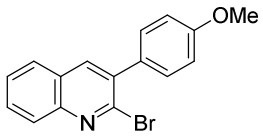
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 115.78 (d, *J*=21.88 Hz, 1 C) 129.22, 129.83, 130.82 (d, *J*=8.45 Hz, 1 C), 131.18 (d, *J*=3.07 Hz, 1 C), 139.99, 149.15, 149.99, 163.30 (d, *J*=250.29 Hz, 1 C).

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 (4i):



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 (1.0 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).

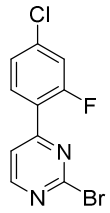
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.34, 113.64, 127.32, 127.34, 127.52, 128.41, 130.22, 130.94, 131.39, 136.77, 137.80, 143.23, 147.35, 159.67.

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 (4l):



2-Bromopyridine (1.0 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).

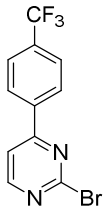
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 117.32 (d, J=26.37 Hz, 1 C), 119.33 (d, J=13.46 Hz, 1 C), 125.55, 131.84, 138.74 (d, J=10.94 Hz, 1 C), 153.29, 159.84, 161.19 (d, J=256.93 Hz), 161.63, 161.68.

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 (4m):



2-Bromopyridine (1.0 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 23 °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).

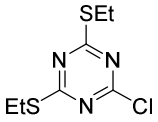
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 115.87, 123.67 (q, *J*=272.36 Hz, 1 C), 126.07 (q, *J*=3.93 Hz, 1 C), 127.80, 133.46 (q, *J*=32.82 Hz, 1 C), 138.27, 153.80, 160.03, 165.32.

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 (4q):



*n*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 23 °C. The milky-white mixture was transferred via syringe to a solution of cyanuric chloride (1.0 equiv, 216 mmol) in THF (50 mL) at -78 °C. The mixture was immediately warmed to 23 °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).

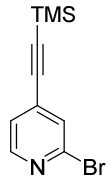
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.03, 25.13, 167.95, 182.82.

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 (4r):



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).

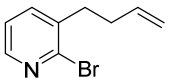
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -0.43, 100.32, 101.96, 124.71, 130.03, 133.74, 142.13, 149.82.

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) $[M+H]^+$: 253.9824.

Synthesis of 2-bromo-3-(but-3-en-1-yl)pyridine (4s):



2-Bromo-3-(bromomethyl)pyridine (1.0 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, 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, 34.59, 115.86, 122.72, 136.82, 138.18, 138.32, 144.37, 147.63.

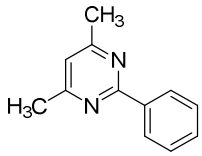
MS (70 eV, EI) m/z (%): 170 (100), 132 (82), 131 (39), 91 (24), 90 (18).

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.

4.2 Preparation of Cross-Coupling Products Using TP2

Synthesis of 4,6-dimethyl-2-phenylpyrimidine (3g):



A solution of **2a** 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 **1h** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 5 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **3g** 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 °C.

^{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).

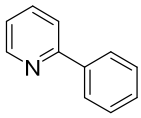
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 24.11, 117.97, 128.24, 128.42, 130.31, 137.94, 164.06, 166.77.

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 (3a):



A solution of **2a** 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 **1a** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °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 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **3a** 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).

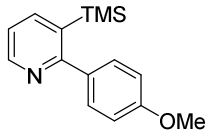
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.60, 122.10, 126.92, 128.74, 128.99, 136.84, 139.24, 149.53, 157.39.

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 (5a):



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 **4a** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5a** 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).

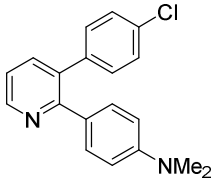
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 0.25, 55.29, 113.29, 121.02, 130.11, 133.30, 136.29, 143.17, 148.91, 159.62, 165.10.

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.

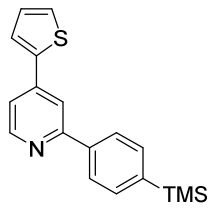
Synthesis of 4-(3-(4-chlorophenyl)pyridin-2-yl)-*N*,*N*-dimethylaniline (5b):



A solution of **2n** 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 **4b** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5b** 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, 111.63, 120.91, 127.49, 128.56, 130.75, 130.85, 132.97, 133.96, 138.32, 139.32, 148.51, 150.10, 157.19.
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 (5c):

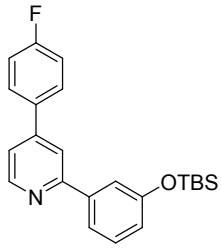


A solution of **2o** in THF (1.0 mmol, 2.0 equiv, 1.2 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **4c** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat.

aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5c** 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, 117.00, 118.52, 125.31, 126.19, 127.10, 128.43, 133.79, 139.57, 141.53, 141.67, 142.16, 150.26, 158.32.
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 (5d):



A solution of **2p** 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 **4d** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of

Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5d** 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).

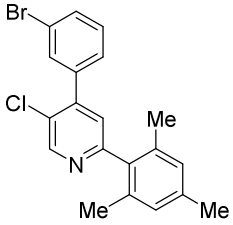
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.32, 18.23, 25.73, 116.15 (d, *J*=21.60 Hz, 1 C), 118.63, 118.88, 120.08, 120.69, 128.85 (d, *J*=8.41 Hz, 1 C), 129.70, 134.63, 134.68, 140.94, 148.18, 150.11, 156.15, 157.99, 163.42 (d, *J*=249.08 Hz, 1 C).

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 (5e):

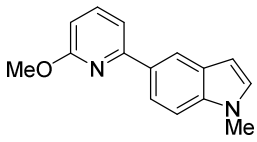


A solution of **2q** in THF (1.0 mmol, 2.0 equiv, 1.1 M) was added dropwise to a suspension of $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **4e** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 5 h before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5e** 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, 21.18, 122.53, 126.20, 127.80, 128.01, 128.54, 130.06, 132.01, 135.59, 135.69, 136.29, 137.98, 138.58, 146.11, 150.09, 158.85.
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 (5f):



A solution of **2r** 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 **4f** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 23 °C for 1 h before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5f** 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).

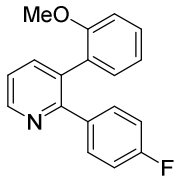
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 32.93, 53.17, 101.85, 107.76, 109.18, 112.39, 119.54, 120.79, 128.77, 129.51, 130.75, 137.32, 139.04, 156.15, 163.63.

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 (5g):



A solution of **2g** 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 **4g** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5g** 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).

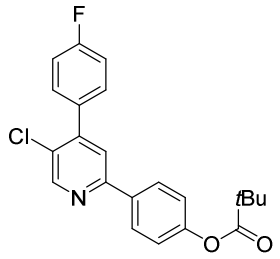
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 54.96, 111.05, 114.42 (d, *J*=21.35 Hz, 1 C), 120.84, 121.87, 128.75, 129.36, 130.54 (d, *J*=8.26 Hz, 1 C), 131.14, 132.73, 137.06, 139.10, 148.21, 155.98, 157.02, 162.36 (d, *J*=246.54 Hz, 1 C).

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 (5h):



A solution of **2l** 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 **4h** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5h** 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).

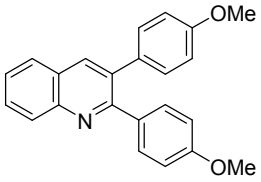
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.13, 39.15, 115.60 (d, *J*=21.64 Hz, 1 C), 121.93, 127.45, 127.91, 128.03, 128.71, 130.86 (d, *J*=8.26 Hz, 1 C), 132.74, 132.79, 135.47, 147.19, 149.83, 152.19, 155.15, 163.07 (d, *J*=249.10 Hz, 1 C), 176.88.

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 (5i):



A solution of **2i** 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 **4i** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5i** 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.

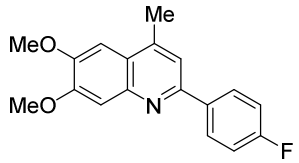
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.81 (s, 3 H), 3.82 (s, 3 H), 6.77 - 6.90 (m, 5H), 7.16 - 7.19 (m, 2 H), 7.42 - 7.44 (m, 2 H), 7.54 (ddd, *J*=8.04, 6.97, 1.17 Hz, 1 H), 7.70 - 7.75 (m, 1 H), 7.84 (dd, *J*=8.19, 1.17 Hz, 1 H), 8.14 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 59.35, 59.42, 117.57, 117.90, 130.74, 131.28, 131.42, 132.80, 133.76, 134.89, 135.63, 136.24, 137.00, 138.23, 141.91, 147.53, 159.32, 163.00, 163.84.

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 **$C_{23}H_{19}NO_2$** (340.1338) $[M-H]^+$:340.1336.

Synthesis of 2-(4-fluorophenyl)-6,7-dimethoxy-4-methylquinoline (5j):

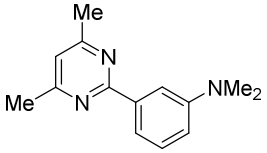


A solution of **2g** in THF (1.0 mmol, 2.0 equiv, 1.05 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **4j** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5j** 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, 56.02, 56.17, 101.46, 108.56, 115.64 (d, *J*=21.64 Hz, 1 C), 117.99, 122.38, 129.06 (d, *J*=8.54 Hz, 1 C), 135.88, 143.36, 144.79, 149.46, 152.36, 153.96, 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.

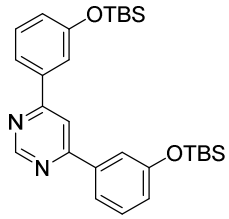
Synthesis of 3-(4,6-dimethylpyrimidin-2-yl)-*N*,*N*-dimethylaniline (5k):



A solution of **2s** 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 **1h** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 30 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5k** 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, 40.91, 112.49, 114.95, 117.16, 117.79, 129.13, 138.86, 150.82, 164.71, 166.57.
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 (5l):



A solution of **2p** 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 **4k** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5l** 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).

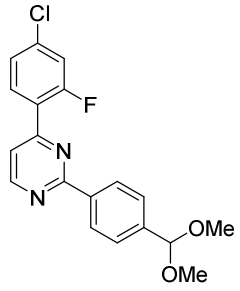
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.27 (s, 12 H), 1.03 (s, 18 H), 7.01 (dd, *J*=7.87, 1.83 Hz, 2 H), 7.40 (t, *J*=7.97 Hz, 2 H), 7.65 (d, *J*=1.83 Hz, 2 H), 7.72 (d, *J*=7.87 Hz, 2 H), 8.02 (s, 1 H), 9.32 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.32, 18.24, 25.72, 112.98, 118.89, 120.17, 122.56, 129.99, 138.58, 156.37, 159.14, 164.47.

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 (5m):



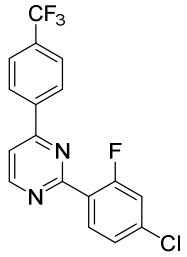
A solution of **2t** in THF (1.0 mmol, 2.0 equiv, 0.9 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv) or $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **4l** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5m** 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, 102.69, 117.24 (d, *J*=21.77 Hz, 1C), 125.39, 127.02, 128.11, 128.76, 129.88, 137.75, 140.72, 142.91, 158.15, 159.27, 161.31 (d, *J*=255.47 Hz, 1C), 163.38, 164.26.
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 (5n):



A solution of **2u** 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 **4m** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5n** 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).

