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CHROMIUM- AND COBALT-CATALYZED CROSS-COUPLING AND AMINATION REACTIONS

AND

SYNTHESIS AND REACTIVITY OF PYRIDO[3,2-*F*][1,7]NAPHTHYRIDINES

VON

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Erklärung

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Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe bearbeitet.

München, 14. April 2016

…….....

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For everything he is, and everything he will be.

“Un oiseau sur un arbre n’a jamais peur que la branche casse.
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mais dans ses propres Ailes.”

- Anonymous -

TABLE OF CONTENTS

A. INTRODUCTION 1

1. OVERVIEW 2

2. PALLADIUM- AND NICKEL-CATALYZED CROSS-COUPLING AND AMINATION REACTIONS 3

2.1 PALLADIUM- AND NICKEL-CATALYZED CROSS-COUPLING REACTIONS 3

2.2 PALLADIUM-CATALYZED AMINATION REACTIONS 5

3. IRON-CATALYZED CROSS-COUPLING AND AMINATION REACTIONS OF AROMATICS AND HETEROAROMATICS 10

3.1 IRON-CATALYZED CROSS-COUPLING REACTIONS OF AROMATIC AND HETEROAROMATIC ELECTROPHILES 10

3.2 IRON-CATALYZED AMINATION REACTIONS OF (HETERO)AROMATIC ELECTROPHILES WITH NITROGEN-NUCLEOPHILES 17

4. COBALT-CATALYZED CROSS-COUPLING AND AMINATION REACTIONS OF AROMATICS AND HETEROAROMATICS 22

4.1 COBALT-CATALYZED CROSS-COUPLING REACTIONS OF AROMATIC AND HETEROAROMATIC ELECTROPHILES 22

4.2 COBALT-CATALYZED AMINATION REACTIONS OF (HETERO)AROMATIC ELECTROPHILES WITH NITROGEN-NUCLEOPHILES 26

5. CHROMIUM-CATALYZED TRANSFORMATIONS 30

6. SYNTHESIS OF PYRIDONAPHTHYRIDINES 34

7. OBJECTIVES 37

B. RESULTS AND DISCUSSION 40

1. COBALT(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN *N*-HETEROCYCLIC HALIDES AND ARYL OR HETEROARYL MAGNESIUM REAGENTS 41

1.1 COBALT-CATALYZED CROSS-COUPLING REACTIONS UTILIZING ISOQUINOLINE AS LIGAND 41

1.2 LIGAND SCREENING FOR THE COBALT-CATALYZED CROSS-COUPLING OF CHLOROPYRIDINES 44

2. CHROMIUM(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN C_{sp^2} CENTERS 51

2.1 PRELIMINARY EXPERIMENTS 51

2.2 CROSS-COUPLING REACTIONS OF 2-HALOGENATED *N*-HETEROCYCLES WITH ARYL GRIGNARD REAGENTS 52

2.3 CROSS-COUPLING REACTIONS OF 2-HALOGENATED (HETERO)ARYL SUBSTITUTED KETONES WITH (HETERO)ARYL GRIGNARD REAGENTS 54

2.4 CROSS-COUPLINGS BETWEEN IMINE-PROTECTED ALDEHYDES AND ORGANOMAGNESIUM REAGENTS 55

2.5 CROSS-COUPLING REACTIONS OF ALKENYL IODIDES WITH ARYL GRIGNARD REAGENTS 56

2.6 CHEMO- AND REGIOSELECTIVE CROSS-COUPLING REACTIONS OF DICHLORINATED HETEROAROMATICS 56

2.7 REMOVAL OF THE CHROMIUM CATALYST 63

3. CHROMIUM(II)-CATALYZED AMINATION OF *N*-HETEROCYCLIC CHLORIDES WITH MAGNESIUM AMIDES **64**
3.1 OPTIMIZATION OF THE REACTION CONDITIONS 64
3.2 CHROMIUM-CATALYZED AMINATION OF SUBSTITUTED 2-CHLOROPYRIDINES 65
3.3 CHROMIUM-CATALYZED AMINATION OF SUBSTITUTED 2-CHLOROQUINOLINES, 1-CHLOROISOQUINOLINE AND 2,3-DICHLOROQUINOXALINE 67
4. SYNTHESIS OF PYRIDO[3,2-*F*][1,7]NAPHTHYRIDINE AND RELATED HETEROCYCLES **70**
4.1 RETROSYNTHETIC ANALYSIS 70
4.2 MULTI-STEP SYNTHESIS OF PYRIDO[3,2-*F*][1,7]NAPHTHYRIDINE AND DERIVATIVES 71
4.3 FUNCTIONALIZATION OF PYRIDO[3,2-*F*][1,7]NAPHTHYRIDINE BY ORGANOLITHIUMS ADDITION 73
5. SUMMARY AND OUTLOOK **76**
5.1 COBALT(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN *N*-HETEROCYCLIC HALIDES AND ARYL OR HETEROARYL MAGNESIUM REAGENTS 76
5.2 CHROMIUM(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN CSP2 CENTERS 78
5.3 CHROMIUM(II)-CATALYZED AMINATION OF *N*-HETEROCYCLIC CHLORIDES WITH MAGNESIUM AMIDES 80
5.4 SYNTHESIS OF PYRIDO[3,2-F][1,7]NAPHTHYRIDINE AND RELATED HETEROCYCLES 81

C. EXPERIMENTAL SECTION **85**

1. GENERAL CONSIDERATIONS **86**
1.1 SOLVENTS 86
1.2 REAGENTS 86
1.3 CONTENT DETERMINATION OF ORGANOMETALLIC REAGENTS 86
1.4 CHROMATOGRAPHY 87
1.5 ANALYTICAL DATA 87
2. COBALT(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN *N*-HETEROCYCLIC HALIDES AND ARYL OR HETEROARYL MAGNESIUM REAGENTS **88**
2.1 STARTING MATERIALS SYNTHESIS 88
2.2 GENERAL PROCEDURES 88
2.3 PREPARATION OF THE SYNTHESIZED *N*-HETEROCYCLIC COMPOUNDS 89
3. CHROMIUM(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN CSP^2 CENTERS **94**
3.1 STARTING MATERIALS SYNTHESIS 94
3.2 GENERAL PROCEDURES 94
3.3 PRODUCT SYNTHESIS ACCORDING TO THE GENERAL PROCEDURES 95
3.4 TREATMENT OF PYRIDINE 14A WITH SCAVENGERS TO EVALUATE RECOVERY AND CHROMIUM LEVELS PRIOR TO CHROMATOGRAPHY 118
4. CHROMIUM(II)-CATALYZED AMINATION OF *N*-HETEROCYCLIC CHLORIDES WITH MAGNESIUM AMIDES **120**
4.1 STARTING MATERIALS SYNTHESIS 120
4.2 GENERAL PROCEDURES 120

4.3 PREPARATION OF THE SYNTHESIZED AMINATED *N*-HETEROCYCLES 120
5. SYNTHESIS OF PYRIDO[3,2-F][1,7]NAPHTHYRIDINE AND RELATED HETEROCYCLES 131
5.1 STARTING MATERIAL SYNTHESIS 131
5.2 GENERAL PROCEDURES 132
5.3 COMPOUNDS SYNTHESIZED ACCORDING TO THE GENERAL PROCEDURES 135

D. REFERENCES 149

LIST OF ABBREVIATIONS

acac	acetylacetonate
Alk	alkyl
Ar	aryl
aq.	aqueous
cat.	catalytic
COD	1,5-cyclooctadiene
CPME	cyclopentyl methyl ether
δ	chemical shifts in parts per million
d	doublet
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DFT	discrete Fourier transform
DG	directing group
DME	dimethoxyethane
DMEDA	dimethylethylenediamine
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
DPPF	bis(diphenylphosphino)ferrocene
DPPP	1,3-bis(diphenylphosphino)propane
DPPY	2-(diphenylphosphino)pyridine
EI	electron-impact ionization
equiv	equivalent
FG	functional group
GC	gas chromatography
h	hour
Het	heteroaryl
HRMS	high resolution mass spectroscopy
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazane
M	molarity
m	*meta*
m	multiplet
NHC	*N*-heterocyclic carbene
min	minute
NMP	*N*-methyl-2-pyrrolidone
m.p.	Melting point
MS	mass spectroscopy
o	*ortho*
p	*para*
q	quartet
R	organic substituent
RT	room temperature
s	singulet
sat.	saturated
TBAF	tetra-*n*-butylammonium fluoride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidyl
TMPDA	*N,N,N',N'*-tetramethyl-1,3-propanediamine
TMS	trimethylsilyl
TP	typical procedure

A. Introduction

1. OVERVIEW

"Catalysis lies at the heart of modern synthetic chemistry: 90% of all commercial chemicals are produced by methods that involve at least one catalytic step."[1]

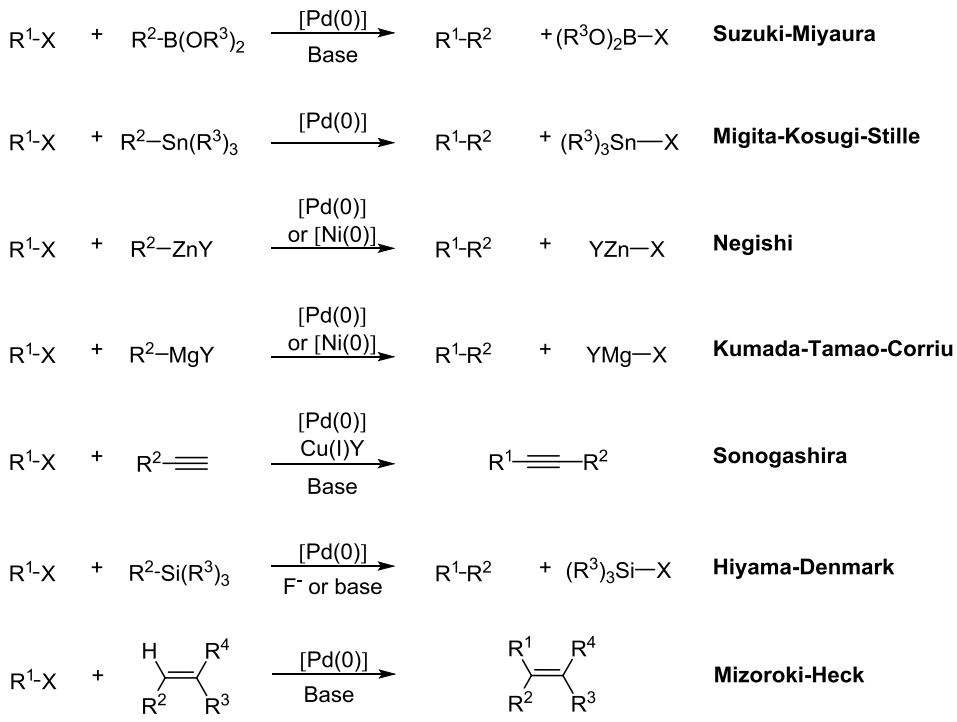
Those words from Q.-L. Zhou point out that, over the last 30 years, the development of metal-catalyzed cross-coupling reactions has revolutionized the way carbon-carbon and carbon-heteroatom bonds are formed. These methods have deeply changed the protocols for the synthesis of natural products[2], building blocks for supramolecular chemistry[3] and self-assembly, organic materials and polymers, as well as for lead compounds in medicinal chemistry[4] from simpler entities.[5]

In particular, the platinum-group metals — ruthenium, rhodium, palladium, osmium, iridium and platinum — are extensively used as catalysts in industries that produce compounds such as agrochemicals, dyes or pharmaceuticals.[6] But as demand for these relatively scarce metals increases, their future availability is a cause for concern.[7]

2. PALLADIUM- AND NICKEL-CATALYZED CROSS-COUPLING AND AMINATION REACTIONS

2.1 PALLADIUM- AND NICKEL-CATALYZED CROSS-COUPLING REACTIONS

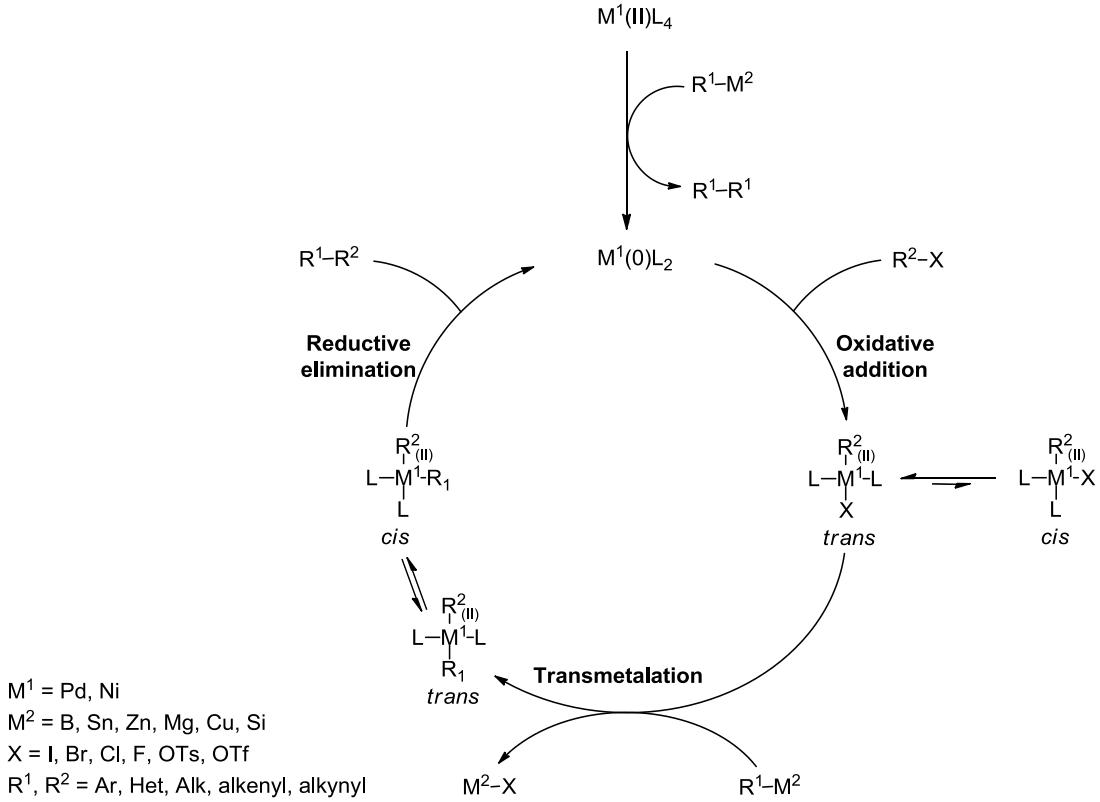
After decades of intensive research, transition metal-catalyzed cross-coupling reactions are nowadays playing a crucial role in organic synthesis.[8] Among them, the very general and selective palladium-catalyzed Stille (involving organotin reagents) and Suzuki (involving boronic acids or esters) cross-coupling reactions have been particularly popular. Other cross-couplings, using different metal species have been developed, offering chemists new methods to achieve C-C bond formations. For instance, the palladium-catalyzed Hiyama (organosilicon reagents), Sonogashira (*in situ* copper acetylides), or the palladium- or nickel-catalyzed Negishi (organozinc reagents), and Kumada reaction (organomagnesium reagents) have proven to be highly valuable tools in organic chemistry (Scheme 1).[9a, 5, 9b] Last but not least, the palladium-catalyzed Heck cross-coupling allows the reaction of an organohalide with an alkene, leading to substituted olefins.[10]



Scheme 1: Representative palladium- and nickel-catalyzed cross-coupling reactions.

These palladium- or nickel-catalyzed cross-coupling reactions have the characteristic to share a common mechanism pathway (Scheme 2). The first step usually involves the *in situ* reduction of the catalyst precursor $M^1(II)L_4$ to the reactive species $M^1(0)L_2$. This step is followed by an oxidative addition to the C-X bond of the electrophile R^2X, affording the *cis* palladium complex. Subsequent transmetalation of the *trans* isomer followed by reductive elimination of the *cis* isomer, provides the

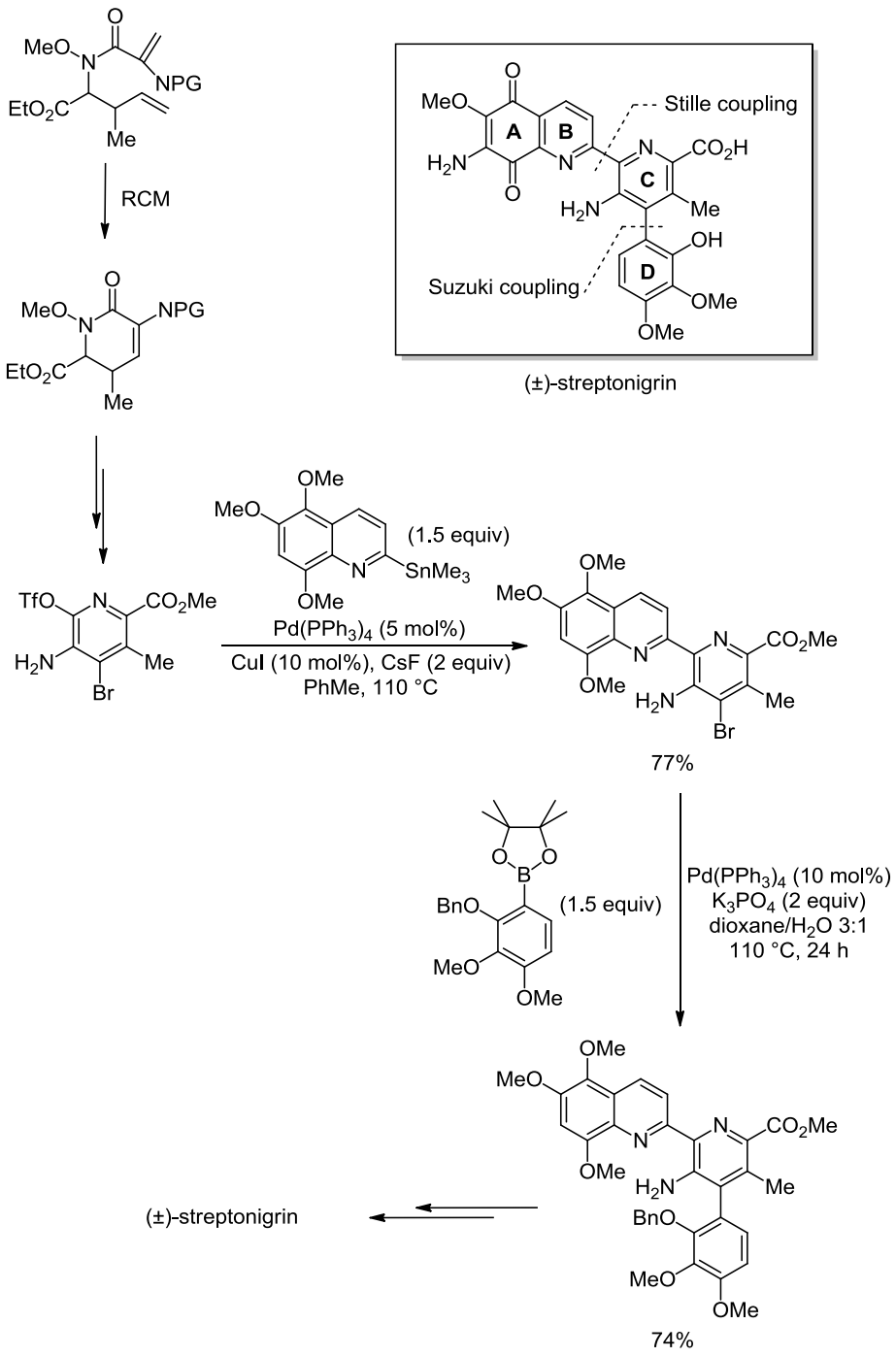
cross-coupling product R^1-R^2, and regenerates the active catalyst $M^1(0)L_2$. Alternatively, M(0) complexes, such as $Pd(PPh_3)_4$ or $Ni(COD)_2$ can also be used. In this case, no preliminary reduction is required. Among the factors influencing the catalysis efficiency, the nature of the ligand L plays an essential role. For instance, electron-rich ligands facilitate the oxidative addition step, whereas electron-poor ligands enhance both the transmetalation and the reductive elimination steps. Thus, when the determining-rate step is the oxidative addition (aryl chlorides used as electrophiles for example), electron-rich ligands are more advantageous and enhance the reaction rate.[5]



Scheme 2: Catalytic cycle of the palladium- and nickel-catalyzed cross-coupling reactions.

The most important and elegant application of cross-coupling reactions is probably the synthesis of pharmaceuticals.[11]

An interesting application is the well-designed total synthesis of the anti-tumor antibiotic (±)-streptonigrin by Donohoe *via* the use of different metal-catalyzed couplings as key reactions (Scheme 3).[12] After few steps including a challenging ring-closure metathesis, the desired pentafunctionalized pyridine could be coupled with the stannylquinoline within a Stille cross-coupling, providing the B-C core of the desired product in 77% yield.[13] Thereafter, Suzuki reaction with activation of the bromine substituent provided the C-D bond formation leading to the tetracyclic compound in 74% yield.

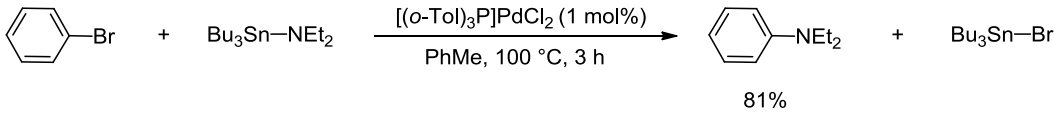


Scheme 3: Key steps in the synthesis of (±)-streptonigrin.

2.2 PALLADIUM-CATALYZED AMINATION REACTIONS

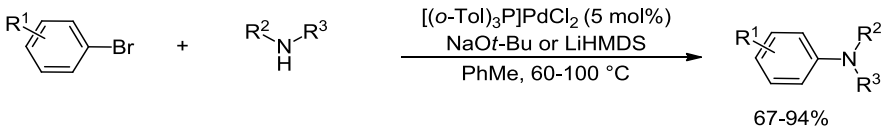
Syntheses of amino-substituted heterocycles are of the utmost importance for pharmaceutical and agrochemical industry due to their high biological activity.[14] These molecules are generally prepared by nucleophilic aromatic substitution[15] but transition metal catalysts for aminations have also been intensively studied.[16]

During the 1980s, few preliminary results suggested that a general metal-catalyzed method to form arylamines from aryl halides could be feasible. In 1983, Migita *et al.* performed the coupling of aryl bromides with tin amides in the presence of a palladium catalyst.[17] Treatment of bromobenzene with an amino-tin compound in the presence of a palladium catalyst provided *N,N*-diethyl-aniline (Scheme 4).



Scheme 4: First Pd-catalyzed aryl amination using tributyltin amides.

In 1995, the groups of Buchwald[18a, 18b, 14c, 18c] and Hartwig[19] independently realized a tremendous improvement by using free amines. Both groups reported the palladium-catalyzed amination of aryl bromides derivatives with secondary amines using a base, such as NaO*t*-Bu or LiHMDS, affording the tertiary arylamines in good to excellent yields (Scheme 5).[20]



Scheme 5: Palladium-catalyzed aryl amination of aryl bromides with secondary amines.

Since then, they have revolutionized this field by developing new classes of ligands and highly active palladium catalysts. Indeed, fine tuning of the ligand has shown the biggest effect and led to two main and complementary classes of ligands: bulky biaryl monophosphine ligands and chelating bisphosphine ligands, such as X-Phos and John-Phos or the Josiphos-type ligand CyPF-*t*-Bu (Figure 1).

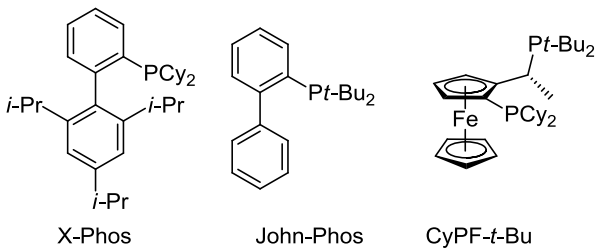
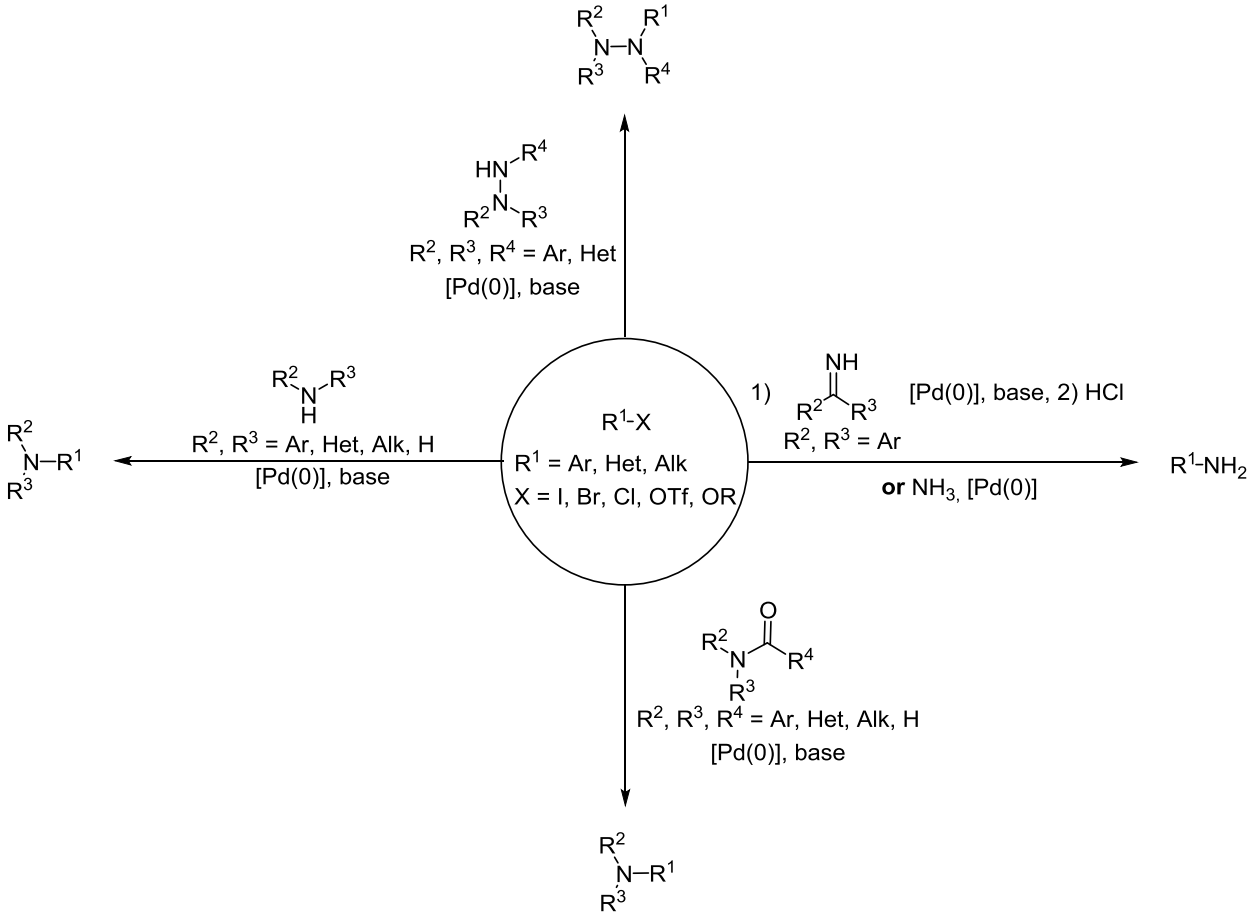


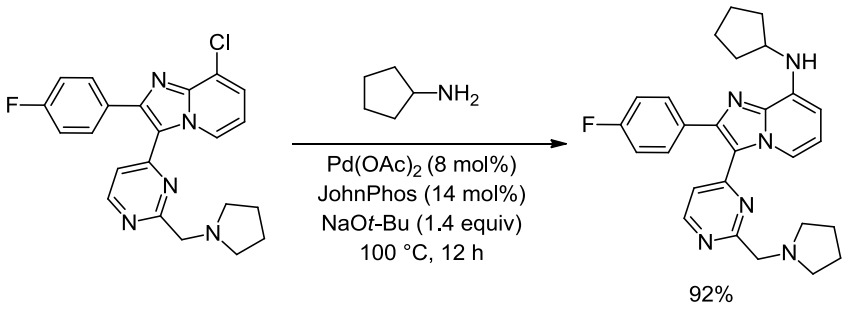
Figure 1: Phosphine ligands for palladium-catalyzed amination reactions.

This new Pd-catalyzed C-N coupling reaction is known today as the Buchwald-Hartwig amination.[21] It now allows a broad range of amination reactions of aryl halides and sulfonates in combination not only with amines, but also with hydrazines, amides, imines, nitrogen-containing heterocycles or ammonia (Scheme 6).[22a, 22b, 18b, 22c, 14d]



Scheme 6: Palladium-catalyzed amination reactions.

Apart from academic interests, the Buchwald-Hartwig amination reaction is also in focus of industrial chemists, since it fulfills the different requirements of modern synthetic methods by its versatility, its reliability and its applicability both on small and large scale syntheses.[16c, 18b] As an illustration, scientists from GlaxoSmithKline used palladium acetate in combination with JohnPhos as a ligand in order to couple cyclopentylamine with the 8-chloroimidazopyridine derivative. This led to the production of novel imidazo[1,2-a]pyridines, which have demonstrated potent activity against the herpes virus (Scheme 7).[23]



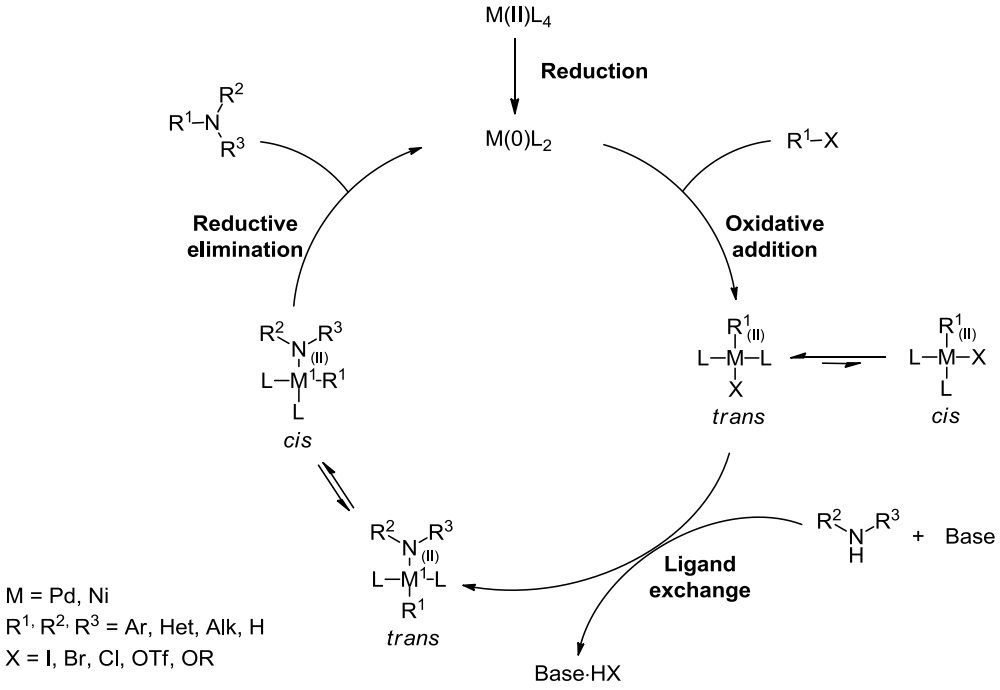
Scheme 7: GSK synthesis of an anti-herpes agent.

On the other hand, nickel-catalyzed amination reactions have received less attention. Buchwald has reported the amination of aryl chlorides in the presence of $Ni(COD)_2$ and DPFF (1,1'-bis(diphenylphosphino)ferrocene) or 1,10-phenanthroline.[24] This methodology was extended by using a heterogeneous Ni(0)/C catalyst[25] or employing 2,2'-bipyridine[26] or *N*-heterocyclic carbenes (NHC)[27] as ligands. However, these reactions required high amounts of nickel catalysts (5-10 mol%) and either unstable or expensive Ni(0) sources like $Ni(COD)_2$ or Ni(II)-precursors and reducing agents like NaH or MeMgBr were required, which are incompatible with several functional groups.

Blackwood, Buchwald and Hartwig have reported a detailed mechanistic study of the amination of aryl halides in the presence of palladium complexes.[28]

Like most Pd-catalyzed reactions, the Buchwald-Hartwig amination requires a Pd(0) or Pd(II) precursor, a ligand to increase the electron density at the metal center, which facilitates the oxidative addition step, a base to deprotonate the amine substrate, and a suitable solvent. Notably, *in situ* palladium systems are used, but as user-friendly alternative, isolated and mostly air-stable palladium complexes are also used. Whereas $Pd_2(dba)_3$ or $Pd(dba)_2$ serve as Pd(0) source, $Pd(OAc)_2$ is the most versatile Pd(II) source in addition to $[\eta^3\text{-}C_3H_5PdCl]_2$ or $Pd(acac)_2$. Unfortunately, the most commonly available $PdCl_2$ is only rarely used.[29]

The first step is the oxidative insertion of the electrophile R^1X to the active metal(0) complex, prior to the amine addition. The base-assisted ligand exchange of the $[RML_2X]$-complex with the amine follows. Reductive elimination of the resulting amido-complex provides the desired amine, and regenerates the active M(0)-complex. If M(+2)-salts are used, the active M(0)-complex has to be generated via reduction from the M(+2)-precursor $M(II)L_4$ (Scheme 8).[30]



Scheme 8: Buchwald-Hartwig amination mechanistic studies.

For the corresponding nickel-catalyzed amination reaction no detailed mechanistic studies have been reported so far, although a similar mechanism is presumed.[27, 31]

3. IRON-CATALYZED CROSS-COUPLING AND AMINATION REACTIONS OF AROMATICS AND HETEROAROMATICS

Although, palladium- and nickel-catalyzed cross-couplings have by far the largest synthetic scope, alternative cross-coupling methods have to be considered.[32] Indeed, with an average price of 18.5 k€/kg,[33] palladium is the bull of any synthesis employing it, especially in the context of manufacturing on larger scales. On the other hand, even though cheaper (8.0 €/kg),[33] the use of nickel-catalyzed processes is tainted by various toxicity aspects undesired for consumer goods and healthcare products.[34] Furthermore, both palladium and nickel catalyst systems usually require the addition of structurally complex and costly ligands of high molecular weight. These practical issues have to be taken into account for industrial applications.

Iron-salts represent ideal alternative precatalysts. Firstly, iron being the most abundant metal in the universe and the second-most abundant metal in the earth´s crust, no supply issue should occur, such as in the case of palladium complexes. Moreover, iron is the most abundant transition metal in the human body (4 g/person) and it is an essential metal in the life cycle of all living organisms. This factor actually represents a big advantage for using iron catalysts in health-care related chemistry, since no severe toxicity and side effects are existing.
The environmentally friendly properties and low price (0.04 €/kg)[33] make iron a catalyst of the future and therefore provide ample motivation for further developments in the field of iron-catalyzed cross-coupling.