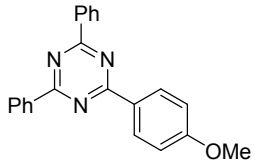
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 114.93, 117.71 (d, *J*=26.19 Hz), 123.86 (q, *J*=272.44), 124.64 (d, *J*=3.99 Hz), 124.92 (d, *J*=8.83 Hz), 125.96 (q, *J*=3.70 Hz), 127.60, 132.71, 132.75, 132.81 (q, *J*=32.74 Hz), 137.12 (d, *J*= 10.25 Hz,), 139.83 (q, *J*=1.14 Hz), 158.28, 161.33 (d, *J*=260.48 Hz), 162.60, 162.75, 162.82.

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 (5o):



A solution of **2i** 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 **4n** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5o** 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).

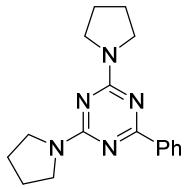
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.45, 113.94, 128.55, 128.77, 128.87, 130.85, 132.31, 136.40, 163.31, 171.18, 171.38.

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.

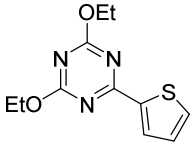
2-phenyl-4,6-di(pyrrolidin-1-yl)-1,3,5-triazine (5p):



A solution of **2a** 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 **4o** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 50 °C for 12 h before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5p** 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, 45.98, 127.97, 128.21, 130.69, 138.07, 163.62, 169.50.
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.

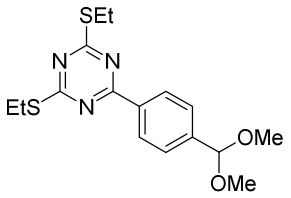
Synthesis of 2,4-diethoxy-6-(thiophen-2-yl)-1,3,5-triazine (5q):



A solution of **2v** 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 **4p** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 12 h before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5q** 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, 64.22, 128.27, 131.71, 132.29, 140.81, 170.59, 172.03.
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 (5r):

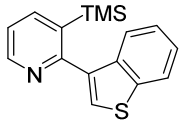


A solution of **2t** in THF (1.0 mmol, 2.0 equiv, 0.9 M) was added dropwise to a suspension of $FeBr_3$ (4.4 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and **4q** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C

for 15 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5r** 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, 24.85, 52.63, 102.51, 126.95, 128.88, 135.21, 142.59, 167.94, 181.30.
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 (5s):



A solution of **2w** 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 **4a** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 24 h before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5s** 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).

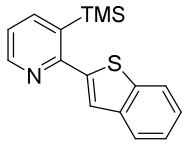
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -0.15, 121.89, 122.43, 123.43, 124.42, 124.55, 125.39, 135.44, 138.94, 139.48, 139.68, 143.21, 149.46, 159.75.

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 (5t):



A solution of **2x** 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 **4a** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 50 °C for 12 h (for $FeBr_3$) or at 23 °C for 12 h (for $CoCl_2$) before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5t** 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).

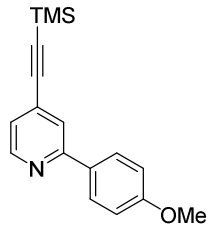
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 0.28, 122.01, 122.29, 123.88, 124.20, 124.37, 124.71, 134.24, 139.61, 140.62, 143.54, 145.80, 149.23, 158.26.

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 (5u):



A solution of **2i** 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 **4r** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 30 min before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5u** 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).

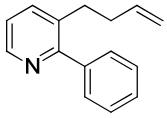
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -0.26, 55.34, 99.26, 102.51, 114.12, 122.00, 123.33, 128.17, 131.31, 131.72, 149.43, 157.15, 160.68.

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 (5v):



A solution of **2a** 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 **4s** (0.5 mmol, 1.0 equiv) in *t*BuOMe (2.5 mL) at 23 °C. The suspension was stirred at 23 °C for 1 h before being quenched with sat. aq. $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and an EDTA (1.0 M, H_2O) solution was added. The mixture was stirred at 23 °C for 15 min, before being filtered through a pad of Celite®. After washing the pad of Celite® with CH_2Cl_2, sat. aq. NaCl 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 **5v** 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, 34.57, 115.34, 122.13, 127.84, 128.17, 128.78, 129.09, 134.60, 137.30, 140.62, 146.97, 158.97.

MS (70 eV, EI) m/z (%): 209 (42), 208 (51), 180 (15), 168 (25). 167 (100),

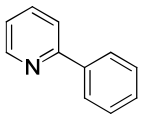
IR ATR ν (cm^{-1}): 3060, 3027, 2977, 2925, 2860, 1640, 1579, 1564, 1495, 1453, 1433, 1421, 1019, 995, 912, 791, 749, 732, 699.

HRMS (EI) for **$C_{15}H_{15}N$** (209.1204) $[M]^+$:208.1126.

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

5.1 Preparation of Cross-Coupling Products Using TP3

Synthesis of 2-phenylpyridine (3a):



A solution of **2a** 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 **1a** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **3a** 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).

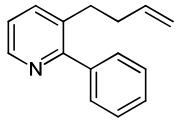
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.6, 122.1, 126.9, 128.7, 128.9, 136.8, 139.2, 149.5, 157.4.

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.

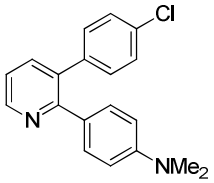
Synthesis of 3-(but-3-en-1-yl)-2-phenylpyridine (5v):



A solution of **2a** 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 **4s** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **5v** 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 (5b):

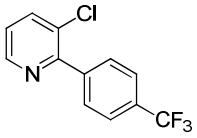


A solution of **2n** in THF (1.2 mmol, 1.2 equiv, 1.2 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **4b** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °C for 90 min before being quenched with brine and extracted 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 **8b** 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 (8a):



A solution of **2y** 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 **4t** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **8a** 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).

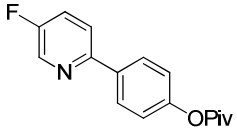
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 123.7, 124.0 (q, *J*=272.1 Hz), 125.0 (q, *J*=3.9 Hz), 129.8, 130.3, 130.8 (q, *J*=32.5 Hz), 138.3, 141.6, 147.8, 155.1.

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 (8b):



A solution of **2l** 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 **4u** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **8b** 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).

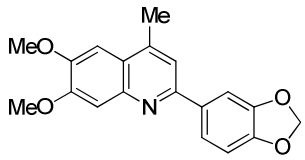
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.1, 39.1, 121.1, 121.2, 121.8, 123.5, 123.7, 127.8, 135.8, 137.5, 137.8, 151.8, 152.9, 152.9, 157.1, 160.5, 176.9.

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 (8c):



A solution of **2k** 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 **4j** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **8c** 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).

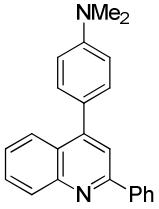
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 19.2, 56.0, 56.1, 101.2, 101.5, 107.7, 108.4, 108.6, 117.9, 121.3, 122.2, 134.3, 143.0, 144.8, 148.2, 148.4, 149.3, 152.2, 154.5.

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.

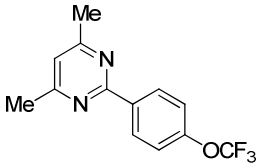
Synthesis of *N*,*N*-dimethyl-4-(2-phenylquinolin-4-yl)aniline (8d):



A solution of **2n** 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 **4v** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **8d** 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 (8e):



A solution of **2z** 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 **1h** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **8e** 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).

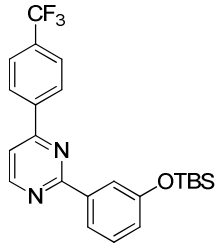
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 24.1, 118.2, 120.5, 120.5 (q, *J*=257.6 Hz), 129.9, 136.6, 150.9, 162.8, 166.9.

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 (8f):



A solution of **2p** 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 **4m** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **8f** 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).

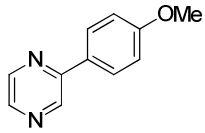
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.3, 18.3, 25.7, 107.6, 108.4, 112.6, 114.8, 119.9, 121.4, 122.9, 123.9 (q, *J*=272.6 Hz), 125.9 (q, *J*=3.9 Hz), 127.6, 129.6, 129.9, 132.4, 140.3, 156.1, 156.7, 158.0, 162.5, 164.5.

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 (8g):



A solution of **2i** 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 **1j** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **8g** 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).

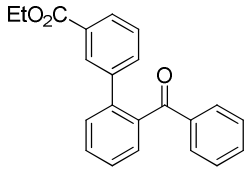
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.4, 114.5, 128.3, 128.8, 141.5, 141.9, 144.0, 152.5, 161.2.

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.

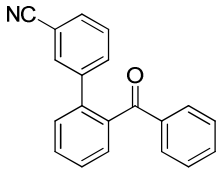
Synthesis of Ethyl 2'-benzoyl-[1,1'-biphenyl]-3-carboxylate (11a):



A solution of **10a** 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 **9** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **11a** 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.

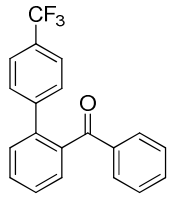
Synthesis of 2'-benzoyl-[1,1'-biphenyl]-3-carbonitrile (11b):



A solution of **10b** 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 **9** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **11b** 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 (11c):



A solution of **2y** 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 **9** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **11c** 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).

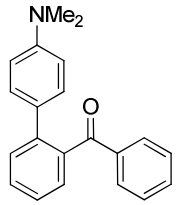
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 198.1, 143.9, 139.9, 138.9, 137.3, 133.2, 130.6, 130.1, 129.9, 129.4 (q, *J*=32.5 Hz), 129.3, 128.9, 128.3, 127.7, 125.2 (q, *J*=3.9 Hz), 124.1 (q, *J*=272.1 Hz).

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 (11d):



A solution of **2n** 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 **9** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **11d** 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.

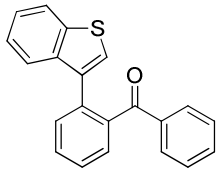
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.75 - 7.68 (m, 2 H), 7.58 - 7.45 (m, 3 H), 7.44 - 7.35 (m, 2 H), 7.33 - 7.24 (m, 2 H), 7.21 - 7.14 (m, 2 H), 6.62 - 6.53 (m, 2 H), 2.87 (s, 6 H).

^{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.

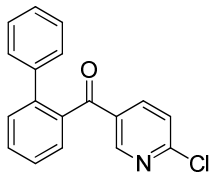
Synthesis of (2-(benzo[*b*]thiophen-3-yl)phenyl)(phenyl)methanone (11e):



A solution of **2w** 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 **9** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °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 **11e** 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.

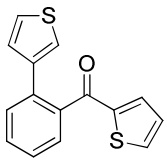
Synthesis of [1,1'-biphenyl]-2-yl(6-chloropyridin-3-yl)methanone (13):



A solution of **2a** 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 **12** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **13** 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 (15):

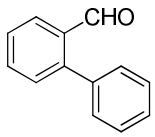


A solution of **10c** in THF (1.2 mmol, 1.2 equiv, 0.8 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and **14** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with brine and extracted 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 **15** 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.

5.2 Preparation of Cross-Coupling Products Using TP4

Synthesis of [1,1'-biphenyl]-2-carbaldehyde (17a):



A solution of **2a** 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 **16** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **17a** 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).

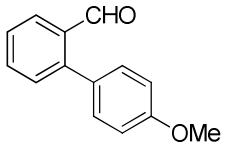
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 192.4, 146.0, 137.7, 133.7, 133.5, 130.8, 130.1, 128.4, 128.1, 127.8, 127.6.

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 (17b):



A solution of **2i** 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 **16** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **17b** 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).