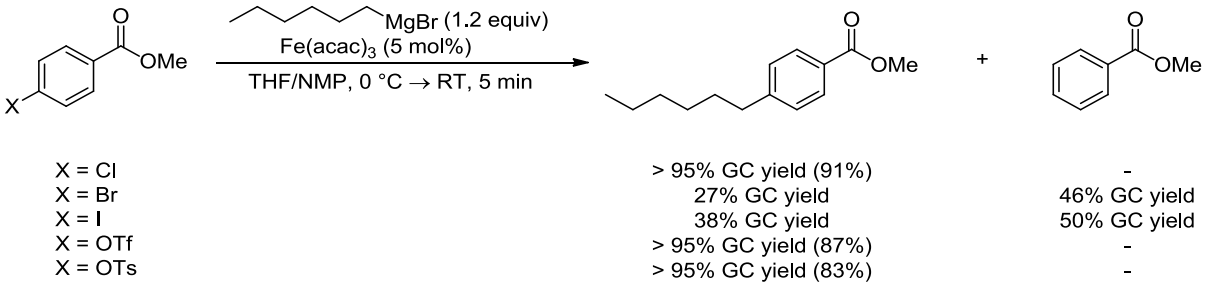
3.1 IRON-CATALYZED CROSS-COUPLING REACTIONS OF AROMATIC AND HETEROAROMATIC ELECTROPHILES

Although the pioneer work of Kochi *et al.* reporting the first iron-based catalyst for cross-coupling reactions appeared already in 1971,[35] which is within a year of the initial reports using palladium and nickel, the progress towards a practical and general protocol for iron-catalyzed cross couplings has not been as rapid as for the development of analogous palladium and nickel-based methodologies. This progress has been partly weakened by a lack of mechanistic understanding for these reactions.[32c]
However, with the central contributions of Cahiez's, Nakamura's and Fürstner's research groups, attention has returned to the use of iron for cross-coupling reactions between alkyl, alkenyl, alkylnyl and (hetero)aryl Grignard reagents with alkyl,[36] alkenyl,[37] alkylnyl[37am, 38] and (hetero)aryl halides, triflates, tosylates, sulfones, and phosphates. This rebirth is partly due to the emergence of detailed mechanistic studies aiming the understanding these processes.[39, 36c, 37ai, 32c]

3.1.1 Substrate scope generalities

Additionally to its environmentally friendly properties, iron catalysts presents a large application scope, which is complementary to those of Pd- and Ni-species. Indeed, a wide range of chlorinated electrophiles, as well as a broad variety of alkyl halides, react well within an iron-mediated Kumada-type cross-coupling, areas in which palladium catalysis shows limitations.

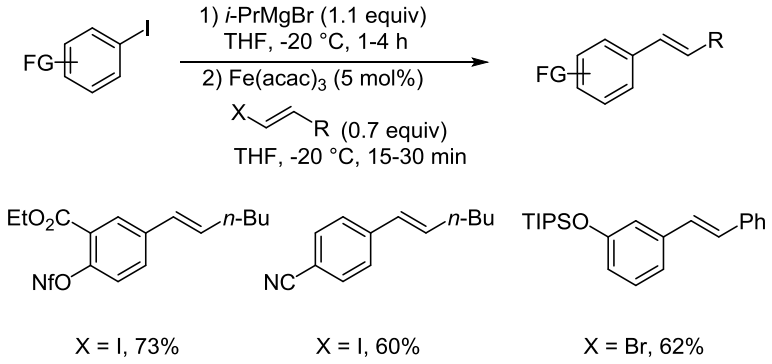
In 2002, Fürstner *et al.* studied the relative cross-coupling rates of aromatic chlorides, bromides and iodides with Grignard reagents.[40] Iron-catalyzed cross-coupling reactions proved to proceed at best with chlorinated aryl electrophile, and led to the least amount of the reduced electrophile side-product (Scheme 9). In the case of bromo- and iodobenzoate, the cross-coupling of *n*-hexylmagnesium bromide led to respectively 46 and 50% GC yields of the reduced byproduct, whereas only 27 and 38% of the desired alkylated coupling product was obtained. On the other hand, methyl-4-chlorobenzoate reacted in virtually quantitative yield in only a few minutes to yield the coupled product, which was obtained in 91% yield after purification. Additionally, the corresponding triflate and tosylate reacted similarly affording the desired product in respectively 87 and 83% yields.



X = Cl	> 95% GC yield (91%)	-
X = Br	27% GC yield	46% GC yield
X = I	38% GC yield	50% GC yield
X = OTf	> 95% GC yield (87%)	-
X = OTs	> 95% GC yield (83%)	-

Scheme 9: Comparison of aromatic halides, triflate and tosylate in iron-catalyzed cross-couplings.

Functional group tolerance of iron-catalyzed cross-coupling reactions is quite broad. Indeed, organomagnesium reagents proved to undergo the desired cross-coupling faster than they reacted with other electrophilic sites present in the substrate. A wide range of electrophiles bearing ketones, aldehydes, esters, ethers, nonaflates, nitriles or trialkylsilyloxy groups were successfully coupled (Scheme 10).[41] This very interesting compatibility showed by versatile iron-mediated couplings is very important for synthetic utility, making this methodology useful for more complex products, such as natural products.

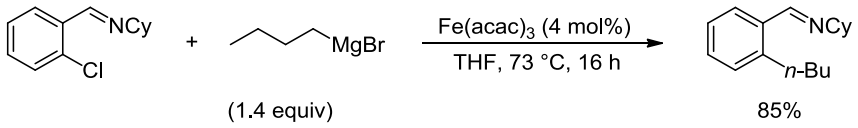


Scheme 10: $Fe(acac)_3$-catalyzed cross-coupling of functionalized aryl Grignard reagents.

Different iron-catalyzed cross-coupling reactions of aromatics and heteroaromatics will be further discussed by the type of nucleophiles used.

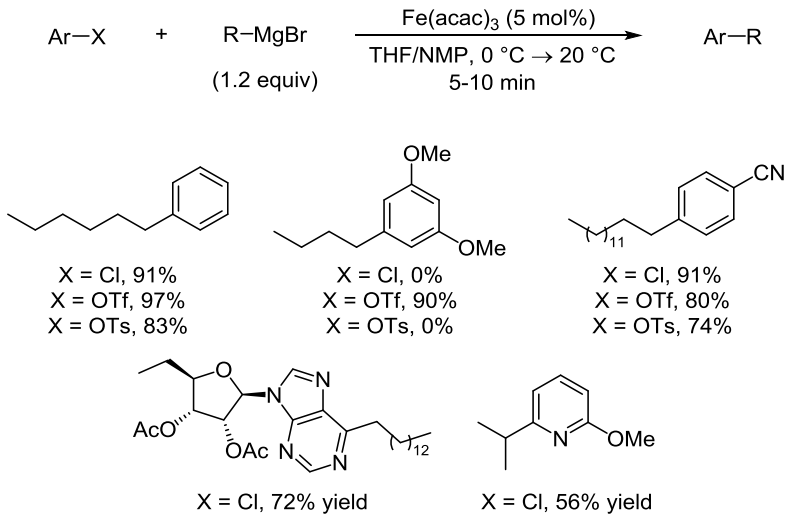
3.1.2 Iron-catalyzed cross-coupling of aromatics and heterocycles with alkyl metal nucleophiles

In the field of iron-catalyzed cross-couplings of aryl electrophiles with alkyl metal nucleophiles, Pridgen *et al.* realized pioneer experiments in 1989 (Scheme 11).[42] *Ortho*-halobenzaldimines were be successfully coupled, and the corresponding substituted imines were obtained in good yield.



Scheme 11: Coupling of halobenzylidene cyclohexylamine with alkyl Grignard reagent.

Fürstner *et al.* developed later general conditions for cross-coupling reactions of alkyl metal species with various aromatic and heteroaromatic halides, triflates and tosylates (Scheme 12).[43a, 43b, 39c, 43c] Noteworthily, alkylmagnesium substrates containing alkene or alkyne moieties could be successfully engaged in such a process.

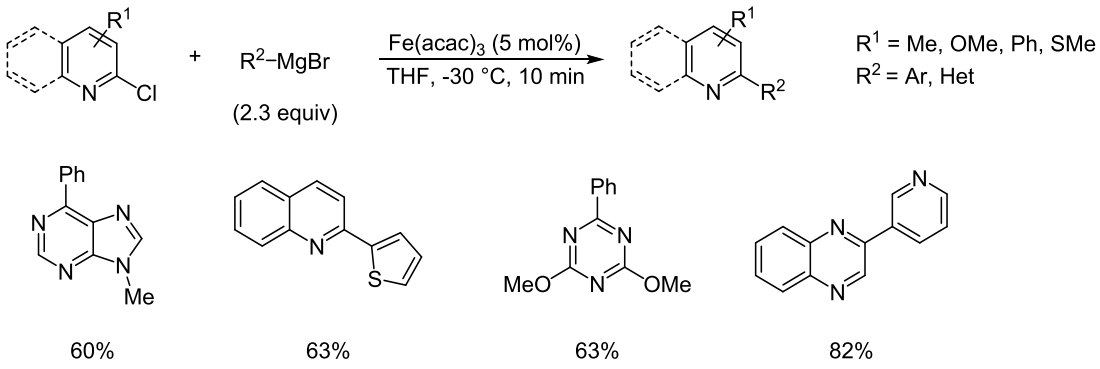


Scheme 12: Iron-catalyzed aryl-alkyl cross-coupling reactions.

3.1.3 Iron-catalyzed cross-coupling of aromatics and heteroaromatics with aryl metal nucleophiles

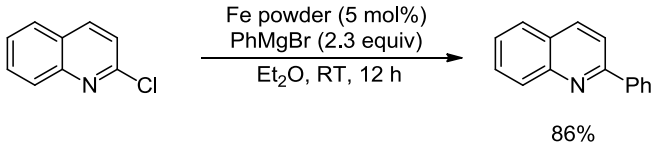
Additionally, the use of aryl metal species with aryl electrophiles was also explored.

In 2002, Fürstner *et al.* reported the first iron-catalyzed unsymmetrical biaryl formation. Under 5 mol% $Fe(acac)_3$ catalysis, a wide range of heteroaromatic halides were successfully coupled with various (hetero)aryl organomagnesium reagents (Scheme 13).[43b] At -30 °C in THF, only 10 min reaction time was required for this ligand-free procedure, showing the high activity of the iron catalyst. However, 2.3 equivalents of Grignard reagent proved to be necessary. This high excess was necessary due to the formation of large amounts of homo-coupling side-product.



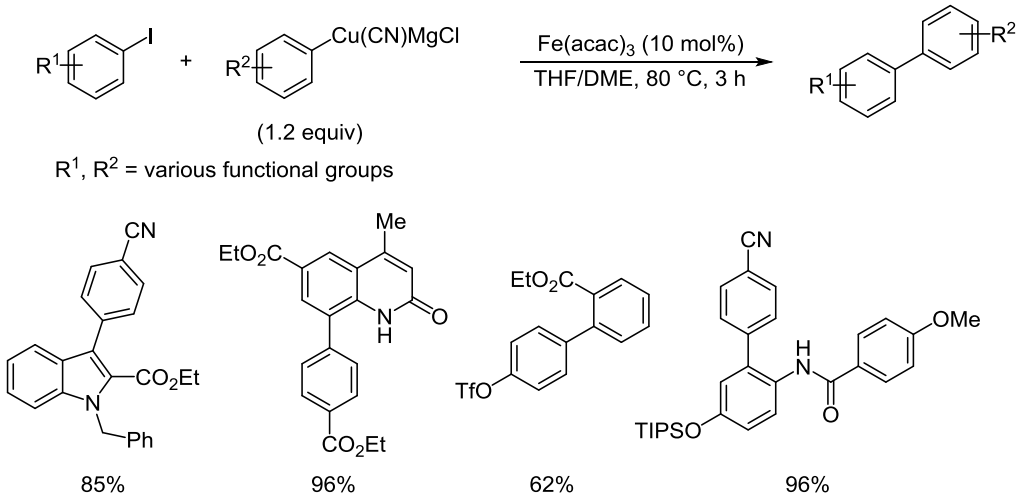
Scheme 13: Iron-catalyzed heteroaryl-(hetero)aryl cross-coupling.

Supporting the involvement of reduced ferrate species in the mechanism, Knochel *et al.* described in 2003 the use of iron powder for the cross-coupling of 2-chloroquinoline with phenylmagnesium bromide (Scheme 14).[44]



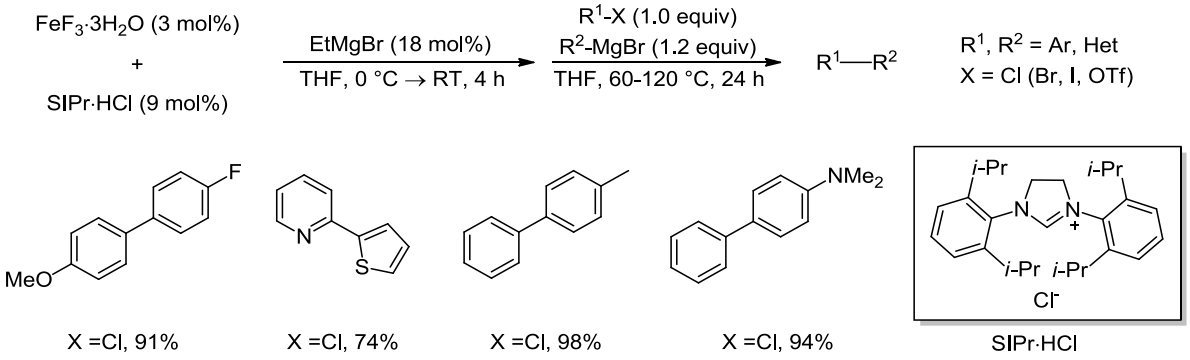
Scheme 14: 2-chloroquinoline cross-coupling catalyzed by iron powder.

Knochel *et al.* further studied Fe-catalyzed aryl-aryl cross-coupling reactions. The undesired homo-coupling byproduct formation could be suppressed by using organocopper reagents resulting from the transmetallation of Grignard reagents (Scheme 15). This relatively mild cross-coupling proceeded at best with aryl iodides in the presence of $Fe(acac)_3$ in THF/DME at 80 °C and showed a broad functional group tolerance.[45]



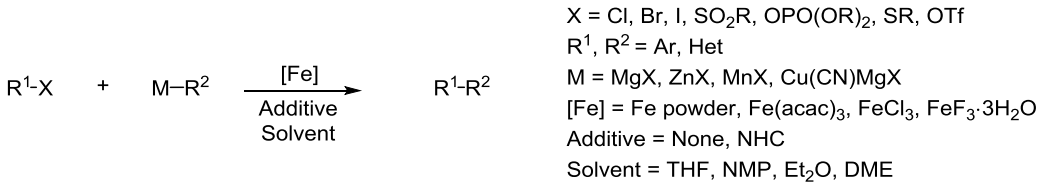
Scheme 15: Iron-catalyzed cross-coupling reactions of organocopper reagents with aryl iodides.

Another major discovery in iron-catalyzed cross-coupling was made by Nakamura *et al.* in 2007, describing a novel catalytic system for the hetero-biaryl coupling based on $FeF_3 \cdot 3H_2O$ and SIPr·HCl (1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride).[46] The iron salt, while treated with the NHC ligand and EtMgBr led to the active iron species, which proved to be critical for high selectivities. The (hetero)aromatic halides and the aryl Grignard reagents were then added to this reaction mixture and stirred at 60-120 °C for 24 h. The desired biaryl coupling products were obtained in high yields with negligible traces of homo-coupling side-product (Scheme 16).



Scheme 16: Biraryl cross-coupling usind FeF_3/NHC as catalytic system.

As a conclusion, various reaction conditions could be set up and a wide range of organomagnesium, organozinc and organomanganese reagents react with aryl and heteroaryl chlorides, triflates and tosylates (Scheme 17).[47a, 37d, 43a, 43b, 47b, 44, 47c-e, 45a, 47f, 47g, 46a, 45b] Unlike aryl chlorides, the corresponding bromides and iodides were prone to reduction of the C-X bonds. The wide substrate scope involved functionalized aromatic compounds bearing ether, sulfonate, nitrile, or heterocycle substituents.



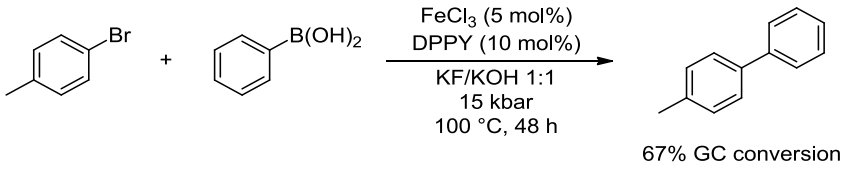
Scheme 17: Non exhaustive reaction conditions for the iron-catalyzed cross-coupling reaction of (hetero)aryl electrophiles with (hetero)aryl metal nucleophiles.

Even though the scope of iron-catalyzed aryl-aryl cross-coupling reactions was considerably extended through the work of Fürstner,[43a, 43b, 39c, 43c, 48] Figadère,[47b] Plé,[47c] Knochel,[44-45] Cahiez,[37p, 44, 47d, 47g] Nakamura[46] and co-workers, it is worth noting that these cross-coupling reactions present a bigger challenge in respect to the corresponding alkyl-aryl, alkyl-alkenyl, aryl-alkenyl or alkynyl cross-coupling reactions that are now well documented. The obstacle to overcome is generally the insufficient catalytic activity of the iron-catalyst, as well as the formation of undesired homo-coupling side-reaction of the organometallic species.[47a, 37d, 47e, 47d, 47f, 49a, 47g, 49b, 49c]

3.1.4 Iron-catalyzed Suzuki and Sonogashira cross-coupling reactions of aromatics

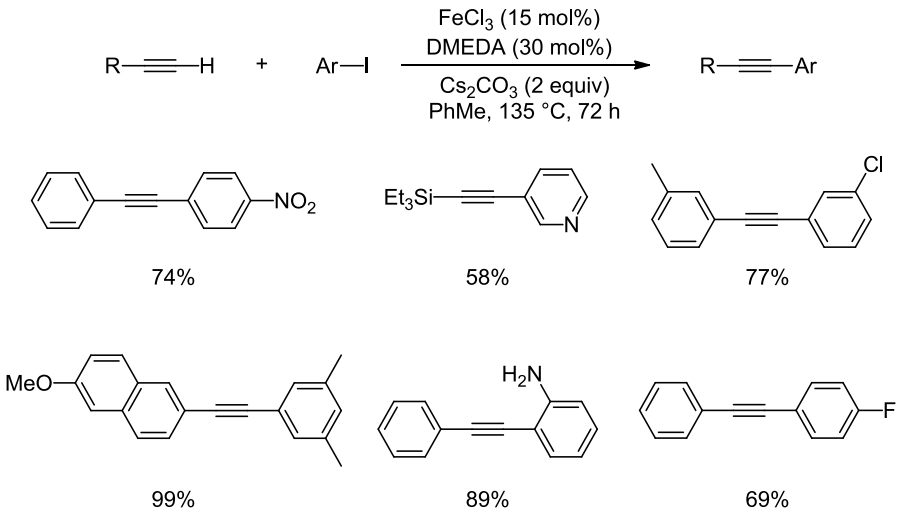
Interestingly, iron-catalyzed Suzuki and Sonogashira cross-coupling reactions are at their infancy.

On the one hand, Young *et al.* developed the first iron-catalyzed liquid-phase Suzuki cross-coupling of aryl halides and aryl boronic acids under high pressure and in the presence of 2-(diphenylphosphino)pyridine (DPPY) as ligand (Scheme 18).[50]



Scheme 18: Iron-catalyzed Suzuki-Miyaura at high pressure.

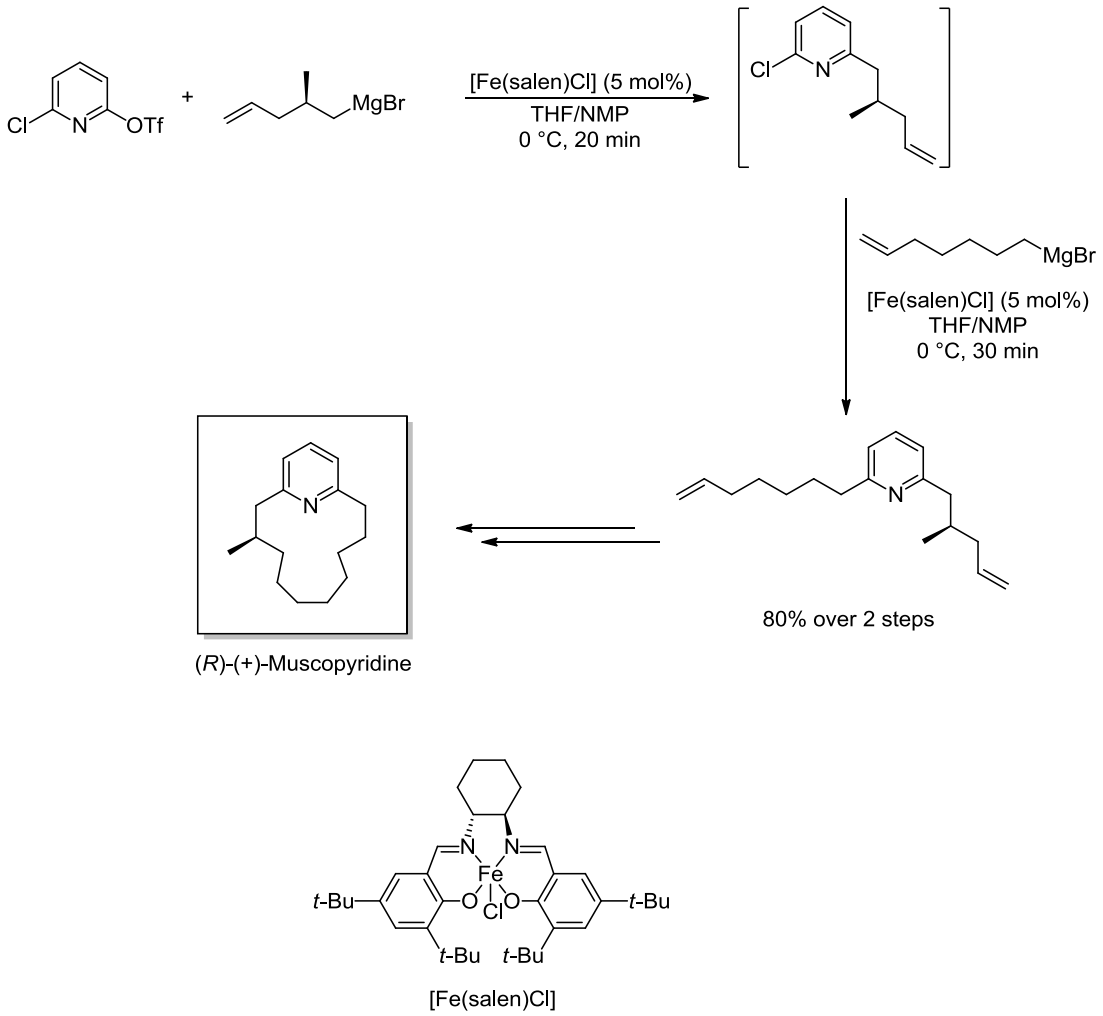
On the other hand, Bolm *et al.* showed the use of iron-catalysts in the coupling of various terminal alkynes with various electron-withdrawing and -donating aryl iodides. The desired arylacetylenes were obtained in good yields under iron(III) chloride-catalysis in combination with *N,N'*-dimethyl-ethylenediamine (DMEDA) as ligand (Scheme 19).[51]



Scheme 19: Iron-catalyzed arylation of terminal alkynes.

3.1.5 Use of iron-catalysis in total synthesis

Due to the versatility of these iron-catalyzed cross-coupling procedures, they are nowadays more and more applied in the total synthesis of natural products. For instance, the highly regioselective and efficient aryl-alkyl cross-coupling methodology developed by Fürstner and co-workers could be highlighted by the synthesis of (*R*)-(+)-Muscopyridine, a natural alkaloid (Scheme 20).[52] The key steps in this synthesis exploited the higher reactivity of triflates over chlorides in Fe-catalyzed aryl-alkyl cross-coupling reactions. In the first step, the difunctional 6-chloropyridin-2-yl trifluoromethanesulfonate was reacted with the appropriate vinyl Grignard reagent to yield predominantly mono-coupling product and the dicoupled product in a ratio of 4:1. This reaction mixture was reacted with a second Grignard reagent to obtain the crude product of the decoupled pyridine precursor in 80% yield. Finally, ring closing metathesis followed by hydrogenation furnished (*R*)-(+)-Muscopyridine.



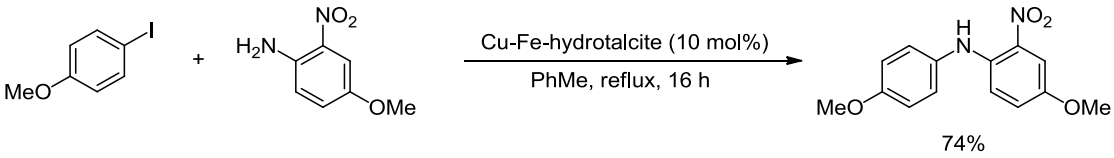
Scheme 20: Key steps in the synthesis of (*R*)-(+)-Muscopyridine.

3.2 IRON-CATALYZED AMINATION REACTIONS OF (HETERO)AROMATIC ELECTROPHILES WITH NITROGEN-NUCLEOPHILES

The metal-catalyzed reaction of a nitrogen-nucleophile and an aryl or heteroaryl halide, commonly known as *N*-arylation, is recognized as one of the most powerful means for the C-N bond formation due to the industrial value of the resulting substituted aromatics and heterocycles.

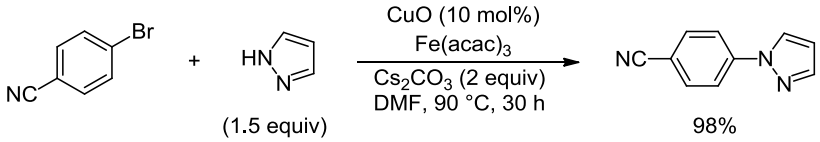
Early attempts of iron-catalyzed C-N bond formation relied on a co-catalysis of iron and copper salts.[53]

In 2006, Wakharkar *et al.* described the *N*-arylation of amines with iodo- and bromoarenes using Cu-Fe-hydrotalcite as catalyst (Scheme 21).[54] A series of arylamines bearing electron-withdrawing and -donating groups were obtained in very good yields under theses simple reaction conditions. The main advantages of this methodology are that no expensive catalyst or ligand is required, as well as any use of base or amine in excess.



Scheme 21: Cu-Fe-hydrotalcite-catalyzed *N*-arylation.

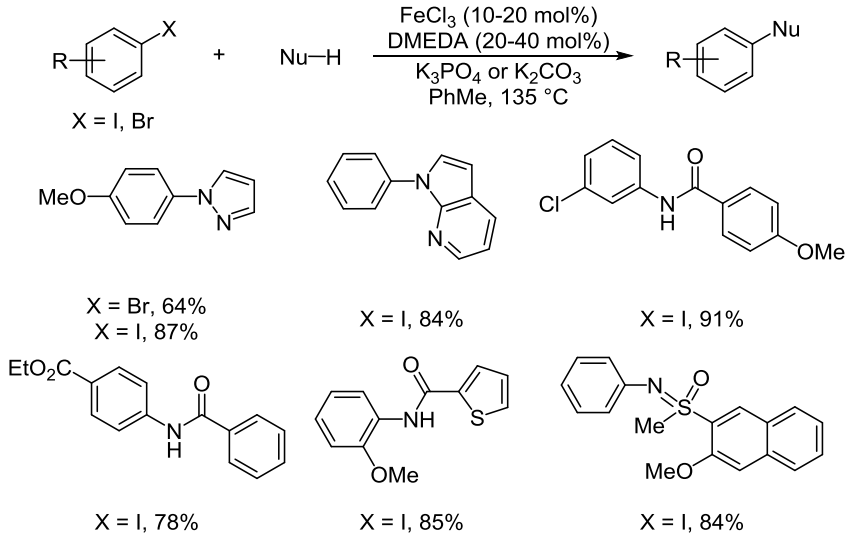
Few months later, the group of Taillefer reported the iron-copper cooperative catalysis for the *N*-arylation of several heterocycles with aryl halides (Scheme 22).[55] The combination of 10 mol% copper(I) oxide and 30 mol% $Fe(acac)_3$ catalyzed the arylation of pyrazole, imidazole, pyrrole, triazoles, indole and pyrrolidinone with electron-deficient and -rich aryl iodides and bromides. Activated aryl chlorides compounds reacted at higher temperatures (140 °C). A solvent-free alternative methodology was developed by Li and co-workers.[56]



Scheme 22: Fe/Co co-catalyzed *N*-arylation of heterocycles.

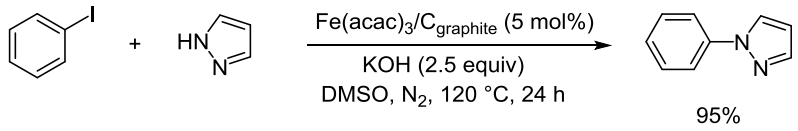
The major drawback of the previously described methodologies is the requirement of a copper salt as second metal source for the catalysis.

In 2007, Bolm *et al.* described the first iron-catalyzed *N*-arylation.[57] Aryl bromides and iodides reacted well with *N*-nucleophiles using iron(III) chloride in combination with DMEDA as catalytic system. This versatile protocol not only allowed the use of *N*-heterocycles, but could also be extended to other nitrogen nucleophiles such as primary amides[58] and sulfoximine derivatives (Scheme 23).[59] Unfortunately, the authors showed that the use of ultrapure $FeCl_3$ (>99.99%) led to only traces of the coupling products. Addition of 5 ppm CuO restored the yields obtained with the original iron catalyst. This indicates that copper is in fact playing a crucial role in this catalysis and that copper impurities are necessary for the arylation to proceed.



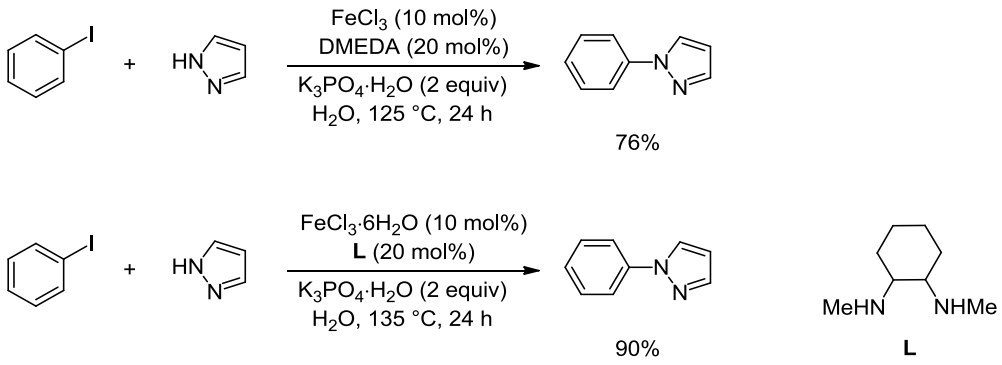
Scheme 23: Iron(III) chloride-catalyzed *N*-arylation.

Rao introduced the use of a recyclable heterogeneous graphite-supported iron catalyst for the *N*-arylation of aromatic amines, benzamide, thiobenzamide, pyrazole, imidazole, benzimidazole, and indole with aryl iodides and bromides (Scheme 24).[60] The developed catalyst could be recycled and reused at least five times without notable decrease of efficiency.



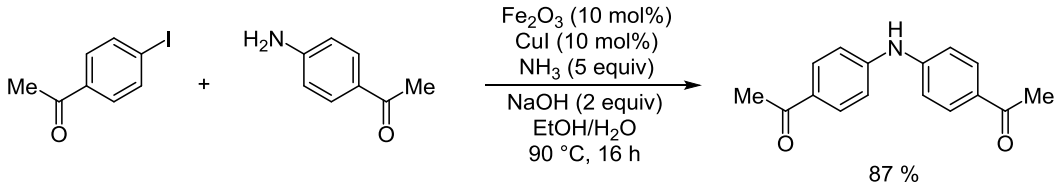
Scheme 24: Graphite-supported iron-catalyzed *N*-arylation.

In 2009, Teo and Kwong reported the *N*-arylation of pyrazole in aqueous medium (Scheme 25).[61] Pyrazoles, indole, 7-azaindole, and benzamide reacted well with aryl iodides under Teo's developed reaction conditions and the *N*-arylated nucleophiles were obtained in moderate to high yields. While Teo uses a combination of $FeCl_3$ and DMEDA, Kwong treated the same heterocycles with $FeCl_3$ and *N,N'*-dimethylcyclohexane-1,2-diamine (**L**). The yields in the desired *N*-arylated heteroarenes are comparatively higher with the second method.



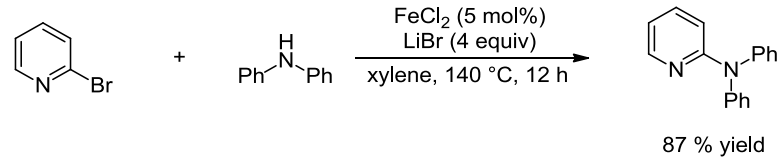
Scheme 25: Teo's and Kwong's iron-catalyzed N-arylation methodologies in aqueous conditions.

Furthermore, a co-catalysis methodology using iron(III) oxide and copper(I) iodide in a solution of aqueous ammonia in ethanol was developed by Darcel *et al.* in 2009.[62] This ligand-free *N*-arylation of aryl iodides with anilines required the use of sodium hydroxide as base (Scheme 26).



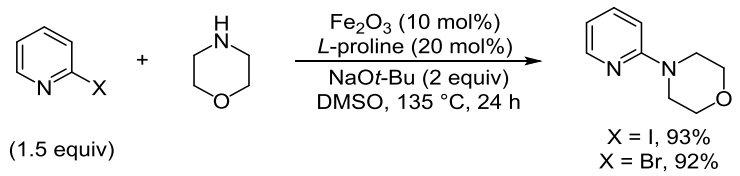
Scheme 26: Fe_2O_3/CuI-catalyzed *N*-arylation.

Not only diaryl- but also triarylamines could be synthesized by iron-catalyzed *N*-arylation. In 2012, Nakamura *et al.* reported the amination of aryl and heteroaryl bromides with magnesium amides under iron(II) chloride catalysis (Scheme 27).[63] The triarylamines were obtained in high yields, in the presence of lithium bromide in xylene at 140 °C. Investigations with stoichiometric amounts of the newly synthesized iron(II) diamide complex and DFT calculations enabled the authors to propose a non-conventional Fe(II)-Fe(IV) mechanism for this reaction.