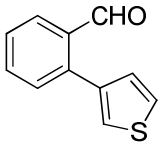
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 192.6, 159.7, 145.6, 133.8, 133.5, 131.3, 130.8, 130.0, 127.6, 127.3, 113.9, 55.4.

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 (17c):



A solution of **10c** 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 **16** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **17c** 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.

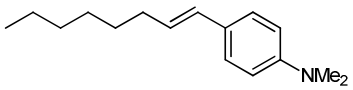
MS (70 eV, EI) m/z (%): 188 (100), 160 (100), 159 (24), 158 (21), 116 (20), 115 (85), 43 (31).

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.

5.3 Preparation of Cross-Coupling Products Using TP5

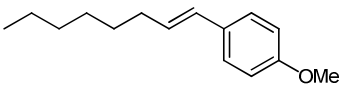
Synthesis of (*E*)-*N*,*N*-dimethyl-4-(oct-1-en-1-yl)aniline (19a):



A solution of **2n** 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 **18** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **19a** 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 (19b):

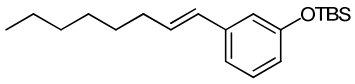


A solution of **2i** in THF (1.5 mmol, 1.5 equiv, 1.3 M) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97 % purity) and alkenyl iodide **18** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °C for 15 min before being quenched with 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 **19b** 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 (19c):



A solution of **2p** 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 **18** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **19c** 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).

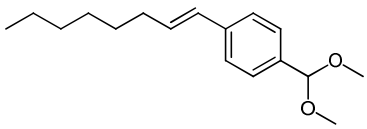
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.4, 14.1, 18.2, 22.6, 25.7, 28.9, 29.3, 31.8, 33.0, 117.5, 118.5, 119.1, 120.1, 129.5, 131.3, 139.5, 155.8.

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 (19d):



A solution of **2t** 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 **18** (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **19d** 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).

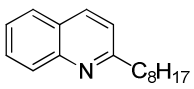
^{13}C NMR (75 MHz, DMSO) δ/ppm: 14.4, 22.5, 28.8, 29.2, 31.6, 32.9, 52.8, 102.9, 125.9, 127.2, 129.6, 131.7, 137.1, 137.9.

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.

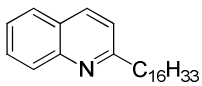
Synthesis of 2-octylquinoline (21a):



A solution of **20a** 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 2-chloroquinoline (**1f**) (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **21a** as a brown oil.

Isolated yield: 77 % (185 mg).
Reaction time: 15 min.
Solvent for purification: *i*-hexane/ethyl acetate 95:5.
^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.87 (t, *J*=6.63 Hz, 3 H), 1.10 - 1.51 (m, 10 H), 1.81 (dt, *J*=15.20, 7.60 Hz, 2 H), 2.88 - 3.05 (m, 2 H), 7.24 - 7.32 (m, 1 H), 7.47 (t, *J*=7.46 Hz, 1 H), 7.59 - 7.83 (m, 2 H), 8.06 (dd, *J*=8.29, 3.87 Hz, 2 H).
^{13}C NMR (75 MHz, DMSO) δ/ppm: 14.07, 22.63, 29.20, 29.47, 29.55, 30.05, 31.83, 39.26, 121.34, 125.66, 126.69, 127.44, 128.67, 129.36, 136.29, 147.69, 163.06.
MS (70 eV, EI) m/z (%): 241 (13), 212 (12), 198 (22), 184 (14), 169 (57), 155 (100), 144 (59), 128 (35), 115 (19).
IR ATR ν (cm^{-1}): 2951, 2921, 1618, 1600, 1562, 1503, 1425, 1309, 1140, 1116, 825, 823, 768, 753, 751, 721.
HRMS (EI) for **$C_{17}H_{23}N$** (241.1830) $[M]^+$: 241.1829.

Synthesis of 2-octylquinoline (21b):



A solution of **20b** 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 2-chloroquinoline (**1f**) (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **21b** as yellowish crystals.

Isolated yield: 74 % (261 mg).
Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 95:5.

m.p.: 49.4 – 51.2 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.88 (t, *J*=6.50 Hz, 3 H), 1.25 (s, 21 H), 1.29 - 1.40 (m, 5 H), 1.82 (dt, *J*=15.00, 7.57 Hz, 2 H), 2.95 - 3.04 (m, 2 H), 7.25 - 7.33 (m, 1 H), 7.49 (t, *J*=7.19 Hz, 1 H), 7.65 - 7.80 (m, 2 H), 8.05 - 8.15 (m, 2 H).

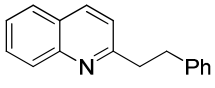
^{13}C NMR (75 MHz, DMSO) δ/ppm: 14.09, 22.67, 29.34, 29.50, 29.53, 29.61, 29.64, 29.67, 30.04, 31.90, 39.06, 121.35, 125.81, 126.70, 127.45, 128.42, 129.55, 136.61, 147.31, 163.00.

MS (70 eV, EI) m/z (%): 353 (22), 352 (37), 310 (10), 212 (14), 198 (16), 184 (13), 170 (46), 157 (23), 156 (100), 144 (63), 128 (16).

IR ATR ν (cm^{-1}): 2953, 2914, 2848, 1616, 1600, 1560, 1502, 1471, 1426, 831, 781, 758, 716.

HRMS (EI) for **$C_{25}H_{38}N$** (352.3004) $[M-1]^+$: 352.3003

Synthesis of 2-octylquinoline (21c):



A solution of **20c** 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 2-chloroquinoline (**1f**) (1 mmol, 1.0 equiv) in THF (5 mL) at 23 °C. The suspension was stirred at 23 °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 **21c** as brown oil.

Isolated yield: 82 % (261 mg).

Reaction time: 15 min.

Solvent for purification: *i*-hexane/ethyl acetate 95:5.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 3.10 - 3.24 (m, 2 H), 3.26 - 3.37 (m, 2 H), 7.15 - 7.37 (m, 6 H), 7.50 (t, *J*=7.46 Hz, 1 H), 7.65 - 7.83 (m, 2 H), 8.05 (d, *J*=8.57 Hz, 1 H), 8.12 (d, *J*=8.57 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO) δ ppm 35.92, 40.87, 121.57, 125.86, 126.01, 126.81, 127.53, 128.40, 128.52, 128.75, 129.48, 136.35, 141.47, 147.83, 161.76.

MS (70 eV, EI) m/z (%): 260 (10), 234 (28), 233 (100), 232 (93), 230 (34), 217 (15), 156 (37), 128 (16), 115 (15), 105 (11), 91 (22).

IR ATR ν (cm^{-1}): 3054, 3924, 2917, 1618, 1598, 1592, 1498, 1495, 1452, 1425, 1309, 1139, 1114, 1075, 841, 818, 747, 721, 696.

HRMS (EI) for **$C_{17}H_{15}N$** (233.1204) $[M]^+$: 233.1197.

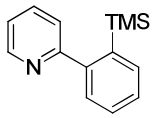
6. Room-Temperature Chromium(II)-Catalyzed Direct Arylation of Pyridines, Aryl Oxazolines and Imines.

6.1 Preparation of Starting Materials

2-(Trimethylsilyl)benzaldehyde was prepared according to the methods describe in the literature.[116]

Starting materials **22** is commercially available.

Synthesis of 2-(2-(trimethylsilyl)phenyl)pyridine (24):[117]



A solution of TMPMgCl·LiCl in THF (4 mmol, 2 equiv, 1.2 M) was added dropwise to a solution of 2-phenylpyridine (**3a**) (310 mg, 2 mmol, 1.0 equiv) in THF (10 ml). The reaction mixture was heated to 55 °C for 50 h. Then, the reaction mixture was cooled down to -30 °C and a solution of TMSCN (0.397 mg, 4 mmol, 2 equiv) in THF (4 ml) was added and slowly warmed up to 23 °C. Reaction mixture was 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 **24** as a colorless oil.

Isolated yield: 54 % (245 mg).

Solvent for purification: *i*-hexane/ethyl acetate 15:1.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.08 (s, 9 H), 7.25 - 7.30 (m, 1 H), 7.37 - 7.53 (m, 4 H), 7.68 - 7.80 (m, 2 H), 8.65 (d, *J*=4.70 Hz, 1 H).

[116] So, S., S.; Burkett, J. A.; Mattson, A. E. *Org. Lett.* **2011**, *13*, 716.
[117] Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.

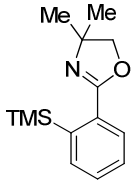
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.81, 122.01, 123.09, 127.48, 128.61, 128.75, 135.46, 136.53, 139.35, 146.74, 148.28, 161.22

MS (70 eV, EI) m/z (%): 212 (100), 213 (19), 182 (34), 98 (9), 44 (42), 43 (12), 41 (6).

IR ATR ν (cm^{-1}): 3050, 2946, 1586, 1569, 1556, 1477, 1423, 1295, 1242, 1150, 1123, 1101, 1021, 990, 832, 797, 747, 726, 680.

HRMS (EI) for **$C_{14}H_{17}NSi$** (226.1052) $[M-H]^+$: 226.1058.

Synthesis of 4,4-dimethyl-2-(2-(trimethylsilyl)phenyl)-4,5-dihydrooxazole (28):



A solution of *n*BuLi in *n*hexane (6 mmol, 1 equiv, 2.55 M) was added dropwise to a solution of 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole (1051 mg, 6 mmol, 1 equiv) in Et_2O (6 ml) at 0 °C. The reaction mixture was stirred 15 min at 0 °C and 30 min at 23 °C. Then a solution of TMSCl (761 mg, 6 mmol, 1 equiv) in Et_2O (30 ml) was added, and the reaction mixture was reflux for 3 h. After cooling down to 23 °C, the reaction mixture was quenched with brine and 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 **28** as a colorless oil.

Isolated yield: 56% (829 mg).

Solvent for purification: *i*-hexane/ethyl acetate 10:1.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 31 (s, 9 H), 1.38 (s, 6 H), 4.08 (s, 2 H), 7.34 - 7.41 (m, 2 H), 7.59 - 7.64 (m, 1 H), 7.86 (dd, *J*=7.19, 1.66 Hz, 1 H).

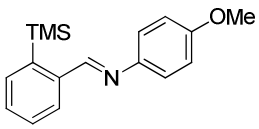
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.66, 28.49, 67.79, 79.06, 128.63, 129.50, 129.69, 133.82, 135.15, 140.17, 163.58.

MS (70 eV, EI) m/z (%): 247 (14), 232 (86), 160 (56), 137 (28), 125 (30), 111 (66), 97 (84), 85 (59), 71 (75), 57 (100), 55 (70).

IR ATR ν (cm^{-1}): 2971, 2958, 2894, 1655, 1462, 1355, 1349, 1307, 1241, 1187, 1128, 1092, 1057, 1038, 989, 966, 923, 834, 779, 730, 687.

HRMS (EI) for **$C_{14}H_{21}NOSi$** (247.1392) $[M]^+$: 247.1379.

Synthesis of 4-methoxy-N-(2-(trimethylsilyl)benzylidene)aniline (32):



A mixture of 2-(trimethylsilyl)benzaldehyde[116] (891 mg, 5 mmol, 1 equiv), anisidine (616 mg, 5 mmol, 1 equiv), Na_2SO_4 (53 mg) and molecular sieves (53 mg) in DCM (5 ml) was stirred at 23 °C for 12 h. The reaction mixture was then filtrated through a pad of Celite®. After washing the pad of Celite® with Et_2O, the crude mixture was purifired using Kugelrohr destillation to yield the desired compound **32** as a light yellow oil.

Isolated yield: 92% (166 mg).