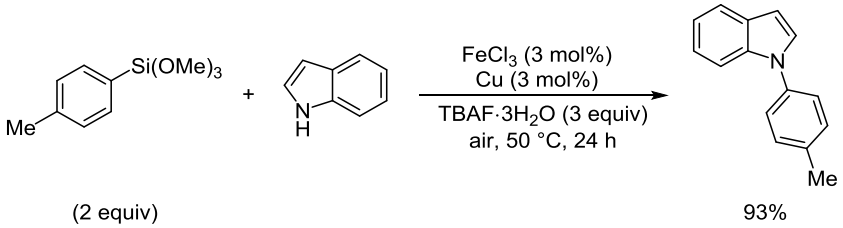
Scheme 27: Iron-catalyzed aromatic amination for nonsymmetrical triarylamine synthesis.

A direct iron-catalyzed coupling of aryl- and alkylamines, as well as *N*-heterocycles with aryl halides has been described by Liu *et al.* in 2008 (Scheme 28).[64] Under the catalysis of Fe_2O_3 and *L*-proline as ligand, a wide range of amines was successfully arylated, mainly with aryl iodides. A microwave-assisted alternative procedure was also developed by the authors. The reaction times were shortened but the use of $Cu(acac)_2$ as co-catalyst proved to be necessary.[65]



Scheme 28: Fe_2O_3-catalyzed *N*-arylation using *L*-proline as ligand.

In 2007, Li *et al.* reported the use of aryl- and vinyl(trimethoxy)silanes as coupling partner in the iron(III) chloride/copper-catalyzed arylation of imidazoles and triazoles (Scheme 29).[56]



Scheme 29: Solvent-free copper/iron co-catalyzed *N*-arylation reactions of nitrogen-containing heterocycles with trimethoxysilanes in air.

As a conclusion, starting with an iron/copper cooperative catalysis, few iron-catalyzed *N*-arylation methodologies have been developed since 2006. However, these results are tainted by further experiments performed by Buchwald and Bolm in 2009.[66] They could show that the "iron-catalyzed" C-X/N-H coupling reactions of pyrazole, benzamide and (thio)phenol were in fact triggered by copper impurities. While using ultrapure $FeCl_3$ (>99.99%), the yields of those *N*-arylations dropped drastically. The addition of trace amounts of Cu_2O (5-10 ppm) restored the original yields, showing the decisive role of copper salts in this catalysis. One should then keep this observation in mind for many iron-catalyzed aminations, since not all new developed methodologies have been tested using copper-free iron salts.

4. COBALT-CATALYZED CROSS-COUPLING AND AMINATION REACTIONS OF AROMATICS AND HETEROAROMATICS

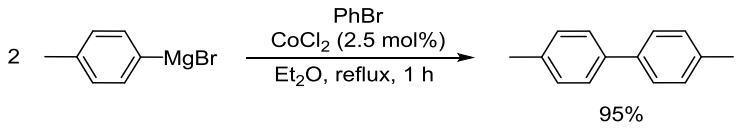
Although there have been striking breakthroughs in the development of iron catalysts for the formation of C-C and C-N bonds, cobalt salts have to be truly considered as an alternative to costly palladium and toxic nickel salts. Cobalt is not only relatively cheap (20.7 €/kg),[55] it also shows in some cases a higher reactivity than the corresponding iron-catalyzed cross-coupling reactions.

4.1 COBALT-CATALYZED CROSS-COUPLING REACTIONS OF AROMATIC AND HETEROAROMATIC ELECTROPHILES

Since the pioneering work of Kharasch and Fields on the metal-catalyzed homo-coupling reaction of aromatic Grignard reagents,[47a] cobalt-catalyzed cross-coupling reactions have received growing attention.

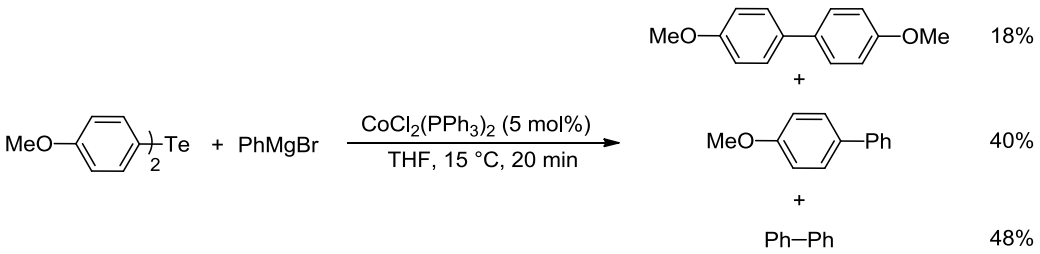
4.1.1 Cobalt-catalyzed cross-coupling of aromatics and heterocycles with aryl metal nucleophiles

The first cobalt-mediated cross-coupling reaction was reported by Gilman and Lichtenwalter in 1939.[67] Nearly quantitative yields of homo-coupling product were obtained by treating aromatic organomagnesium reagents with stoichiometric amount of cobalt halides. In 1941, Kharasch *et al.* developed the first cobalt-catalyzed symmetrical aryl-aryl homo-coupling, using 2.5 mol% of $CoCl_2$ and a stoichiometric amount of oxidant, allowing the oxidation of the reduced cobalt(0) species into the active Co(II) complex after reductive elimination (Scheme 30).[47a]



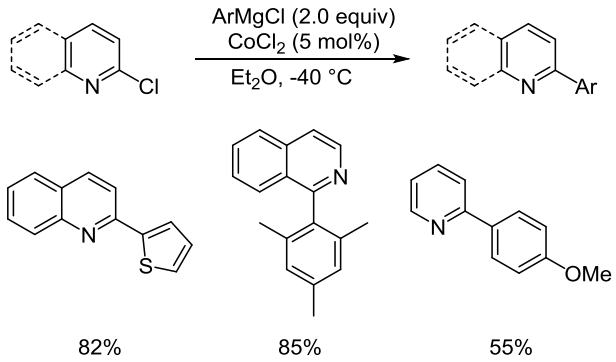
Scheme 30: First cobalt-catalyzed aryl-aryl cross-coupling.

One had to wait four decades to see the development of the first unsymmetrical cobalt-catalyzed biaryl formation by Uemura *et al.* (Scheme 31).[68] Diaryltellurides could be moderately coupled with aromatic Grignard reagents under 5 mol% $CoCl_2(PPh_3)_2$ catalysis. However, because of the formation of a significant amount of homo-coupling side product, the purification of the desired unsymmetrical product proved to be difficult.

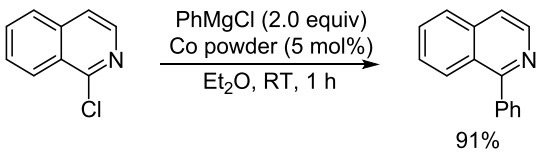


Scheme 31: Cobalt-catalyzed cross-coupling of organotellurides.

In 2003, a collaborative work between the groups of Knochel and Cahiez led to the publication of an efficient cobalt-catalyzed cross-coupling methodology between activated heteroaryl chlorides with (hetero)aryl Grignard reagents (Scheme 32).[44] Even though 2 equivalents of organomagnesium reagents were necessary, the desired coupling products were obtained in excellent yields. Steric hindrance did not show any big influence in these reactions conditions, since Grignard reagents such as mesitylmagnesium bromide could also react well. Interestingly, the authors could demonstrate the use of cobalt powder as catalyst for particular cases (Scheme 33). Furthermore, Oshima *et al.* reported a similar but alternative protocol using cobalt(II) acatylacetonate in diethylether one year later.[69]



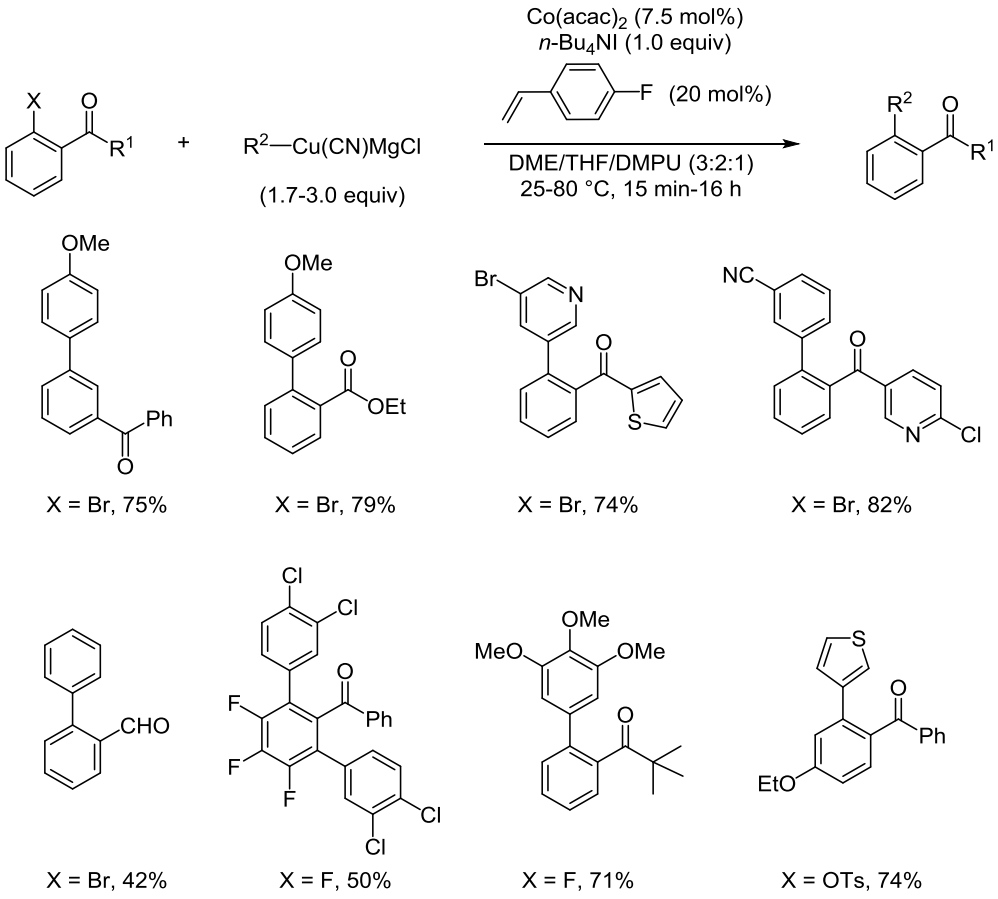
Scheme 32: Cobalt-catalyzed cross-couplings of heteroaryl chlorides and (hetero)aryl Grignard reagents.



Scheme 33: Cobalt powder-mediated heteroaryl-aryl cross-coupling reaction.

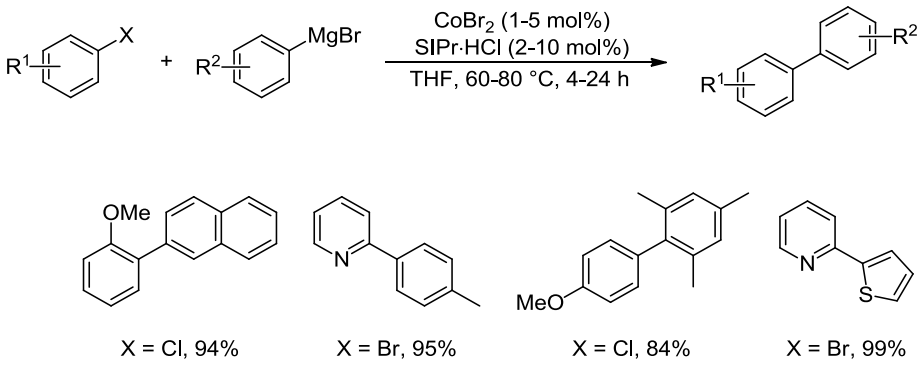
Moreover, Knochel *et al.* described the cobalt-catalyzed cross-coupling of aryl- and heteroarylcyanocuprates with various halogenated aromatic carbonyls (Scheme 34). *Ortho*-bromo, chloro, fluoro and tosyl aromatic ketones, esters and aldehydes reacted well under these reaction conditions, and a wide range of polyfunctional biaryls were obtained in high yields. The use of

1 equivalent tetrabutylammonium iodide and 20 mol% 4-fluorostyrene, as well as 3 equivalents organocuprate proved to be essential for the reaction with the halide. Interestingly, the use of a THF/DME/DMPU mixture instead of THF as solvent greatly decreased the reaction time (15 min instead of 21 h). It is also worth to note that *meta*- and *para*-aromatic halides showed only moderate conversion due to the position of the activating carbonyl group.[70]



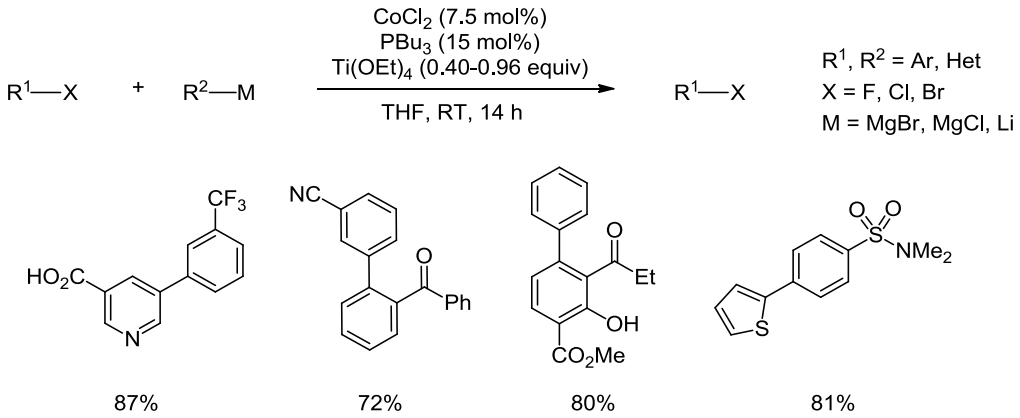
Scheme 34: Co-catalyzed cross-coupling of cyanocuprates with (hetero)aryl halides.

In parallel with the development of the corresponding iron-catalyzed cross-coupling, Nakamura *et al.* reported in 2009 the alternative cobalt-catalyzed cross-coupling of heroaromatic halides and non-activated aryl halides with aryl Grignard reagent (Scheme 35).[46b] The catalytic system was based on the use of $FeF_3 \cdot 3H_2O$ and SIPr·HCl (1,3-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride). Interestingly, the two described methodologies seem complementary, since better results were obtained with aromatic iodides and bromides under Co-catalysis, whereas higher yields were obtained with aromatic chlorides under FeF_3-catalysis.



Scheme 35: Co-catalyzed cross-coupling between non-activated (hetero)aryl halides and aryl Grignard reagent.

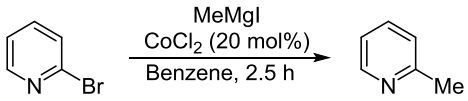
A cobalt/titanium co-catalysis was reported by Duan *et al.* in 2013, enabling the cross-coupling of aryl halides not only with aryl Grignard reagents, but also with aromatic organolithium compounds (Scheme 36).[71] The use of 0.4 equivalents $Ti(OEt)_4$ proved to have a beneficial effect, since no homo-coupling byproduct was formed from the organometallic reagent. This methodology showed a wide functional group tolerance as carboxylic acid, alcohol or amide could be present on the electrophile.



Scheme 36: Co/Ti cooperative catalysis towards the synthesis of biaryls.

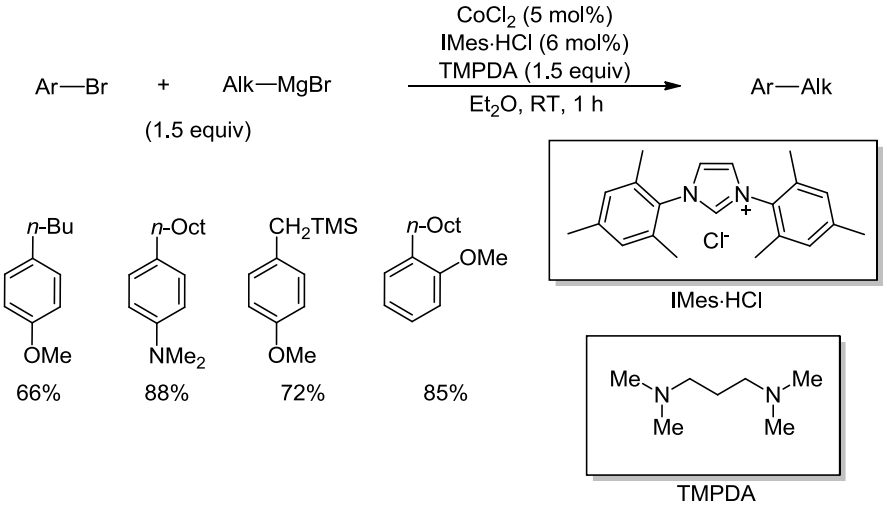
4.1.2 Cobalt-catalyzed cross-coupling of aromatics and heterocycles with alkyl metal nucleophiles

The first example of cobalt-catalyzed cross-coupling of heteroaromatics with alkyl metal nucleophile was reported by Hey *et al.* in 1969.[72] He discovered that the reaction between 2-bromopyridine and methylmagnesium iodide could be dramatically improved by the presence of catalytic amounts of cobalt(II) chloride (Scheme 37). However, these reaction conditions were not very general, since low yields were obtained in other cases.



Scheme 37: First cobalt-catalyzed cross-coupling of heterocycles with alkyl Grignard reagents.

Until today, the only efficient cobalt-catalyzed cross-coupling methodology between aryl halides and aliphatic Grignard reagents has been developed by Oshima *et al.* in 2008 (Scheme 38).[73] This very interesting alternative to the corresponding palladium and nickel protocols used aromatic bromides as electrophiles with primary alkyl Grignard reagents. The desired biaryls are obtained in good to excellent yield, exploiting $CoCl_2$ and the NHC IMes·HCl as catalytic system, and in the presence of *N,N,N',N'*-tetramethyl-1,3-propadiamine (TMPDA).

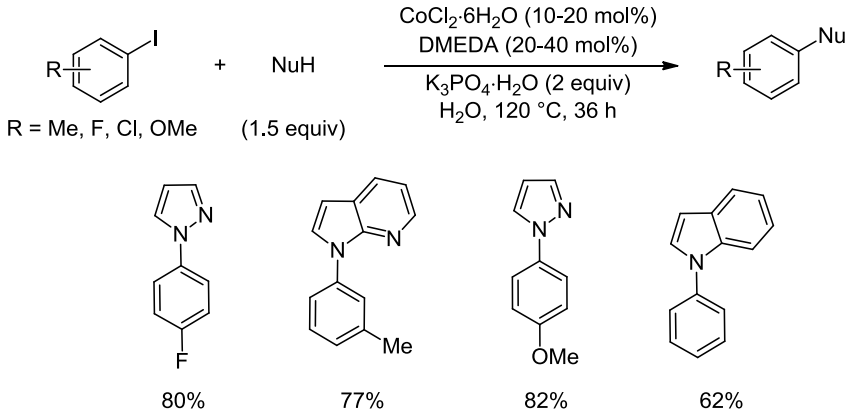


Scheme 38: Cobalt-catalyzed aryl-alkyl cross-coupling reactions.

4.2 COBALT-CATALYZED AMINATION REACTIONS OF (HETERO)AROMATIC ELECTROPHILES WITH NITROGEN-NUCLEOPHILES

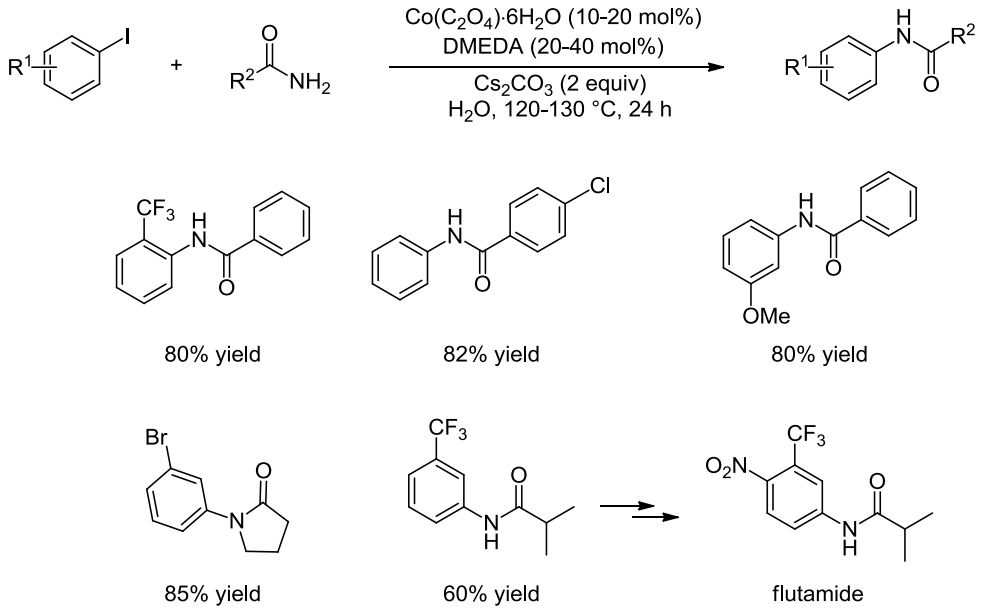
The field of cobalt-catalyzed amination reaction, as an alternative to the Pd-catalyzed Buchwald-Hartwig amination, is nowadays at its infancy.

The very first report of cobalt-catalyzed *N*-arylation was published by Teo *et al.* in 2009 (Scheme 39). This cross-coupling of nitrogen heterocycles with electrophilic aryl iodides was performed under 10 mol% $CoCl_2$ catalysis used in combination with 20 mol% of the chelating *N,N'*-dimethylethylenediamine (DMEDA), and in the presence of 2 equivalents K_3PO_4 as base. It is worth to note that these *N*-arylations proceeded in water and without the need for any other reducing agent or electrochemical methods.[74]



Scheme 39: Cobalt-catalyzed *N*-arylation of *N*-nucleophiles in water.

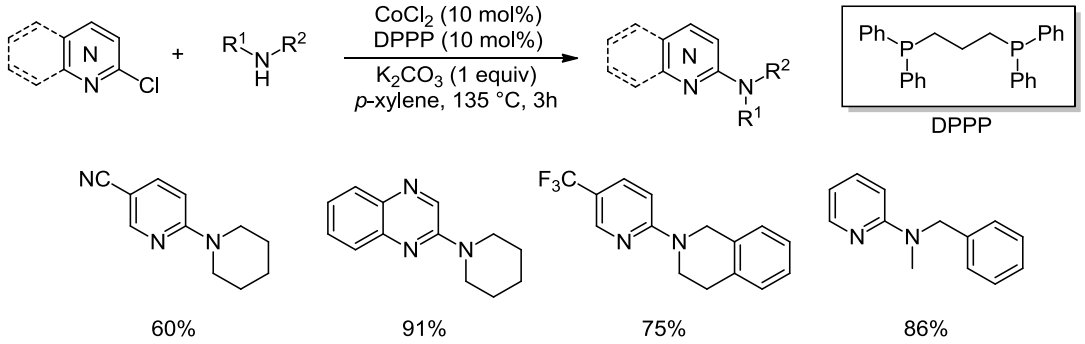
Teo *et al.* further extended this methodology to the use of both aliphatic and aryl amides with a wide range of aryl and heteroaryl iodides (Scheme 40).[75] Contrary to the previously described method, the amide-coupling required $Co(C_2O_4)$ as catalyst instead of $CoCl_2$. The amine ligand DMEDA has remained but the preferred base was in this case Cs_2CO_3. Good to excellent yields in the desired substituted amides were obtained under those aqueous conditions. Moreover, they could successfully apply this protocol to the synthesis of prostate anticancer drug flutamide and derivatives.



Scheme 40: Cobalt-catalyzed amination of aryl iodides by aliphatic and aryl amides in water.

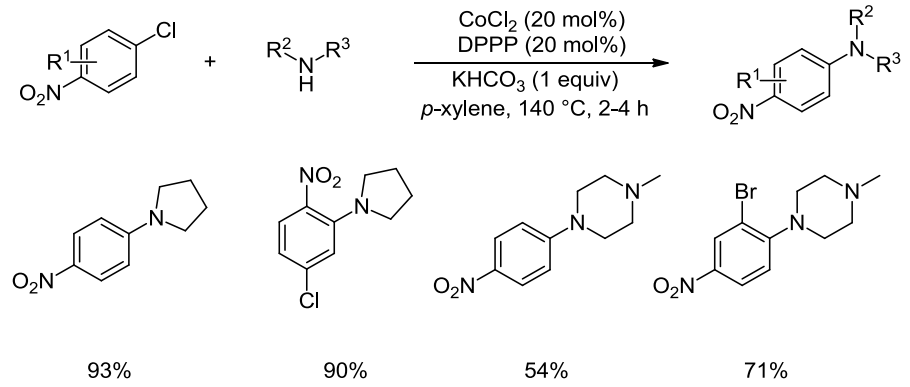
In 2009, Toma *et al.* reported the cobalt(II) chloride-catalyzed amination of secondary amines with *N*-aromatic 2-chlorides (Scheme 41).[76] Using potassium carbonate as base and 1,3-bis(diphenyl-phosphanyl)propane (DPPP) as ligand, this cobalt-catalyzed approach led to the desired tertiary amines in high yields. These *N*-aromatic-containing tertiary amines should be of interest for further

use as building blocks for bioactive molecules.



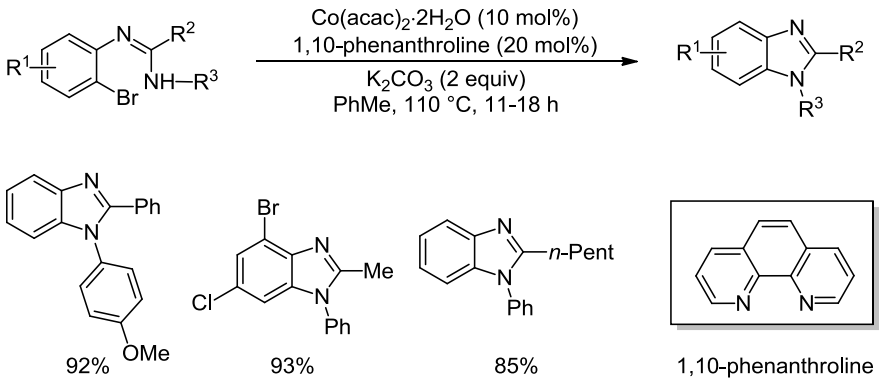
Scheme 41: Cobalt-catalyzed C-N bond forming reaction between *N*-aromatic 2-chlorides and secondary amines.

One year later, a new methodology for the preparation of nitro-substituted tertiary amines was described by these authors under similar reaction conditions (Scheme 42).[77] The combination of $CoCl_2$ and the phosphane ligand DPPP was maintained, as well as the use of *p*-xylene at 140 °C. However, the authors preferred exploiting $KHCO_3$ as base, which showed better results than the previously used K_2CO_3. Interestingly, these *N*-arylations were completely *ortho*- and *para*-selective, since *meta*-substituted halides showed to be unreactive in these reaction conditions. An analog methodology was developed by Chatterjee *et al.* using alumina-supported cobalt(II) bromide.[78]



Scheme 42: Cobalt-catalyzed C-N bond forming reaction between chloronitrobenzenes and secondary amines.

Finally, an intramolecular Co-catalyzed amination protocol was reported towards the synthesis of substituted benzimidazoles (Scheme 43). A combination of $Co(acac)_2 \cdot 2H_2O$ and 1,10-phenanthroline proved to catalyze the cyclization of (*Z*)-*N*'-(2-halophenyl)-*N*-phenylamidines in the presence of K_2CO_3 at 110 °C. This simple and air-stable methodology furnished the desired benzimidazoles in high yields.[79]



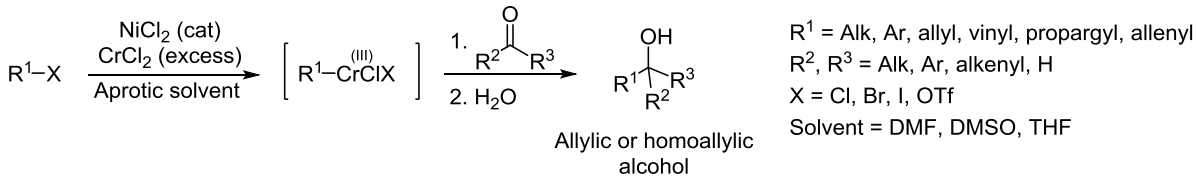
Scheme 43: Cobalt-catalyzed intramolecular amination towards the synthesis of substituted benzimidazoles.

5. CHROMIUM-CATALYZED TRANSFORMATIONS

Even though chromium ranks among the most abundant elements on earth,[80] chromium-catalyzed transformations remain under-developed compared to other transition-metal catalysts, such as palladium, nickel, iron or cobalt salts.

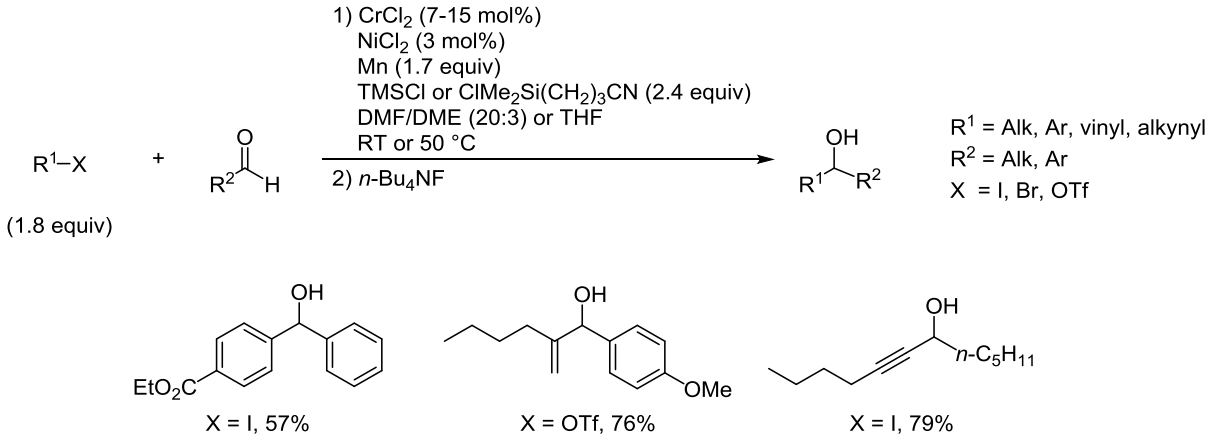
In 1919, Hein *et al.* pioneered the field by preparing the first organochromium reagent. The treatment of chromium(III) chloride with phenyl Grignard led to the formation of a bis(arene)chromium species.[81] It took not less than four decades to finally clarify the correct structure of this complex.[82]

In 1977, Nozaki and Hiyama and co-workers reported the first carbonyl addition of allyl halides by means of chromous salt.[83] The authors, in parallel of Kishi's independent work, improved the synthesis of (homo)allylic alcohols in 1986 by discovering that traces of nickel salts enhance the catalytic effect on the formation of the C-Cr(III) bond.[84] This finding led to the development of the so-called Nozaki-Hiyama-Kishi reaction,[85] especially useful for less reactive substrates, such as alkenyl and aryl halides or triflates, in Barbier-type addition reactions (Scheme 44). This standard tool using stoichiometric or excess amounts of chromium salts has found many applications and various coupling reactions were published.[86]



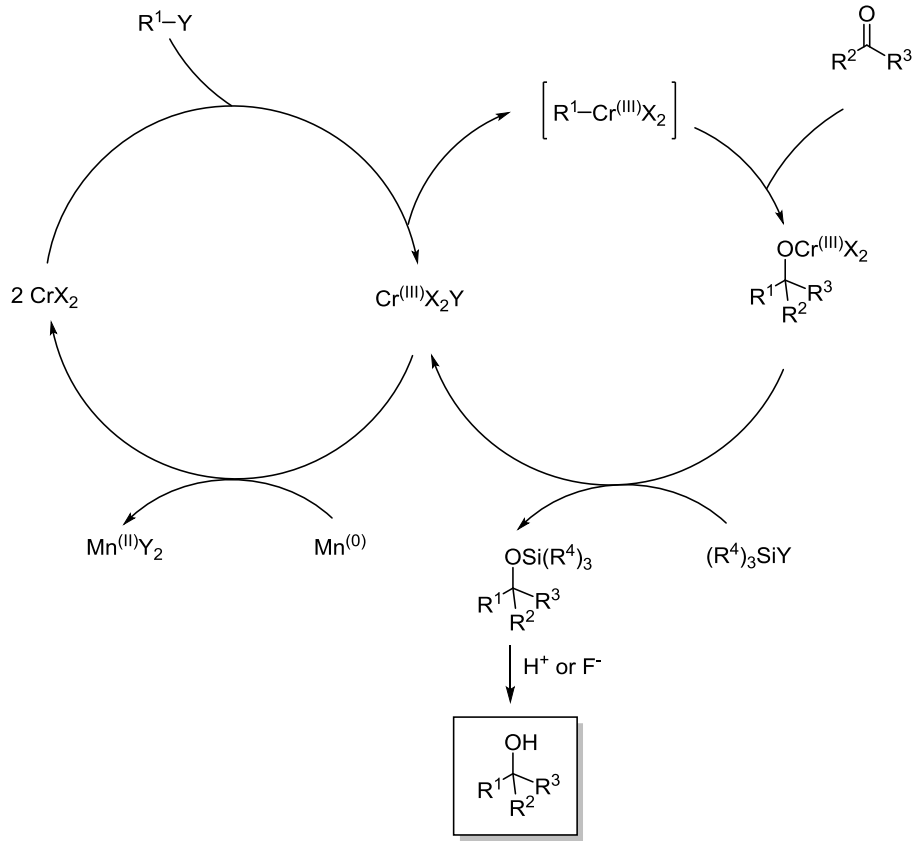
Scheme 44: Chromium-mediated and nickel-catalyzed Nozaki-Hiyama-Kishi reaction.

A significant progress in this chromium-mediated methodology was done by Fürstner *et al.* in 1996, who reported the use of catalytic quantities of chromium salt.[87] The developed catalytic system involved 7-15 mol% of chromium(II) or (III) chloride doped with nickel(II) chloride and manganese powder as stoichiometric reductive agent. Chlorosilane served as essential additive for ligand exchange, helping the dissociation of the product from the chromium (Scheme 45). It was noted that other chromium salts such as Cp_2Cr or $CpCrCl_2 \cdot THF$ could be used as well as precatalyst.