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.40 (s, 9 H), 3.84 (s, 3 H), 6.96 (d, *J*=8.85 Hz, 2 H), 7.24 (d, *J*=8.57 Hz, 2 H), 7.44 (t, *J*=8.29 Hz, 2 H), 7.65 (d, *J*=7.46 Hz, 1 H), 8.08 (d, *J*=7.19 Hz, 1 H), 8.77 (s, 1 H).

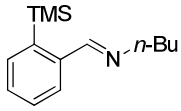
^{13}C NMR (75 MHz, DMSO) δ ppm 1.00, 55.49, 114.50, 114.83, 116.62, 122.12, 128.38, 129.35, 129.80, 130.59, 135.02, 141.05, 141.51, 144.75, 158.26, 158.95, 172.65.

MS (70 eV, EI) m/z (%): 283 (5), 270 (6), 269 (20), 268 (100), 253 (6), 134 (7), 123 (13).

IR ATR ν (cm^{-1}): 2952, 2890, 1692, 1681, 1615, 1592, 1510, 1503, 1465, 1437, 1296, 1240, 1179, 1116, 1073, 1031, 825, 754, 725, 689.

HRMS (EI) for **$C_{17}H_{21}NOSi$** (283.1392) $[M]^+$: 283.1388.

Synthesis of *N*-(2-(trimethylsilyl)benzylidene)butan-1-amine (33):



A mixture of 2-(trimethylsilyl)benzaldehyde[116] (891 mg, 5 mmol, 1 equiv), butan-1-amine (365 mg, 5 mmol, 1 equiv), Na_2SO_4 (53 mg) and molecular sieves (53 mg) in DCM (5 ml) was stirred at 23 °C for 12 h. The reaction mixture was, then, filtrated through a pad of Celite®. After washing the pad of Celite® with Et_2O, the crude mixture was purifired using Kugelrohr destillation to yield the desired compound **33** as a colorless oil.

Isolated yield: 94% (166 mg).

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.36 (s, 9 H), 0.96 (t, *J*=7.33 Hz, 3 H), 1.34 - 1.48 (m, 2 H), 1.65 - 1.79 (m, *J*=7.36, 7.36, 7.26, 7.05 Hz, 2 H), 3.63 (t, *J*=6.91 Hz, 2 H), 7.39 (quin, *J*=6.43 Hz, 2 H), 7.58 (d, *J*=6.63 Hz, 1 H), 7.92 (d, *J*=6.91 Hz, 1 H), 8.59 (s, 1 H).

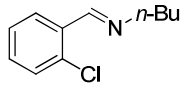
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.82, 13.88, 20.50, 32.85, 61.48, 127.47, 129.21, 129.28, 134.60, 140.05, 141.57, 161.41.

MS (70 eV, EI) m/z (%): 218 (90), 190 (54), 163 (78), 162 (48), 253 (6), 161 (100), 111 (41), 97 (59), 83 (71), 69 (72), 55 (70), 43 (57).

IR ATR ν (cm^{-1}): 2957, 2928, 2874, 1656, 1639, 1465, 1433, 1376, 1250, 1241, 1120, 1077, 975, 832, 753, 721, 689.

HRMS (EI) for **$C_{14}H_{22}NSi$** (233.1600) $[M-H]^+$: 233.1512.

Synthesis of *N*-(2-(trimethylsilyl)benzylidene)butan-1-amine (35):



A mixture of 2-chlorobenzaldehyde (703 mg, 5 mmol, 1 equiv), butan-1-amine (365 mg, 5 mmol, 1 equiv), Na_2SO_4 (53 mg) and molecular sieves (53 mg) in DCM (5 ml) was stirred at 23 °C for 12 h. The reaction mixture was, then, filtrated through a pad of Celite®. After washing the pad of Celite® with Et_2O, the crude mixture was purifired using Kugelrohr destillation to yield the desired compound **35** as a colorless oil.

Isolated yield: 87 % (170 mg).

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.95 (t, *J*=7.33 Hz, 3 H) 1.40 (dq, *J*=14.89, 7.38 Hz, 2 H) 1.58 - 1.78 (m, *J*=7.36, 7.36, 7.26, 7.05 Hz, 2 H) 3.65 (t, *J*=6.91 Hz, 2 H) 7.20 - 7.39 (m, 3 H) 8.01 (dd, *J*=7.19, 1.93 Hz, 1 H) 8.69 (s, 1 H).

^{13}C NMR (75 MHz, DMSO) δ/ppm: 13.85, 20.42, 32.92, 61.56, 126.92, 128.26, 129.68, 131.21, 133.40, 134.88, 157.44.

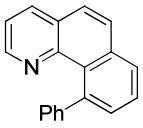
MS (70 eV, EI) m/z (%): 196 (100), 148 (4), 140 (7), 102 (3), 89 (8).

IR ATR ν (cm^{-1}): 2955, 2928, 2871, 2827, 1637, 1593, 1567, 1467, 1439, 1372, 1273, 1210, 1122, 1050, 1028, 899, 867, 751, 705.

HRMS (EI) for **$C_{11}H_{15}ClN$** (196.0893) $[M+H]^+$: 196.0885.

6.2 Preparation of Arylated Products Using TP6

Synthesis of 10-phenylbenzo[*h*]quinoline (23a):



According to **TP6**, a solution of PhMgCl (**2a**) in THF (1.12 mmol, 4 equiv, 1.62 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (3.4 mg, 0.028 mmol, 0.1 equiv) and benzo[*h*]quinoline (**22**) (50 mg, 0.28 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (5.3 mg, 0.42 mmol, 1.5 equiv) was added dropwise at 23 °C. Reaction mixture was stirred at 23 °C for 24 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 **23a** as a colorless oil.

Isolated yield: 95 %.

Solvent for purification: *i*-hexane, than toluene.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 7.15 - 7.49 (m, 6 H), 7.57 (dd, *J*=7.33, 1.24 Hz, 1 H), 7.61 - 7.77 (m, 2 H), 7.78 - 8.00 (m, 2 H), 8.10 (dd, *J*=8.02, 1.94 Hz, 1 H), 8.45 (dd, *J*=4.28, 1.80 Hz, 1 H).

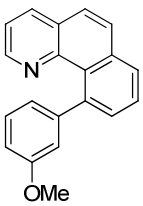
^{13}C NMR (75 MHz, DMSO) δ/ppm: 121.06, 125.71, 125.88, 127.07, 127.23, 127.38, 127.93, 128.32, 128.72, 128.89, 131.49, 134.99, 135.29, 141.68, 146.29, 146.67, 146.79.

MS (70 eV, EI) m/z (%): 255 (25), 254 (100), 127 (16), 127 (6), 126 (12), 45 (5), 42 (30).

IR ATR ν (cm^{-1}): 3046, 3023, 2957, 2928, 2859, 1619, 1587, 1565, 1509, 1492, 1442, 1416, 1393, 1323, 1181, 1132, 1081, 1026, 1014, 989, 960, 924, 833, 756, 729, 696.

HRMS (EI) for **$C_{19}H_{12}N$** (254.0970) $[M-H]^+$: 254.0964.

Synthesis of 10-phenylbenzo[*h*]quinoline (23b):



According to **TP6**, solution of **10d** in THF (1.12 mmol, 4 equiv, 1.62 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (3.4 mg, 0.028 mmol, 0.1 equiv) and benzo[*h*]quinoline (**22**)

(50 mg, 0.28 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (5.3 mg, 0.42 mmol, 1.5 equiv) was added dropwise at 23 °C. Reaction mixture was stirred at 23 °C for 24 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 **23b** as a colorless oil.

Isolated yield: 90 %.

Solvent for purification: *i*-hexane, than toluene.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 3.81 (s, 3 H), 6.89 - 7.03 (m, 3 H,) 7.28 - 7.39 (m, 2 H), 7.59 (d, *J*=7.19 Hz, 1 H), 7.63 - 7.74 (m, 2 H), 7.86 (d, *J*=8.85 Hz, 1 H), 7.93 (d, *J*=7.74 Hz, 1 H), 8.08 (dd, *J*=7.88, 1.52 Hz, 1 H), 8.49 (dd, *J*=4.15, 1.66 Hz, 1 H).

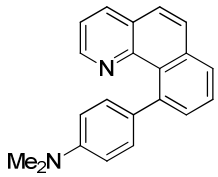
^{13}C NMR (75 MHz, DMSO) δ ppm 55.24, 111.49, 114.39, 121.08, 121.47, 125.94, 127.00, 127.21, 128.00, 128.23, 128.30, 129.01, 131.30, 134.96, 135.13, 141.46, 146.73, 146.95, 147.84, 159.02.

MS (70 eV, EI) m/z (%): 285 (35), 284 (100), 270 (11), 268 (7), 242 (11), 241 (31), 239 (4), 120 (14).

IR ATR ν (cm^{-1}): 3045, 2931, 1598, 1577, 1481, 1450, 1410, 1316, 1284, 1218, 1165, 1130, 1047, 1038, 859, 830, 777, 748, 728, 698, 666.

HRMS (EI) for **$C_{20}H_{15}NO$** (284.1075) $[M-H]^+$: 284.1069

Synthesis of 4-(benzo[*h*]quinolin-10-yl)-N,N-dimethylaniline (23c):



According to **TP6**, a solution of **2n** in THF (2 mmol, 4 equiv, 0.76 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and benzo[*h*]quinoline (**22**) (90 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 24 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 **23c** as a light brownish oil.

Isolated yield: 87 %.

Solvent for purification: *i*-hexane, than toluene.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 3.04 (s, 6 H), 6.83 (d, *J*=8.57 Hz, 2 H), 7.23 - 7.35 (m, 3 H), 7.55 - 7.61 (m, 1 H), 7.62 - 7.70 (m, 2 H), 7.85 (t, *J*=8.71 Hz, 2 H), 8.07 (dd, *J*=7.88, 1.52 Hz, 1 H), 8.53 (dd, *J*=4.15, 1.66 Hz, 1 H).

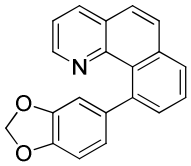
^{13}C NMR (75 MHz, DMSO) δ/ppm: 40.95, 112.04, 120.90, 125.75, 127.06, 127.13, 127.31, 128.36, 129.17, 129.57, 131.80, 135.01, 135.13, 135.17, 141.94, 146.86, 147.22, 149.08.

MS (70 eV, EI) m/z (%): 299 (13), 298(62), 297 (100), 281 (32), 252 (16), 149 (16), 126 (10).

IR ATR ν (cm^{-1}): 3037, 2856, 2794, 1608, 1518, 1439, 1415, 1340, 1323, 1221, 1194, 1163, 1131, 1081, 1057, 945, 906, 836, 810, 760, 731.

HRMS (EI) for **$C_{21}H_{17}N_2$** (297.1392) $[M-H]^+$: 297.1385.

Synthesis of 10-(benzo[d][1,3]dioxol-5-yl)benzo[*h*]quinoline (23d):



According to **TP6**, a solution of **2k** in THF (2 mmol, 4 equiv, 0.82 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and benzo[*h*]quinoline (**22**) (90 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. Reaction mixture was stirred at 23 °C for 24 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 **23d** as a yellow crystals.

Isolated yield: 67 %

Solvent for purification: *i*-hexane, than toluene.