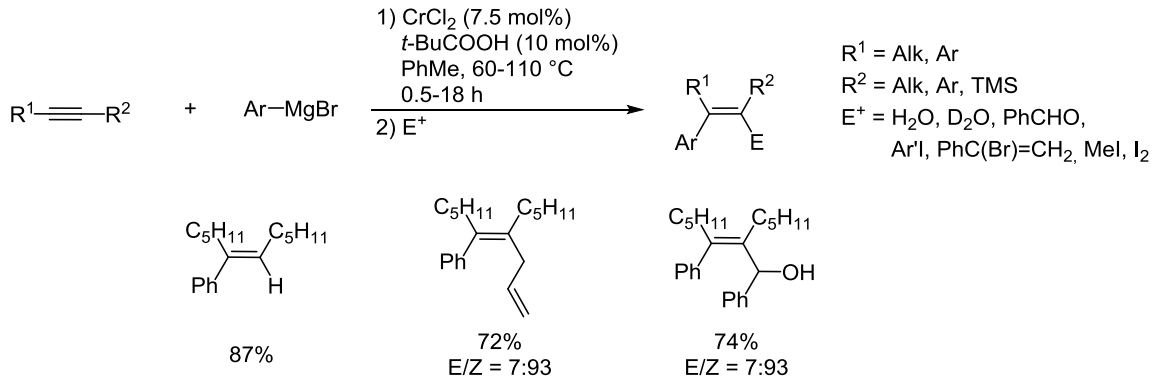
Scheme 45: Chromium-catalyzed Nozaki-Hiyama-Kishi reaction.

The mechanism of the chromium(II)-catalyzed Nozaki-Hiyama-Kishi, in contrary to its nickel(II)-mediated analogue, relies on both the use of Mn(0) and a chlorosilane (Scheme 46). First, the proposed catalytic cycle starts with the reaction of two equivalents CrY_2 with the organic halide. Cr^{+2} being a one-electron donor, 2 equivalents of complex are necessary for the formation of the organochromium complex R^1CrX_2 and CrX_2Y. R^1CrX_2 adds then to the carbonyl, forming the chromium alkoxide. The high stability of the O-Cr^{+3} bond hampering the formation of the (homo)allylic alcohol, the necessary chlorosilane realizes the ligand exchange with the chromium alkoxide, leading to the desired alcohol after deprotection. A second equivalent of CrX_2Y is then released and reduced by manganese(0), enabling its further re-use in the catalytic cycle.



Scheme 46: Mechanism of the chromium-catalyzed Nozaki-Hiyama-Kishi reaction.

The development of further chromium-catalyzed processes needed to wait till 2007. Oshima *et al.* described the arylmagnesiation of unfunctionalized alkynes in the presence of pivalic acid and catalytic amounts of chromium(III) chloride (Scheme 47).[88] The alkenylmagnesium intremediates reacted with various electrophiles, leading to the desired tetrasubstituted olefins in good yields and high *cis*-stereoselectivity.

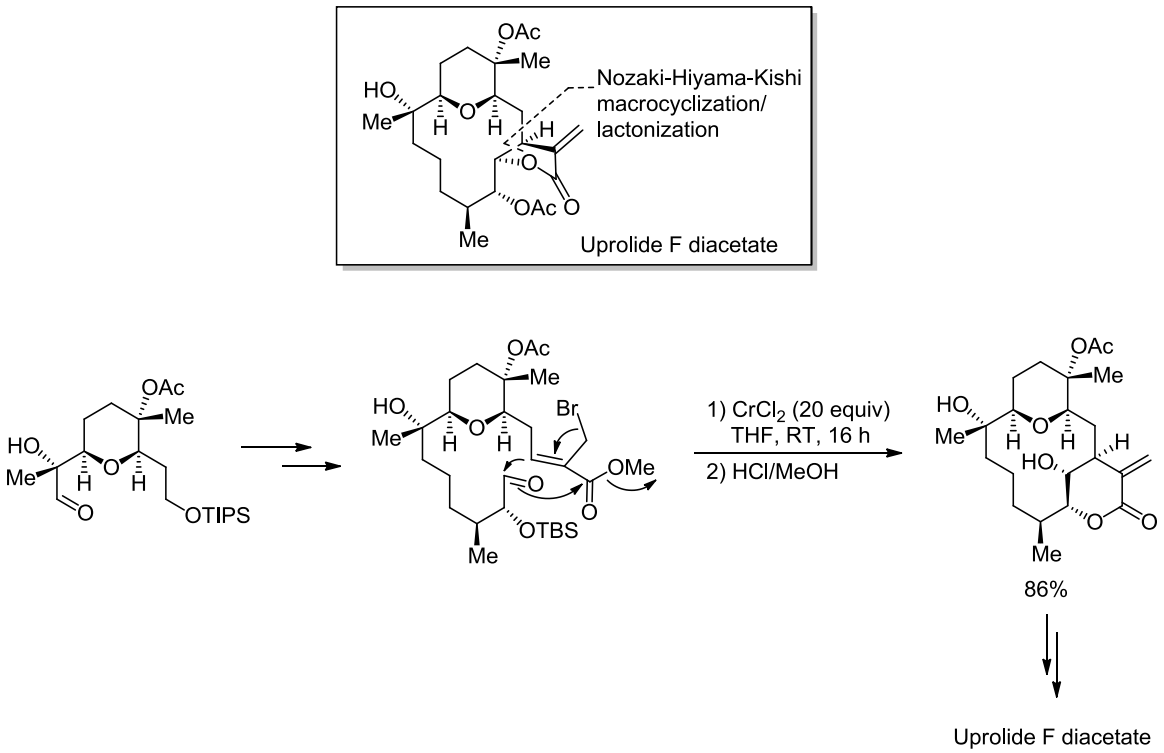


Scheme 47: Chromium-catalyzed arylmagnesiation of alkynes.

Since the development of the first organochromium reagent, chromium catalysis has attracted high

interest. Various useful chromium-mediated synthetic methods have been developed, such as the Takai-Uchimoto olefination,[89] ethylene oligomerization[90] and polymerization,[91] alcohol and carbonyl oxidation,[92] aldol[93] and Diels-Alder[94] reactions. These common tools in organic chemistry generally show good functional group compatibility and high selectivity, and are of widespread use in total synthesis as key steps for the preparation of sophisticated natural products.

As an illustration, one can for instance cite the use of the Nozaki-Hiyama-Kishi reaction as key macrocyclisation in the total synthesis of cytotoxic cembranolide uprolide F diacetate (UFD) performed by Tong and co-workers (Scheme 48).[95]



Scheme 48: Enantioselective total synthesis of Uprolide F acetate using Nozaki-Hiyama-Kishi macrocyclization.

Despite these achievements, chromium-catalyzed organic reactions still remain underdeveloped in comparison to other transition metal catalysts, and considerable more effort should be dedicated to discover new transformations and broaden the reaction scope of this field. Until now, no chromium-catalyzed cross-coupling methodology has been described yet. This possible expansion of the chromium catalysis palette would represent an extension to the use of alternative metal salts in cross-coupling reactions.[96]

6. SYNTHESIS OF PYRIDONAPHTHYRIDINES

Nitrogen heterocycles, and particularly pyridines as well as pyridine-based compounds play diverse roles in organic chemistry. As ligands, solvents or catalysts, they facilitate reactions; thus the description of new cores and applications abound each year.[97]

Additionally, pyridine-based molecules are also used in material science, where their optical and physical properties are highly valued (*e.g.* fluorescent probe or organic solar cells). Moreover, the medical potential of six-membered *N*-heteroaromatics remains an area of intense research, as pyridines are frequent subunits of medicinally relevant compounds.[98, 14d]

Among those scaffolds, not only substituted pyridines[99] but also a number of privileged ring systems have been extensively studied, such as quinolines,[100] isoquinolines,[101] acridines[102] or diazines. Annelated six-membered *N*-heteroaromatics bearing one nitrogen atom per ring such as naphthyridines[103] are much less investigated, and the corresponding triazaanthracenes[104] and triazaphenanthrenes[105] are almost unknown. Pyridonaphthyridines, a particular type of azaphenanthrenes, result from the fusion of three pyridines without any bridged nitrogen (Figure 2).

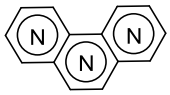
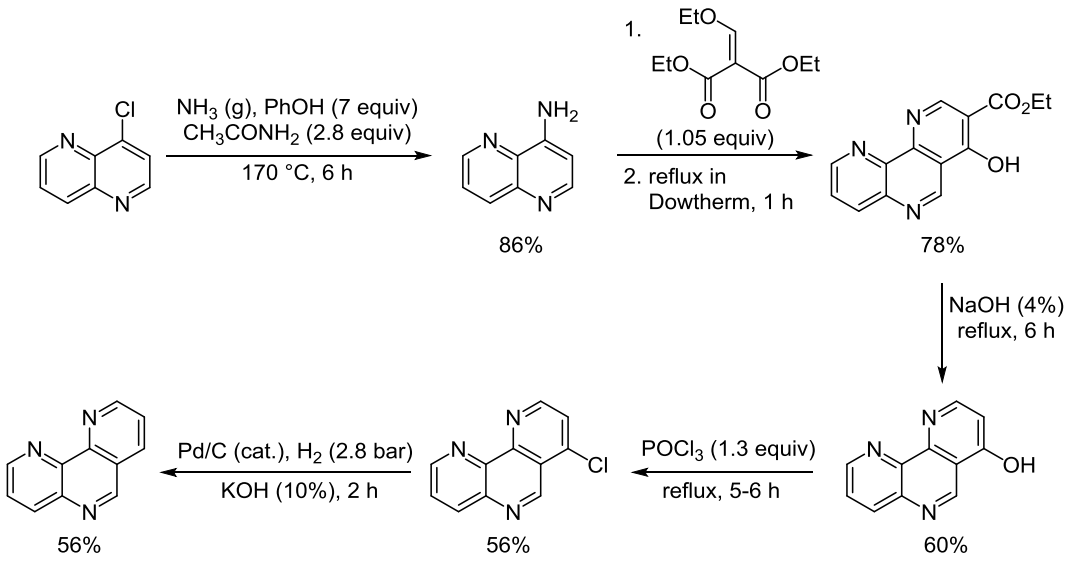


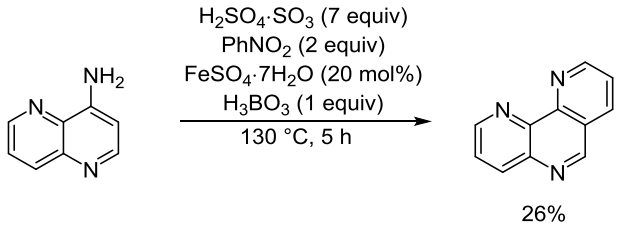
Figure 2: Pyridonaphthyridines.

The first pyridonaphthyridine synthesis was reported by Case and Brennan in 1959 (Scheme 49).[106] After amination of 4-chloro-1,5-naphthyridine, the key step of this synthesis was the cyclization of 4-amino-1,5-naphthyridine in the presence of ethyl ethoxymethylenemalonate, leading to the 3-ring intermediate in 78% yield over 2 steps. Further decarboxylation, chlorination and reduction led to pyrido[3,2-*c*][1,5]naphthyridine in 15% overall yield in 6 synthetic steps.



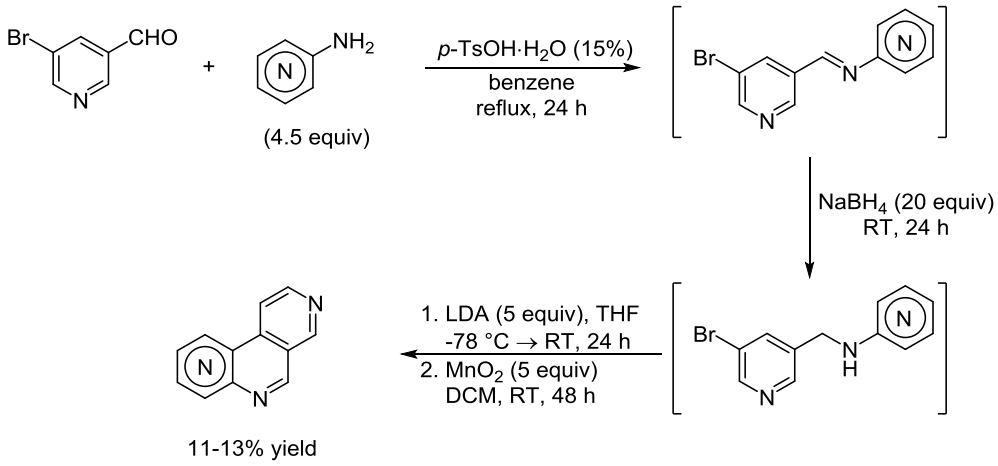
Scheme 49: Synthesis of pyrido[3,2-*c*][1,5]naphthyridine by Case and Brennan.

Furthermore, in 1975, Hamada *et al.* described the synthesis of the same regioisomer *via* a Skraup-type reaction.[107] 4-Amino-1,5-naphthyridine reacted with oleum, iron(II) sulfate and boric acid in glycerol, using nitrobenzene as oxidizing agent. This one-step synthesis provided the desired pyrido[3,2-*c*][1,5]naphthyridine in 26% yield (Scheme 50).



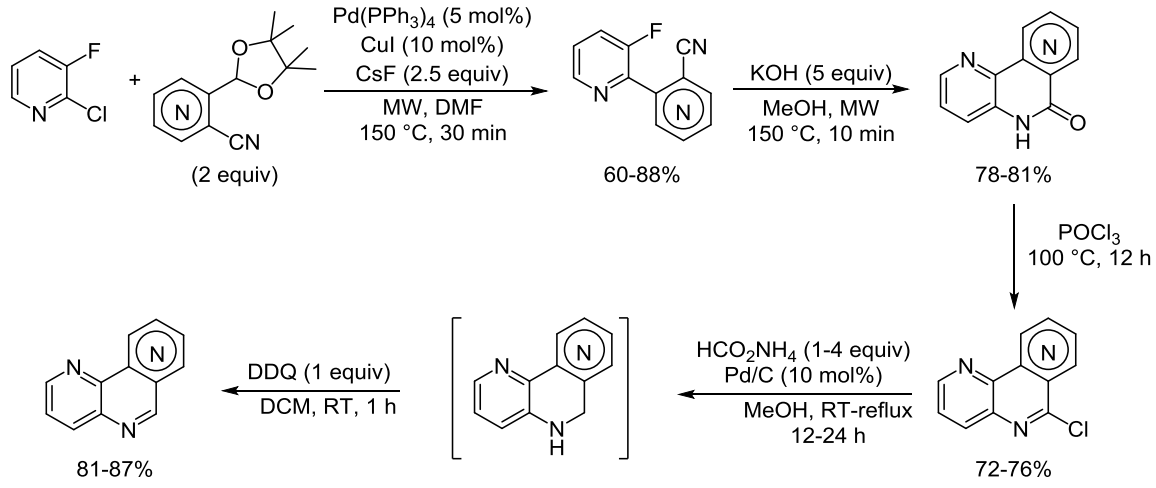
Scheme 50: Skraup-synthesis towards pyrido[3,2-*c*][1,5]naphthyridine.

Pyrido[3,4-*c*][1,8]naphthyridine and pyrido[3,4-*c*][1,7]naphthyridine were prepared by Nutaitis and Brennan in 2004.[108] Condensation and subsequent reduction of 5-bromonicotinaldehyde with an excess of either 2- or 3-aminopyridine afforded the cyclisation precursor, which led after treatment with LDA at -78 °C and MnO_2-mediated aromatization to the desired azaphenanthrenes in 11 and 13% overall yield (Scheme 51).



Scheme 51: Formation of pyrido[3,4-*c*][1,8]naphthyridine and pyrido[3,4-*c*][1,7]naphthyridine.

Moreover, Rault *et al.* reported the first multi-step synthesis towards the formation of pyridonaphthyridines including a metal-catalyzed cross-coupling step.[109] Indeed, the Pd-catalyzed Suzuki cross-coupling of 2-chloro-3-fluoropyridine with 3 different *ortho*-cyanopyridylboronic esters provided the required bipyridines in 60-88% yield (Scheme 52). After KOH-mediated anionic ring closure, pyridonaphthyridinone intermediates were obtained in 78-81% yield. Chlorodehydroxylation and dehalogenation furnished the final pyrido[4,3-*c*][1,5]naphthyridine, pyrido[3,4-*c*][1,5]naphthyridine and pyrido[2,3-*c*][1,5]naphthyridine in 30-44% overall yield.



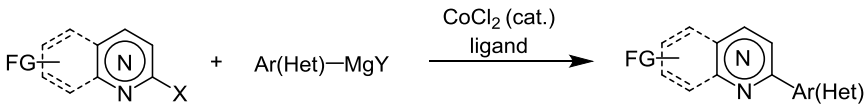
Scheme 52: 4-Step synthesis of pyrido[4,3-*c*][1,5]naphthyridine, pyrido[3,4-*c*][1,5]naphthyridine and pyrido[2,3-*c*][1,5]naphthyridine.

7. OBJECTIVES

With the increasing pressure to reduce energy consumption, to protect the environment, and to conserve natural resources, catalysis is clearly a mean towards this goal for synthetic chemists. Late transition-metal catalysts, particularly in cooperation with organometallic species, have become an indispensable tool to accomplish efficient and selective multiple syntheses. In particular, palladium- and nickel-catalyzed cross-couplings have been widely used for the introduction of various functional groups into unsaturated substances such as aromatic rings, alkenes or alkynes. However, on one side, the constantly increasing price of palladium complexes as well as its declining availability, and on the other side, the toxicological concerns linked with nickel salts, are encouraging the quest for alternative metals. Those metal substitutes should fit different requirements: they should be ecologically-friendly, readily available, as well as relatively cheap, and should show high catalytic activity and chemical selectivity to be applicable in both total syntheses and modern industrial manufacturing processes.

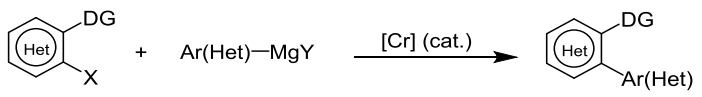
In this context, relatively low-cost and low-toxic iron and cobalt salts are viable alternatives. Even though iron- and cobalt-catalyzed alkyl-aryl, alkyl-alkenyl, aryl-alkenyl, and alkynyl-coupling reactions are well documented, the corresponding aryl-aryl cross-coupling methodologies still need to be improved.