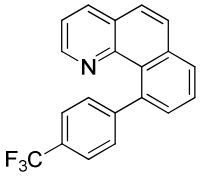
m.p.: 134.8 – 136.4 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 6.04 (br. s., 2 H), 6.81 - 6.94 (m, 2 H), 7.38 (dd, *J*=8.02, 4.42 Hz, 2 H), 7.56 (dd, *J*=7.33, 1.24 Hz, 1 H), 7.61 - 7.75 (m, 2 H), 7.81 - 7.96 (m, 2 H), 8.13 (dd, *J*=8.02, 1.66 Hz, 1 H), 8.60 (dd, *J*=4.42, 1.66 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO) δ/ppm: 100.79, 107.70, 110.02, 121.14, 121.56, 125.86, 127.22, 127.36, 127.98, 128.47, 128.64, 131.62, 135.09, 135.76, 139.93, 141.13, 145.94, 146.27, 146.81, 146.94.

MS (70 eV, EI) m/z (%): 299 (36), 298(100), 241 (9), 240 (10), 239 (9), 120 (11), 119 (6).
IR ATR ν (cm^{-1}): 2920, 1447, 1332, 1220, 1181, 1033, 931, 836, 805, 766, 731.
HRMS (EI) for **$C_{20}H_{12}NO_2$** (298.0868) $[M-H]^+$: 298.0865.

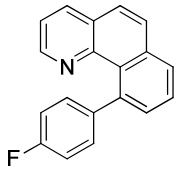
Synthesis of 10-(4-(trifluoromethyl)phenyl)benzo[*h*]quinoline (23e):



According to **TP6**, a solution of **2y** in THF (2 mmol, 4 equiv, 0.90 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and benzo[*h*]quinoline (**22**) (90 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 38 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 **23e** as beige crystals.

Isolated yield: 66 %
Solvent for purification: *i*-hexane, than toluene.
m.p.: 101.3 – 103.1 °C.
^{1}H NMR (300 MHz, DMSO) δ/ppm: 7.35 (dd, *J*=8.02, 4.15 Hz, 1 H) 7.40 - 7.57 (m, 3 H) 7.57 - 7.78 (m, 4 H) 7.89 (d, *J*=8.57 Hz, 1 H) 7.98 (d, *J*=7.74 Hz, 1 H) 8.12 (dd, *J*=8.02, 1.66 Hz, 1 H) 8.42 (dd, *J*=4.28, 1.52 Hz, 1 H).
^{13}C NMR (75 MHz, DMSO) δ/ppm: 121.27, 124.29 (q, *J*=3.65 Hz), 124.76 (q, *J*=271.80 Hz), 126.08, 127.14, 127.31, 127.83 (*J*=31.98 Hz), 128.28, 128.52, 128.68, 129.01, 131.14, 134.97, 135.50, 140.17, 146.16, 146.79, 150.02.
MS (70 eV, EI) m/z (%): 323 (34), 322 (100), 352 (17), 161 (5), 151 (5), 126 (9), 43 (15).
IR ATR ν (cm^{-1}): 3048, 2962, 2923, 1615, 1590, 1567, 1508, 1421, 1403, 1320, 1151, 1103, 1061, 1014, 833, 827, 761, 729, 679.
HRMS (EI) for **$C_{20}H_{11}NO_2$** (322.0844) $[M-H]^+$: 322.0843.

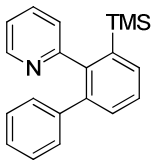
Synthesis of 10-(4-fluorophenyl)benzo[*h*]quinoline (23f):



According to **TP6**, a solution of **2g** in THF (2 mmol, 4 equiv, 1.05 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and benzo[*h*]quinoline (**22**) (90 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 24 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 **23f** as beige crystals.

Isolated yield: 86 %.
Solvent for purification: *i*-hexane, than toluene.
m.p.: 117.7 – 119.3 °C.
^{1}H NMR (300 MHz, DMSO) δ/ppm: 7.10 (t, *J*=8.71 Hz, 1 H), 7.19 - 7.47 (m, 4 H), 7.53 (d, *J*=7.19 Hz, 1 H), 7.60 - 7.79 (m, 2 H), 7.86 (d, *J*=8.85 Hz, 1 H), 7.94 (d, *J*=7.74 Hz, 1 H), 8.09 (d, *J*=8.02 Hz, 1 H), 8.40 - 8.50 (m, 1 H).
^{13}C NMR (75 MHz, DMSO) δ/ppm: 113.96, 114.25, 121.13, 125.99, 127.02, 127.26, 128.13, 128.29, 129.00, 130.09, 130.20, 131.49, 135.01, 135.30, 140.65, 142.18, 142.23, 146.70, 146.83, 159.95, 163.17.
MS (70 eV, EI) m/z (%): 323 (34), 322 (100), 352 (17), 161 (5), 151 (5), 126 (9), 43 (15).
IR ATR ν (cm^{-1}): 3048, 2923, 2847, 1587, 1513, 1502, 1420, 1209, 1156, 1132, 1090, 1015, 829, 810, 758, 730.
HRMS (EI) for **$C_{19}H_{11}N_1F_1$** (272.0876) $[M-H]^+$: 272.0867.

Synthesis of 2-(3-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)pyridine (25a):



According to **TP6**, a solution of **2a** in THF (2 mmol, 4 equiv, 1.66 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 2-(2-(trimethylsilyl)phenyl)pyridine (**24**) (113.5 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °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 **25a** as white crystals.

Isolated yield: 92 %.

Solvent for purification: *i*-hexane/ethyl acetate 10:1.

m.p.: 84.8 – 86.8 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: -0.01 (s, 9 H), 6.90 (d, *J*=7.74 Hz, 1 H), 6.95 - 7.29 (m, 6 H), 7.32 - 7.53 (m, 3 H), 7.70 (dd, *J*=7.19, 1.38 Hz, 1 H), 8.62 (d, *J*=4.42 Hz, 1 H).

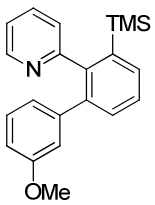
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.31, 121.78, 126.26, 126.36, 127.54, 127.58, 129.81, 130.81, 134.11, 135.40, 139.89, 140.80, 141.66, 145.16, 148.12, 160.67.

MS (70 eV, EI) m/z (%): 290 (6), 289 (23), 288 (100), 258 (18), 149 (6), 135 (4).

IR ATR ν (cm^{-1}): 2948, 2923, 1726, 1584, 1471, 1402, 1239, 1142, 1054, 1021, 854, 833, 751, 699.

HRMS (EI) for **$C_{20}H_{20}NSi$** (302.1365) $[M-H]^+$: 302.1359.

Synthesis of 2-(3'-methoxy-3-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)pyridine (25b):



According to **TP6**, a solution of **10d** in THF (2 mmol, 4 equiv, 1.09 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 2-(2-(trimethylsilyl)phenyl)pyridine (**24**) (113.5 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °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 **25b** as a colorless oil.

Isolated yield: 79 %.

Solvent for purification: *i*-hexane/ethyl acetate 10:1.

^{1}H NMR (300 MHz, DMSO) δ/ppm: -0.01 (s, 9 H), 3.59 (s, 3 H), 6.58 (d, *J*=1.66 Hz, 1 H), 6.64 - 6.74 (m, 2 H), 6.92 (d, *J*=7.74 Hz, 1 H), 7.01 - 7.18 (m, 2 H), 7.35 - 7.50 (m, 3 H), 7.70 (dd, *J*=6.77, 2.07 Hz, 1 H), 8.63 (d, *J*=4.42 Hz, 1 H).

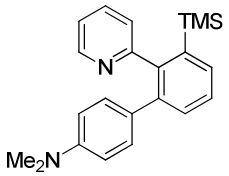
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.31, 55.08, 112.87, 114.81, 121.77, 122.29, 126.28, 127.49, 128.60, 130.66, 134.19, 135.39, 139.91, 140.62, 143.05, 145.25, 148.15, 158.78, 160.84.

MS (70 eV, EI) m/z (%): 320 (6), 319 (30), 318 (100), 302 (15), 274 (16), 244 (6), 158 (5).

IR ATR ν (cm^{-1}): 3057, 2949, 1599, 1585, 1564, 1487, 1474, 1463, 1430, 1400, 1315, 1299, 1245, 1222, 1178, 1146, 1037, 989, 887, 834, 762, 747, 702.

HRMS (EI) for **$C_{21}H_{23}NOSi$** (333.1549) $[M]^+$: 333.1552.

Synthesis of N,N-dimethyl-2'-(pyridin-2-yl)-3'-(trimethylsilyl)-[1,1'-biphenyl]-4-amine (25c):



According to **TP6**, a solution of **2u** in THF (2 mmol, 4 equiv, 1.10 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 2-(2-(trimethylsilyl)phenyl)pyridine (**24**) (113.5 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 4 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 **25c** as redish crystals.

Isolated yield: 85 %.

Solvent for purification: *i*-hexane/ethyl acetate 10:1.

m.p.: 138.5 – 140.2 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: -0.02 (s, 9 H), 2.89 (s, 6 H), 6.56 (d, *J*=8.57 Hz, 2 H), 6.89 - 6.97 (m, 3 H), 7.12 (dd, *J*=6.36, 4.98 Hz, 1 H), 7.37 - 7.47 (m, 3 H), 7.64 (dd, *J*=6.63, 2.21 Hz, 1 H), 8.63 (d, *J*=4.15 Hz, 1 H).

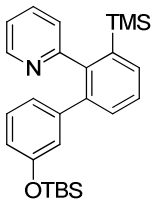
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.34, 40.71, 112.12, 121.55, 126.33, 127.44, 130.42, 130.60, 130.92, 133.42, 135.20, 139.77, 140.66, 145.37, 148.35, 148.59, 161.35.

MS (70 eV, EI) m/z (%): 333 (8), 332 (25), 331 (100), 317 (8), 316 (6), 315 (27), 165 (15), 43 (31).

IR ATR ν (cm^{-1}): 2949, 2928, 1610, 1587, 1522, 1477, 1401, 1350, 1239, 1194, 1155, 1057, 990, 946, 846, 836, 799, 762, 749.

HRMS (EI) for **$C_{22}H_{26}N_2Si$** (346.1865) $[M]^+$: 346.1852.

Synthesis of 2-(3'-((tert-butyldimethylsilyl)oxy)-3-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)pyridine (25d):



According to **TP6**, a solution of **2p** in THF (2 mmol, 4 equiv, 0.80 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 2-(2-(trimethylsilyl)phenyl)pyridine (**24**) (113.5 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °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 **25d** as white crystals.

Isolated yield: 83 %.

Solvent for purification: *i*-hexane/ethyl acetate 15:1.

m.p.: 60.8 – 62.5 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: -0.02 (s, 9 H), 0.08 (s, 6 H), 0.93 (s, 9 H), 6.53 - 6.74 (m, 3 H), 6.91 (d, *J*=7.99 Hz, 1 H), 7.00 (t, *J*=7.80 Hz, 1 H), 7.08 - 7.15 (m, 1 H), 7.36 - 7.40 (m, 2 H), 7.45 (t, *J*=7.51 Hz, 1 H), 7.69 (dd, *J*=7.41, 1.36 Hz, 1 H), 8.61 (d, *J*=4.09 Hz, 1 H).

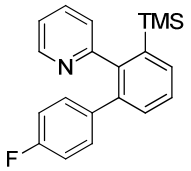
^{13}C NMR (75 MHz, DMSO) δ/ppm: -4.43, 0.33, 18.13, 25.65, 118.15, 121.70, 121.74, 123.18, 126.14, 127.34, 128.49, 130.72, 134.17, 135.11, 139.89, 140.57, 143.21, 145.40, 148.42, 154.91, 160.82.

MS (70 eV, EI) m/z (%): 420 (14), 419 (37), 418 (100), 402 (6), 180 (14), 73 (13).

IR ATR ν (cm^{-1}): 2955, 2929, 2853, 1599, 1583, 1563, 1483, 1471, 1454, 1398, 1299, 1250, 1213, 1191, 1160, 1051, 939, 881, 833, 776, 749, 675.

HRMS (EI) for **$C_{26}H_{35}NOSi_2$** (433.2257) $[M]^+$: 433.2235.

Synthesis of 2-(4'-fluoro-3-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)pyridine (25e):



According to **TP6**, a solution of **2g** in THF (2 mmol, 4 equiv., 0.80 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 2-(2-(trimethylsilyl)phenyl)pyridine (**24**) (113.5 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °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 **25e** as white crystals.

Isolated yield: 84 %.

Solvent for purification: *i*-hexane/ethyl acetate 10:1.

m.p.: 72.0 – 73.8 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: -0.02 (s, 9 H), 6.78 - 6.91 (m, 3 H), 7.03 (dd, *J*=8.57, 5.53 Hz, 2 H), 7.13 (dd, *J*=6.91, 5.25 Hz, 1 H), 7.36 - 7.49 (m, 3 H), 7.70 (d, *J*=7.46 Hz, 1 H), 8.61 (d, *J*=4.70 Hz, 1 H).

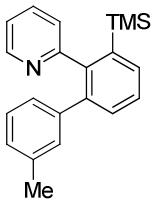
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.28, 114.33, 114.61, 121.76, 126.18, 127.48, 130.69, 131.23, 134.18, 135.23, 137.73, 139.74, 139.98, 145.60, 148.48, 159.90, 160.74, 163.16.

MS (70 eV, EI) m/z (%): 308 (7), 307 (25), 306 (100), 276 (21), 153 (2).

IR ATR ν (cm^{-1}): 2949, 2925, 1584, 1508, 1474, 1416, 1245, 1237, 1219, 1157, 1093, 1044, 1013, 856, 836, 805, 793, 749, 686.

HRMS (EI) for **$C_{20}H_{20}FNSi$** (321.1349) $[M]^+$: 321.1321.

Synthesis of 2-(3'-methyl-3-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)pyridine (25f):



According to **TP6**, a solution of **2b** in THF (2 mmol, 4 equiv, 0.90 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 2-(2-(trimethylsilyl)phenyl)pyridine (**24**) (113.5 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 6 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 **25f** as a colorless oil.

Isolated yield: 89 %.

Solvent for purification: *i*-hexane/ethyl acetate 15:1.

^{1}H NMR (300 MHz, DMSO) δ/ppm: -0.03 (s, 9 H), 2.18 (s, 3 H), 6.79 - 7.15 (m, 6 H), 7.31 - 7.48 (m, 3 H), 7.67 (dd, *J*=6.91, 1.94 Hz, 1 H), 8.60 (d, *J*=4.42 Hz, 1 H).

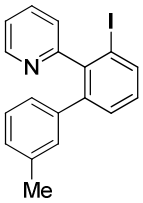
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.32, 21.22, 121.59, 126.19, 126.84, 126.91, 127.36, 127.38, 130.71, 130.76, 133.97, 135.00, 137.06, 139.79, 140.80, 141.60, 145.59, 148.35, 161.03.

MS (70 eV, EI) m/z (%): 316 (10), 306 (17), 304 (23), 303 (27), 302 (100), 272 (16), 245 (22), 244 (66), 127 (14), 105 (11), 57 (15), 44 (22).

IR ATR ν (cm^{-1}): 3053, 2948, 1604, 1586, 1564, 1474, 1400, 1260, 1244, 1144, 1062, 1021, 989, 882, 834, 781, 761, 744, 706, 671.

HRMS (EI) for **$C_{21}H_{22}NSi$** (316.1522) $[M-H]^+$: 316.1524

Synthesis of 2-(3-iodo-3'-methyl-[1,1'-biphenyl]-2-yl)pyridine (25fa):



To a solution of **25f** (317.5 mg, 1 mmol, 1.0 equiv) in CH_2Cl_2 (5 ml) was added dropwise ICl (496 mg, 3.5 mmol, 3.5 equiv) at 0 °C. Reaction mixture was warm up to 23 °C and then was stirred under reflux for 12 h, before being quenched with sat. aq. $Na_2S_2O_3$ 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 **25fa** as a colourless oil.

Isolated yield: 56 %.

Solvent for purification: *i*-hexane/ethyl acetate 15:1.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 2.18 (s, 3 H) 6.74 - 7.05 (m, 5 H) 7.07 - 7.19 (m, 2 H) 7.39 (d, *J*=7.74 Hz, 1 H) 7.50 (td, *J*=7.67, 1.52 Hz, 1 H) 7.95 (d, *J*=7.74 Hz, 1 H) 8.62 (d, *J*=4.42 Hz, 1 H).

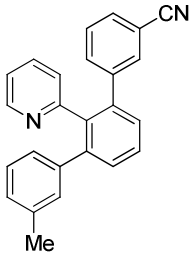
^{13}C NMR (75 MHz, DMSO) δ/ppm: 21.20, 99.24, 122.06, 125.26, 126.42, 127.46, 127.47, 129.66, 129.91, 130.22, 135.78, 137.22, 138.26, 140.68, 142.78, 143.62, 148.65, 161.31.

MS (70 eV, EI) m/z (%): 372 (16), 371 (96), 370 (100), 244 (41), 243 (67), 242 (31), 149 (22), 71 (23), 43 (28).

IR ATR ν (cm^{-1}): 2956, 2918, 2856, 1722, 1587, 1564, 1547, 1445, 1418, 1270, 1126, 1121, 1072, 1020, 989, 960, 776, 744, 704.

HRMS (EI) for **$C_{18}H_{14}IN$** (370.0093) $[M-1]^+$: 370.0081.

Synthesis of 3''-methyl-2'-(pyridin-2-yl)-[1,1':3',1''-terphenyl]-3-carbonitrile (27):



A solution of **26** in THF (0.45 mmol, 1.5 equiv, 0.31 M) was added dropwise to a mixture of $Pd(dba)_2$ (4.7 mg, 0.009 mmol, 0.03 equiv), tris(2-furyl)phosphine (4.2 mg, 0.018 mmol, 0.06 equiv) and 2-(3-iodo-3'-methyl-[1,1'-biphenyl]-2-yl)pyridine (**25fa**) (111.4 mg, 0.3 mmol, 1 equiv) in THF (0.3 ml) at 23 °C. The reaction mixture was stirred at 50 °C for 15 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 **27** as white crystals.

Isolated yield: 70 %.

Solvent for purification: *i*-hexane/ethyl acetate 15:1.

m.p.: 125.5-127.2 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 2.20 (s, 3 H), 6.75 - 6.89 (m, 2 H), 6.89 - 7.14 (m, 4 H), 7.17 - 7.45 (m, 6 H), 7.46 - 7.58 (m, 2 H), 8.32 (d, *J*=4.70 Hz, 1 H).

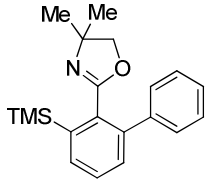
^{13}C NMR (75 MHz, DMSO) δ/ppm: 21.22, 111.78, 118.68, 121.24, 126.59, 126.70, 127.27, 127.55, 128.39, 128.42, 128.99, 129.91, 130.28, 130.43, 132.98, 133.95, 135.19, 137.32, 138.44, 139.53, 140.84, 142.20, 142.96, 148.60, 158.18.

MS (70 eV, EI) m/z (%): 379 (7), 347 (9), 346 (51), 345 (100), 343 (6), 303 (2), 172 (4), 165 (5).

IR ATR ν (cm^{-1}): 3051, 2919, 1590, 1575, 1473, 1436, 1401, 805, 780, 758, 734, 706, 698, 681.

HRMS (EI) for **$C_{25}H_{17}N_2$** (345.1392) $[M-1]^+$: 345.1387.

Synthesis of 4,4-dimethyl-2-(3-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)-4,5-dihydrooxazole (29a):



According to **TP6**, a solution of **2a** in THF (2 mmol, 4 equiv, 1.10 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 4,4-dimethyl-2-(2-(trimethylsilyl)phenyl)-4,5-dihydrooxazole (**28**) (123.7 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °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 **29a** as a colorless oil.

Isolated yield: 91 %.

Solvent for purification: *i*-hexane/ethyl acetate 10:1.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.35 (s, 9 H), 1.10 (s, 6 H), 3.81 (s, 2 H), 7.28 - 7.45 (m, 7 H), 7.55 - 7.59 (m, 1 H).

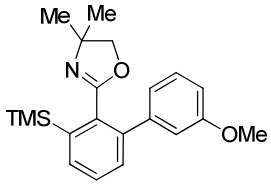
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.21, 27.97, 67.87, 78.82, 125.80, 126.99, 127.66, 128.11, 128.45, 129.07, 130.49, 133.38, 134.03, 139.20, 141.30, 142.26, 162.77

MS (70 eV, EI) m/z (%): 323 (29), 322 (100), 308 (30), 252 (8), 236 (19), 220 (10), 42 (11).

IR ATR ν (cm^{-1}): 3054, 2965, 2892, 1659, 1462, 1443, 1413, 1363, 1344, 1286, 1246, 1210, 1183, 1146, 1097, 1033, 961, 920, 854, 836, 760, 751, 697.

HRMS (EI) for **$C_{20}H_{24}NOSi$** (322.1627) $[M-H]^+$: 322.1631.

Synthesis of 2-(3'-methoxy-3-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (29b):



According to **TP6**, a solution of **10d** in THF (2 mmol, 4 equiv, 0.84 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 4,4-dimethyl-2-(2-(trimethylsilyl)phenyl)-4,5-dihydrooxazole (**28**) (123.7 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 5 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 **29b** as a beij oil.

Isolated yield: 85 %.

Solvent for purification: *i*-hexane/ethyl acetate 6:1.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.34 (s, 9 H), 1.11 (s, 6 H), 3.79 (s, 3 H), 3.84 (s, 2 H), 6.85 (d, *J*=8.23 Hz, 1 H), 6.94 (br. s., 1 H), 6.97 (d, *J*=7.68 Hz, 1 H), 7.24 (t, *J*=7.68 Hz, 1 H), 7.31 (d, *J*=7.41 Hz, 1 H), 7.40 (t, *J*=7.41 Hz, 1 H), 7.56 (d, *J*=7.41 Hz, 1 H).

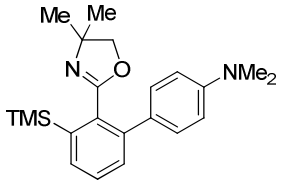
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.20, 27.93, 55.25, 67.82, 78.92, 112.96, 114.49, 121.66, 128.47, 128.67, 130.39, 133.45, 133.83, 139.23, 142.14, 142.60, 158.99, 162.83.

MS (70 eV, EI) m/z (%): 353 (17), 352 (58), 338 (18), 281 (17), 266 (42), 236 (16), 126 (59), 61 (16).

IR ATR ν (cm^{-1}): 3056, 2960, 2926, 1664, 1636, 1599, 1574, 1493, 1461, 1363, 1321, 1288, 1223, 1216, 1174, 1094, 1035, 960, 918, 868, 775, 759, 697.

HRMS (EI) for **$C_{21}H_{26}NO2Si$** (352.1733) $[M-H]^+$: 352.1725.

Synthesis of 2'-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-N,N-dimethyl-3'-(trimethylsilyl)-[1,1'-biphenyl]-4-amine (29c):



According to **TP6**, a solution of **2n** in THF (2 mmol, 4 equiv, 1.10 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 4,4-dimethyl-2-(2-(trimethylsilyl)phenyl)-4,5-dihydrooxazole (**28**) (123.7 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 15 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 **29c** as dark violet crystals.

Isolated yield: 72 %.

Solvent for purification: *i*-hexane/ethyl acetate 7:1, then 4:1.

m.p.: 162.8 – 164.6 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.34 (s, 9 H), 1.19 (s, 6 H), 2.96 (s, 6 H), 3.86 (s, 2 H), 6.76 (d, *J*=8.29 Hz, 2 H), 7.25 - 7.32 (m, 3 H), 7.38 (t, *J*=7.60 Hz, 1 H), 7.49 - 7.54 (m, 1 H).

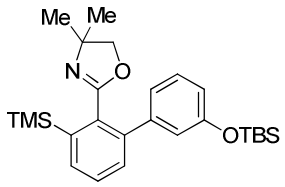
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.28, 28.13, 29.68, 40.91, 67.82, 78.90, 112.28, 128.46, 129.75, 130.81, 132.76, 134.04, 139.07, 142.23, 149.56, 163.28.

MS (70 eV, EI) m/z (%): 366 (18), 365 (13), 352 (29), 351 (100), 279 (9), 139 (7).

IR ATR ν (cm^{-1}): 2959, 2919, 2855, 1659, 1608, 1523, 1461, 1355, 1292, 1280, 1250, 1240, 1193, 1164, 1096, 1053, 1035, 961, 942, 920, 835, 813, 767.

HRMS (EI) for **$C_{22}H_{30}N_2OSi$** (366.2127) $[M]^+$: 366.2130.

Synthesis of 2-(3'-((tert-butyldimethylsilyl)oxy)-3-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (29d):



According to **TP6**, a solution of **2p** in THF (2 mmol, 4 equiv, 0.77 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 4,4-dimethyl-2-(2-(trimethylsilyl)phenyl)-4,5-dihydrooxazole (**28**) (123.7 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 12 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 **29d** as a colorless oil.

Isolated yield: 78 %.

Solvent for purification: *i*-hexane/ethyl acetate 9:1.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.19 (s, 6 H), 0.35 (s, 9 H), 0.98 (s, 9 H), 1.15 (s, 6 H), 3.83 (s, 2 H), 6.79 (dd, *J*=8.02, 1.38 Hz, 1 H), 6.90 (t, *J*=1.80 Hz, 1 H), 6.98 (d, *J*=7.74 Hz, 1 H), 7.18 (t, *J*=8.02 Hz, 1 H), 7.24 - 7.32 (m, 1 H), 7.40 (t, *J*=7.60 Hz, 1 H), 7.53 - 7.59 (m, 1 H).

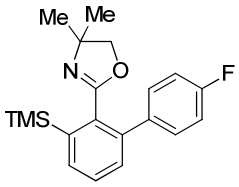
^{13}C NMR (75 MHz, DMSO) δ/ppm: -4.40, 0.24, 18.14, 25.66, 28.00, 67.89, 78.90, 118.38, 120.94, 122.31, 128.43, 128.53, 130.40, 133.39, 139.19, 142.00, 142.70, 149.57, 155.02, 162.78.

MS (70 eV, EI) m/z (%): 454 (18), 453 (43), 452 (100), 439 (14), 438 (34), 308 (10), 73 (28).

IR ATR ν (cm^{-1}): 2957, 2929, 2984, 2857, 1660, 1602, 1580, 1484, 1462, 1301, 1285, 1248, 1222, 1211, 1096, 1035, 949, 919, 830, 778, 763, 698.

HRMS (EI) for **$C_{26}H_{38}NO_2Si_2$** (452.2441) $[M-H]^+$: 452.2429.

Synthesis of 2-(4'-fluoro-3-(trimethylsilyl)-[1,1'-biphenyl]-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (29e):



According to **TP6**, a solution of **2g** in THF (2 mmol, 4 equiv, 0.77 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 4,4-dimethyl-2-(2-(trimethylsilyl)phenyl)-4,5-dihydrooxazole (**28**) (123.7 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °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 **29e** as a colorless oil.

Isolated yield: 87 %.

Solvent for purification: *i*-hexane/ethyl acetate 10:1.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.34 (s, 9 H), 1.12 (s, 6 H), 3.84 (s, 2 H), 7.03 (t, *J*=8.77 Hz, 2 H), 7.25 - 7.30 (m, 1 H), 7.31 - 7.44 (m, 3 H), 7.57 (dd, *J*=7.51, 1.07 Hz, 1 H).

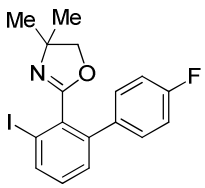
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.17, 28.01, 67.86, 78.91, 114.42, 114.63, 128.57, 130.53, 130.68, 130.75, 133.58, 137.18, 137.21, 139.39, 141.16, 160.95, 163.39.

MS (70 eV, EI) m/z (%): 342 (8), 341 (32), 340 (100), 327 (15), 326 (53), 255 (10), 254 (17), 165 (8).

IR ATR ν (cm^{-1}): 2966, 2894, 1659, 1602, 1511, 1462, 1451, 1421, 1364, 1344, 1286, 1246, 1220, 1158, 1093, 1046, 1034, 1015, 985, 961, 920, 857, 834, 796, 762, 711.

HRMS (EI) for **$C_{20}H_{23}FNOSi$** (340.1533) $[M-H]^+$: 340.1529.

Synthesis of 2-(4'-fluoro-3-iodo-[1,1'-biphenyl]-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (29ea):



To a solution of **29e** (341.5 mg, 1 mmol, 1 equiv) in DCM (0.2 M) was added dropwise ICl (568.3 mg, 3.5 mmol, 3.5 equiv) at 0 °C. Reaction mixture was warmed up to 23 °C and then heated under reflux for 6 h, before being quenched with sat. aq. $Na_2S_2O_3$ 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 **29ea** as light yellow crystals.

Isolated yield: 86 %.

Solvent for purification: *i*-hexane/ethyl acetate 10:1, then 3:1.

m.p.: 101.5 – 102.6 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 1.18 (s, 6 H), 3.93 (s, 2 H), 7.04 (t, *J*=8.51 Hz, 2 H), 7.12 (t, *J*=7.82 Hz, 1 H), 7.29 (d, *J*=7.68 Hz, 1 H), 7.31 - 7.41 (m, 2 H), 7.83 (d, *J*=7.96 Hz, 1 H).

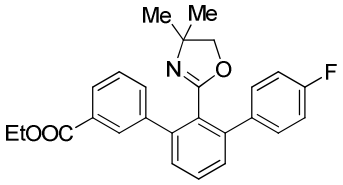
^{13}C NMR (75 MHz, DMSO) δ/ppm: 27.61, 68.00, 79.47, 96.83, 114.77, 114.91, 129.32, 130.44, 130.49, 130.89, 134.05, 135.85, 135.87, 138.08, 142.54, 161.69, 162.38, 163.33.

MS (70 eV, EI) m/z (%): 394 (85), 308 (22), 252 (11), 197 (15), 191 (12), 126 (45), 70 (14), 61 (18), 57 (17), 44 (97), 43 (100).

IR ATR ν (cm^{-1}): 2970, 2960, 1673, 1604, 1595, 1509, 1449, 1363, 1347, 1289, 1211, 1160, 1094, 1039, 1024, 961, 922, 836, 784, 747.

HRMS (EI) for **$C_{17}H_{14}FNOI$** (394.0104) $[M-H]^+$: 394.0092.

Synthesis of ethyl 2''-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-4''-fluoro-[1,1':3',1''-terphenyl]-3-carboxylate (31):



A solution of **30** in THF (0.45 mmol, 1.5 equiv, 0.71 M) was added dropwise to a mixture of $Pd(dba)_2$ (4.7 mg, 0.009 mmol, 0.03 equiv), tris(2-furyl)phosphine (4.2 mg, 0.018 mmol, 0.06 equiv) and 2-(3-iodo-3'-methyl-[1,1'-biphenyl]-2-yl)pyridine (**29ea**) (118.0 mg, 0.3 mmol, 1 equiv) in THF (0.3 ml) at 23 °C. The reaction mixture was stirred at 50 °C for 15 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 **31** as a yellowish oil.

Isolated yield: 92 %.

Solvent for purification: *i*-hexane/ethyl acetate 4:1, then 3:1.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.90 (s, 6 H), 1.35 (t, *J*=7.19 Hz, 3 H), 3.60 (s, 2 H), 4.35 (q, *J*=7.19 Hz, 2 H), 7.05 (t, *J*=8.71 Hz, 2 H), 7.32 - 7.53 (m, 6 H), 7.64 (d, *J*=7.74 Hz, 1 H), 8.03 (d, *J*=7.74 Hz, 1 H), 8.13 (s, 1 H).

^{13}C NMR (75 MHz, DMSO) δ/ppm: 14.34, 27.38, 61.00, 67.67, 79.01, 114.63, 114.91, 127.90, 128.06, 128.60, 128.76, 129.02, 129.55, 129.80, 130.22, 130.48, 130.59, 130.86, 133.31, 136.47, 136.51, 140.73, 141.25, 141.31, 160.99, 166.40.

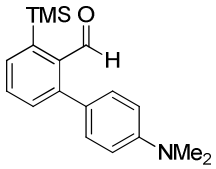
MS (70 eV, EI) m/z (%): 417 (29), 416 (100), 316 (4), 272 (10), 257 (5), 149 (9), 55 (10), 40 (4).

IR ATR ν (cm^{-1}): 2966, 2926, 1716, 1664, 1606, 1512, 1460, 1365, 1288, 1256, 1236, 1159, 1125, 1104, 1034, 960, 840, 802, 755, 696.

HRMS (EI) for **$C_{26}H_{23}FNO_3$** (416.1662) $[M-H]^+$: 416.1656.

6.3 Preparation of Arylated Products Using TP7

Synthesis of 4'-(dimethylamino)-3-(trimethylsilyl)-[1,1'-biphenyl]-2-carbaldehyde (34aa and 34ba):



According to **TP7**, a solution of **2n** in THF (2 mmol, 4 equiv, 1.1 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 2-(4-methoxystyryl)phenyl)trimethylsilane (**32**) (141.2 mg, 0.5 mmol, 1 equiv) or *N*-(2-(trimethylsilyl)benzylidene)butan-1-amine (**33**) (116.7 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 16 h (**34aa**) or 3 h (**34ba**), before being quenched with an aq. solution of HCl (2M) and extracted with EtOAc. The organic layer was washed with brine and dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield **34aa** or **34ba** as a redish oil.

Isolated yield of 34aa: 76 %

34ba: 73 %

Solvent for purification: *i*-hexane/ethyl acetate 95:5.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.35 (s, 9 H), 3.04 (s, 6 H), 6.85 (d, *J*=7.74 Hz, 2 H), 7.24 - 7.29 (m, 2 H), 7.42 - 7.47 (m, 1 H), 7.55 (t, *J*=7.46 Hz, 1 H), 7.70 (d, *J*=7.19 Hz, 1 H), 9.99 (s, 1 H).

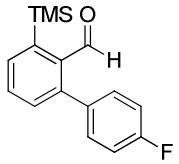
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.33, 40.70, 112.35, 131.17, 131.79, 131.86, 132.08, 134.19, 138.32, 142.20, 147.32, 149.82, 194.47.

MS (70 eV, EI) m/z (%): 297 (26), 283 (23), 282 (100), 266 (8), 237 (11), 208 (12), 165 (8), 141 (10), 140 (18).

IR ATR ν (cm^{-1}): 2946, 2923, 2851, 1680, 1607, 1571, 1523, 1453, 1445, 1381, 1353, 1244, 1195, 1179, 1143, 1049, 946, 860, 837, 820, 795, 763, 671.

HRMS (EI) for **$C_{18}H_{23}NOSi$** (297.1549) $[M]^+$: 297.1549.

Synthesis of 4'-fluoro-3-(trimethylsilyl)-[1,1'-biphenyl]-2-carbaldehyde (34ab and **34bb):**



According to **TP7**, a solution of **2g** in THF (2 mmol, 4 equiv., 1.02 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv.) and 2-(4-methoxystyryl)phenyl)trimethylsilane (**32**) (141.2 mg, 0.5 mmol, 1 equiv.) or *N*-(2-(trimethylsilyl)benzylidene)butan-1-amine (**33**) (116.7 mg, 0.5 mmol, 1 equiv.) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv.) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 16 h (**34ab**) or 2 h (**34bb**), 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 **34ab** or **34bb** as white crystals.

Isolated yield of 34ab: 61 %.

34ab: 88 %.

Solvent for purification: *i*-hexane/ethyl acetate 95:5.

m.p.: 65.3 – 66.9 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.34 (s, 9 H), 7.15 (t, *J*=8.57 Hz, 2 H), 7.30 - 7.43 (m, 3 H), 7.58 (t, *J*=7.60 Hz, 1 H), 7.77 (d, *J*=7.46 Hz, 1 H), 9.95 (s, 1 H).

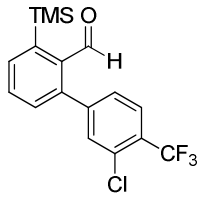
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.23, 115.18, 115.46, 131.60, 131.71, 132.01, 134.98, 135.19, 138.37, 142.62, 145.99, 161.00, 164.28, 193.65.

MS (70 eV, EI) m/z (%): 258 (23), 257 (100), 196 (3), 183 (22), 165 (4).

IR ATR ν (cm^{-1}): 2950, 2860, 1686, 1599, 1503, 1379, 1245, 1228, 848, 839, 800, 763.

HRMS (EI) for **$C_{15}H_{14}OFSi$** (257.0798) $[M\text{-}CH_3]^+$: 257.0786.

Synthesis of 3'-chloro-4'-(trifluoromethyl)-3-(trimethylsilyl)-[1,1'-biphenyl]-2-carbaldehyde (34ac):



According to **TP7**, a solution of **10e** in THF (2 mmol, 4 equiv, 1.01 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 2-(4-methoxystyryl)phenyl)trimethylsilane (**32**) (141.2 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 25 h, 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 **34ac** as a yellow oil.

Isolated yield: 75 %.

Solvent for purification: *i*-hexane/ethyl acetate 95:5.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.35 (s, 9 H), 7.38 (d, *J*=7.74 Hz, 1 H), 7.47 (dd, *J*=8.16, 1.80 Hz, 1 H), 7.57 - 7.66 (m, 2 H), 7.71 (d, *J*=1.94 Hz, 1 H), 7.82 (d, *J*=7.46 Hz, 1 H), 9.96 (s, 1 H).

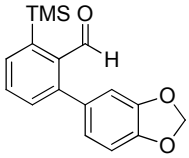
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.19, 122.59 (q, *J*=273.58 Hz), 128.32, 128.61 (q, *J*=5.41 Hz), 131.36, 131.53, 132.21 (q, *J*=1.99 Hz), 132.25, 134.21, 135.70, 135.95, 138.22, 143.34, 144.11, 192.71.

MS (70 eV, EI) m/z (%): 343 (35), 342 (21), 341 (100), 307 (5), 170 (4).

IR ATR ν (cm^{-1}): 2946, 2853, 1696, 1571, 1482, 1402, 1379, 1323, 1285, 1245, 1175, 1136, 1130, 1110, 1035, 906, 872, 835, 798, 764, 703, 672, 662.

HRMS (EI) for **$C_{16}H_{13}OClF_3Si$** (341.0376) $[M\text{-}CH_3]^+$: 341.0382.

Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-6-(trimethylsilyl)benzaldehyde (34ad):



According to **TP7**, a solution of **2k** in THF (2 mmol, 4 equiv, 1.10 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and 2-(4-methoxystyryl)phenyl)trimethylsilane (**32**) (141.2 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 16 h, 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 **34ad** as a yellow viscous oil.

Isolated yield: 67 %.

Solvent for purification: *i*-hexane/ethyl acetate 95:5.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.34 (s, 9 H), 6.04 (s, 2 H), 6.71 - 7.04 (m, 3 H), 7.36 - 7.45 (m, 1 H), 7.56 (t, *J*=7.46 Hz, 1 H), 7.73 (d, *J*=7.46 Hz, 1 H), 9.97 (s, 1 H).

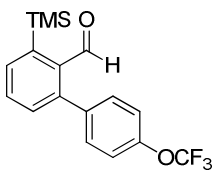
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.25, 101.36, 108.09, 110.34, 124.08, 131.67, 131.90, 132.82, 134.87, 138.52, 142.40, 146.69, 147.58, 147.73, 193.93.

MS (70 eV, EI) m/z (%): 284 (24), 283 (100), 253 (12), 242 (11), 209 (10), 165 (7), 141 (10).

IR ATR ν (cm^{-1}): 2949, 2894, 1693, 1680, 1502, 1488, 1455, 1437, 1386, 1336, 1243, 1222, 1180, 1105, 1038, 1031, 936, 907, 838, 795, 763, 673.

HRMS (EI) for **$C_{17}H_{18}O_3Si$** (298.1025) $[M]^+$: 298.1019.

Synthesis of 4'-(trifluoromethoxy)-3-(trimethylsilyl)-[1,1'-biphenyl]-2-carbaldehyde (34bc):



According to **TP7**, a solution of **2z** in THF (2 mmol, 4 equiv, 1.10 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and *N*-(2-(trimethylsilyl)benzylidene)butan-1-amine (**33**) (116.7 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 3 h, 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 **34bc** as white crystals.

Isolated yield: 75 %.

Solvent for purification: *i*-hexane/ethyl acetate 100:1, then 30:1.

m.p.: 65.8 – 67.6 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.34 (s, 9 H), 7.27 - 7.33 (m, 2 H), 7.39 (d, *J*=8.29 Hz, 3 H), 7.59 (t, *J*=7.46 Hz, 1 H), 7.78 (d, *J*=7.46 Hz, 1 H), 9.95 (s, 1 H).

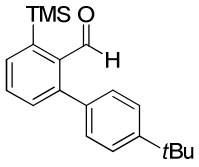
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.19, 120.45 (*J*=157.50 Hz), 120.70, 131.40, 131.60, 132.05, 135.44, 137.73, 138.30, 142.77, 145.54, 149.05, 193.40.

MS (70 eV, EI) m/z (%): 324 (18), 323 (100), 249 (11), 165 (10), 82 (10), 69 (16), 44 (21).

IR ATR ν (cm^{-1}): 2949, 2894, 1693, 1680, 1502, 1488, 1455, 1437, 1386, 1336, 1243, 1222, 1180, 1105, 1038, 936, 907, 838, 795, 763, 673.

HRMS (EI) for **$C_{16}H_{14}F_3O_2Si$** (323.0715) $[M-CH_3]^+$: 323.0710.

Synthesis of 4'-(trifluoromethoxy)-3-(trimethylsilyl)-[1,1'-biphenyl]-2-carbaldehyde (34bd):



According to **TP7**, a solution of **10f** in THF (2 mmol, 4 equiv, 0.94 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (6.1 mg, 0.05 mmol, 0.1 equiv) and *N*-(2-(trimethylsilyl)benzylidene)butan-1-amine (**33**) (116.7 mg, 0.5 mmol, 1 equiv) at 23 °C. Then, 2,3-dichlorobutane (9.5 mg, 0.75 mmol, 1.5 equiv) was added dropwise at 23 °C. The reaction mixture was stirred at 23 °C for 1.5 h, 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 **34bd** as white crystals.

Isolated yield: 74 %.

Solvent for purification: *i*-hexane/ethyl acetate 200:1.

m.p.: 76.3 - 78.3 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.34 (s, 9 H), 1.38 (s, 9 H), 7.30 (d, *J*=8.29 Hz, 2 H), 7.39 - 7.51 (m, 3 H), 7.57 (t, *J*=7.46 Hz, 1 H), 7.74 (d, *J*=7.19 Hz, 1 H), 9.97 (s, 1 H).

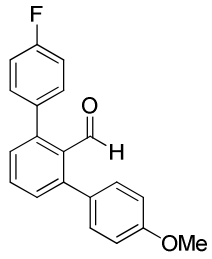
^{13}C NMR (75 MHz, DMSO) δ/ppm: 0.27, 31.34, 34.63, 125.21, 129.87, 131.76, 131.89, 134.81, 135.95, 138.38, 142.23, 147.20, 150.95, 194.20.

MS (70 eV, EI) m/z (%): 296 (25), 295 (100), 239 (5), 221 (4), 179 (3), 165 (6), 126 (14), 57 (11).

IR ATR ν (cm^{-1}): 2962, 2886, 1669, 1569, 1456, 1406, 1246, 1182, 1113, 1082, 1016, 859, 836, 796, 748, 669, 668.

HRMS (EI) for **$C_{19}H_{23}OSi$** (295.1518) $[M\text{-}CH_3]^+$: 295.1525.

Synthesis of 4'-(trifluoromethoxy)-3-(trimethylsilyl)-[1,1'-biphenyl]-2-carbaldehyde (37):



A solution of **2i** in THF (2 mmol, 4 equiv, 1.0 M) was added dropwise to a mixture of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv) and **35** (116.7 mg, 0.5 mmol, 1 equiv) at 23 °C. The suspension was stirred at 23 °C for 2 h. Then anhydrous $CrCl_2$ (12.2 mg, 0.1 mmol, 0.1 equiv) and a solution of **2g** were added followed by the dropwise addition of 2,3-dichlorobutane (190 mg, 1.5 mmol, 1.5 equiv). The reaction mixture was stirred at 23 °C for addtional 1 h, 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 **37** as light yellow crystals.

Isolated yield: 65 %.

Solvent for purification: *i*-hexane/ethyl acetate 100:1, then 10:1

m.p.: 83.0 – 84.8 °C.

^{1}H NMR (300 MHz, DMSO) δ/ppm: 3.86 (s, 3 H), 6.97 (d, *J*=8.57 Hz, 2 H), 7.10 (t, *J*=8.71 Hz, 2 H), 7.23 - 7.34 (m, 5 H), 7.40 (d, *J*=7.74 Hz, 1 H), 7.56 (t, *J*=7.60 Hz, 1 H), 9.93 (s, 1 H).

^{13}C NMR (75 MHz, DMSO) δ/ppm: 55.31, 113.77, 114.85, 115.14, 130.16, 130.42, 130.94, 131.01, 131.12, 131.31, 131.54, 133.14, 135.91, 135.96, 142.71, 144.54, 159.46, 160.73, 164.00, 193.54.

MS (70 eV, EI) m/z (%): 306 (100), 275 (27), 263 (11), 233 (20), 207 (5), 170 (7), 139 (4).

IR ATR ν (cm^{-1}): 2923, 2845, 1699, 1604, 1507, 1456, 1292, 1253, 1213, 1172, 1038, 1017, 835, 805, 744, 677.

HRMS (EI) for **$C_{20}H_{15}FO_2$** (306.1056) $[M]^+$: 306.1050.