Hence, the first goal of this work was to extend the scope and search for better ligands for the (iso)quinoline-accelerated $CoCl_2$-catalyzed methodology for the coupling of (hetero)aryl halides and (hetero)aryl Grignard reagents (Scheme 53).[110]



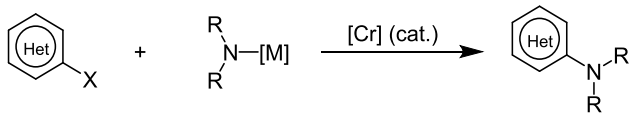
Scheme 53: Attempted cobalt-catalyzed cross-coupling reactions.

In order to find alternative complexes for the use in Csp^2-Csp^2 cross-coupling reactions also other metals than the widely used ones like palladium should be investigated. For this reason, the application of Cr-salts was investigated in the C-C bond formation of (hetero)aromatics with (hetero)aryl magnesium reagents (Scheme 54).[111]



Scheme 54: Attempted chromium-catalyzed cross-coupling reactions.

Moreover, the methodology described above should then be further extended to the replacement of palladium in Buchwald-Hartwig amination reactions. Hence, the Cr-catalyzed C-N bond formation was intensively studied.[112]



Scheme 55: Attempted Cr-catalyzed Buchwald-Hartwig aminations.

Due to the potential applications of *N*-heterocycles in medicinal chemistry and material science, the preparation of almost unknown annelated six-membered *N*-heteroaromatics was investigated. Attention was paid in particular to the synthesis and the functionalization of pyrido[3,2-*f*][1,7]naphthyrdine using metal-catalyzed cross-coupling and amination reactions as key steps (Figure 3).[113]

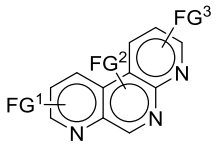
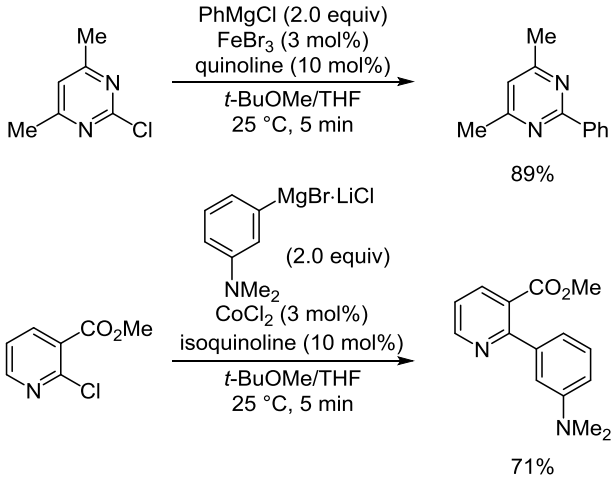


Figure 3: Metal-catalyzed multi-step synthesis of pyrido[3,2-*f*][1,7]naphthyrdine and derivatives.

B. Results and Discussion

1. COBALT(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN *N*-HETEROCYCLIC HALIDES AND ARYL OR HETEROARYL MAGNESIUM REAGENTS

Knochel *et al.* demonstrated in 2013 the ability of quinoline and isoquinoline to act as efficient ligand for the iron- and cobalt-catalyzed cross-coupling of *N*-heteroaryl halides with aryl Grignard reagents (Scheme 56).[114]

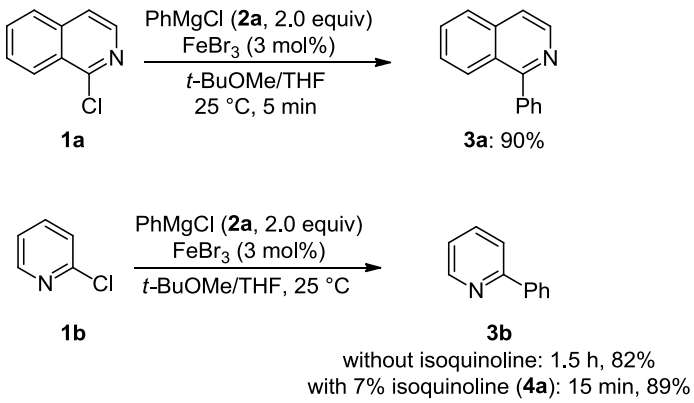


Scheme 56: Ligand-accelerated Fe- and Co-catalyzed cross-coupling reactions.

The following work presents an extension of the scope of the cobalt-catalyzed cross-coupling methodology, as well as a study of other *N*-heterocycles used as potential ligands for this procedure.

1.1 COBALT-CATALYZED CROSS-COUPLING REACTIONS UTILIZING ISOQUINOLINE AS LIGAND

Preliminary experiments were showing that the reaction of 1-chloroisoquinoline (**1a**) and PhMgCl (**2a**) in presence of 3% $FeBr_3$ took only 5 min in the solvent mixture *t*-BuOMe/THF, and provided the cross-coupling product 1-phenylisoquinoline (**3a**) in 90% yield. In comparison, the cross-coupling of 2-chloropyridine (**1b**) required 1.5 h under the same conditions until completion and gave 2-phenylpyridine (**3b**) in 82% yield (Scheme 57). The reactivity difference of these substrates led us to postulate that the catalytically active iron species, generated *in situ*, may contain an isoquinoline fragment as ligand.[115, 114a] A similar accelerating effect of isoquinoline (**4a**) was observed in Co-catalyzed cross-coupling reactions.

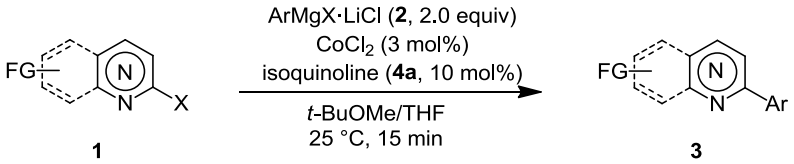


Scheme 57: Iron-catalyzed cross-coupling reactions of 1-chloroisoquinoline (1a) or 2-chloropyridine (1b) with PhMgCl (2a).

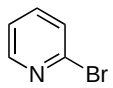
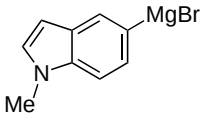
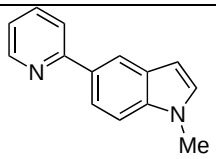
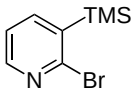
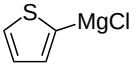
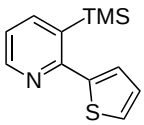
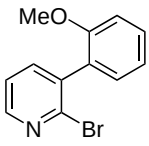
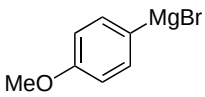
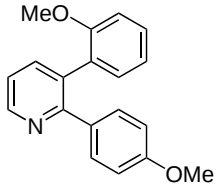
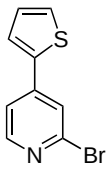
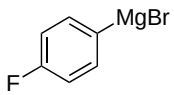
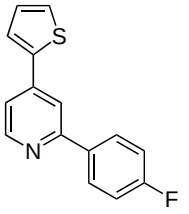
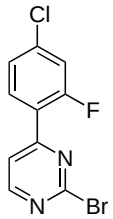
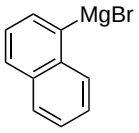
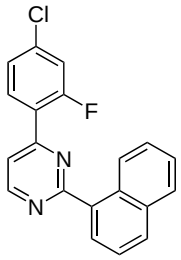
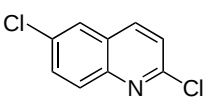
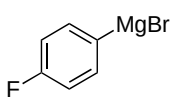
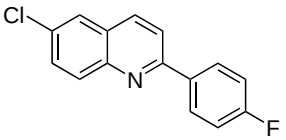
The reaction scope of cobalt-catalyzed cross-coupling reactions in the presence of isoquinoline **4a** as key ligand in the solvent mixture *t*-BuOMe/THF was further investigated. Various *N*-heterocycles have successfully been coupled with both aromatic and heteroaromatic Grignard reagents under cobalt(II) chloride catalysis.

This way, 2-bromopyridine (**1c**) could be readily coupled with the methyl-indole magnesium reagent **2b**, providing the desired pyridine **3c** in 61% isolated yield (Table 1, entry 1). TMS-substituted 2-bromopyridine **1d** underwent the Co-catalyzed coupling with the thiophene organomagnesium reagent **2c** to furnish the respective 2,3-disubstituted bis-heteroaromatic compound **3d** in 49% yield after 15 min at 25 °C (entry 2). The 2,3- and 2,4-disubstituted pyridines **1e** and **1f** reacted with electron-rich (**2d**) and -poor (**2e**) Grignard reagents, resulting in the corresponding 2,3- and 2,4-bisarylated pyridines **3e** and **3f** in good yield (69-70% yield, entries 3 and 4).
Also the arylated 2-bromopyrimidine **1g** could be used in such cross-coupling reaction, enabling the access to the naphthalene-substituted pyrimidine **3g** in 57% yield (entry 5). Another *N*-heterocycle, 2,6-dichloroquinoline (**1h**), reacted with (4-fluorophenyl)magnesium bromide (**2e**) and provided the desired quinoline **3h** in 63% after 15 min at 25 °C (entry 6).

Table 1: Room-temperature Co-catalyzed cross-coupling reactions between *N*-heterocyclic halides and arylmagnesium reagents.



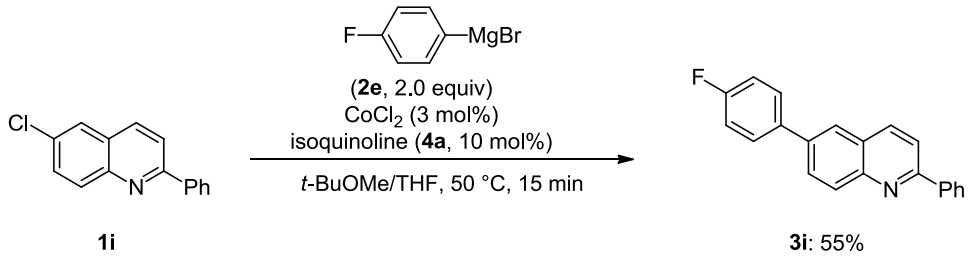
1 **3**

Entry	Starting material	Grignard reagent	Product[a]
			
1	**1c**	**2b**	**3c**: 61%
			
2	**1d**	**2c**	**3d**: 49%
			
3	**1e**	**2d**	**3e**: 69%
			
4	**1f**	**2e**	**3f**: 70%
			
5	**1g**	**2f**	**3g**: 57%
			
6	**1h**	**2e**	**3h**: 63%

[a]Isolated yields of analytically pure product.

During the course of the investigations, it was found that not only the 2-position of halogenated

quinolines, but also the 6-position can be functionalized using cobalt(II) chloride as catalyst in combination with isoquinoline (**4a**) as ligand (Scheme 58). 6-Chloro-2-phenyl-quinoline **1i** underwent a cross-coupling reaction with 4-fluorophenylmagnesium bromide (**2e**) in a moderate yield of 55%. Interestingly, the formation of the diarylation products from **1i** was not observed (Table 1, entry 6), probably due to the fact that the cross-coupling at position 2 is faster than at position 6.



1i **3i**: 55%

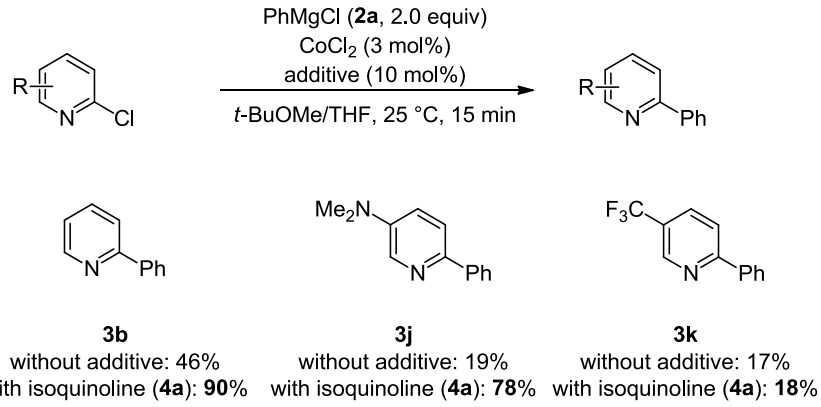
Scheme 58: Co-catalyzed cross-coupling reaction between 6-chloroquinoline 1i and organomagnesium reagent 2e.

1.2 LIGAND SCREENING FOR THE COBALT-CATALYZED CROSS-COUPLING OF CHLOROPYRIDINES

During the scope investigation of this cobalt-catalyzed cross-coupling methodology, it was observed that the accelerating effect of isoquinoline (**4a**) was extremely depending on the nature of the substrate (Scheme 59).

For instance, 2-chloropyridine (**1b**) reacted with phenylmagnesium chloride (**2a**) in 46% yield in the absence of ligand. This cross-coupling was greatly improved by addition of 10 mol% isoquinoline (**4a**) and led to the desired 2-phenylpyridine (**3b**) in 90% yield after 15 min at 25 °C. The catalytic activity of isoquinoline (**4a**) in the cross-coupling of 2-chloro-5-(dimethylamino)pyridine is even more remarkable: whereas only 19% of the desired phenylated pyridine **3j** is achieved without additive, 78% product could be isolated after 15 min by using isoquinoline (**4a**) as ligand.

Interestingly, an erosion of the efficiency occurred when more electron-withdrawing substrates were present: 2-phenyl-5-(trifluoromethyl)pyridine **3k** could only be obtained with 17% yield. Unfortunatelly, only an minor improvement was achieved by the use of 10 mol% isoquinoline (**4a**). This observation led to the search for a more universal ligand, which could accelerate the cobalt-catalyzed cross-coupling reaction of substrates bearing either electron-donating or -withdrawing substitutents.

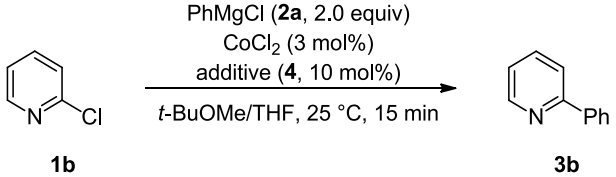


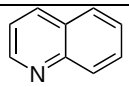
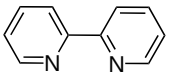
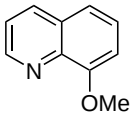
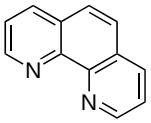
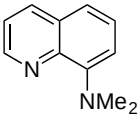
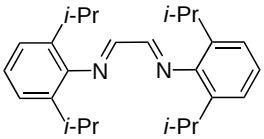
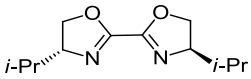
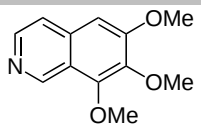
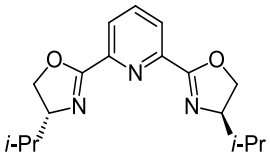
Scheme 59: Substituent effect on Co-catalyzed cross-couplings leading to pyridines 3b, 3j and 3k.

The screening of various quinoline- and isoquinoline-related heterocycles, as well as other nitrogen-containing additives was then performed systematically on the three previously discussed pyridine systems. The comparison of the 2-chloropyridine **1b** with the electron-rich 2-chloro-5-(dimethylamino)pyridine **1j** and the electron-poor 2-chloro-5-(trifluoromethyl)pyridine **1k** was chosen to get a better insight into the reactivity differences.

The screening of various additives for the cobalt-catalyzed cross-coupling reaction of 2-chloropyridine (**1b**) with phenylmagnesium chloride (**2a**) is shown in Table 2. A negative effect was observed by addition of 10 mol% pyridine (**4b**), 2,2'-bipyridine (**4c**), 1,10-phenanthroline (**4d**) or the bis-imine and bis-oxazoline compounds **4e** and **4f** as ligand, leading to the desired product only in unsatisfactory yields (28-37%, entries 1-5). Interestingly, Pybox ligand (**4g**), usually known for enhancing Ni-catalyzed cross-couplings[116] suppressed the reaction of the substrate with the Grignard reagent, probably due to the strong chelation of the cobalt with the ligand (entry 6). In contrary, a significant improvement of the reaction was detected with all quinolines and isoquinolines that were tested. The 8-substituted quinolines **4i** and **4j** (entries 8 and 9) showed a slight decrease of the catalytic activity in comparison with quinoline (**4h**, entry 7), since 65% yield of 2-phenylpyridine (**3b**) was observed, whereas 71% yield was achieved with the latter one. The ligand of choice for this cross-coupling proved to be isoquinoline (**4a**) with its 90% yield (entry 10). An erosion of the rate enhancement occurred when the isoquinoline core was bearing electron-donating substituents (**4k**, entry 11).

Table 2: Screening of various additives for the Co-catalyzed cross-coupling reaction of 2-chloropyridine (1b) with PhMgCl (2a).

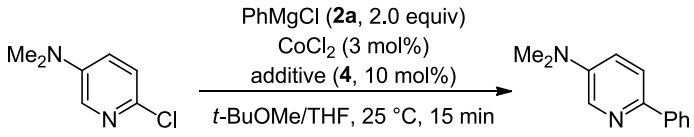


Entry	Additive	Yield **(%)**[a]	Entry	Additive	Yield **(%)**[a]
1	 **4b**	28	7	 **4h**	71
2	 **4c**	30	8	 **4i**	65
3	 **4d**	29	9	 **4j**	65
4	 **4e**	37	10	**4a**	**90**
5	 **4f**	34	11	 **4k**	68
6	 **4g**	0	12	No additive	49

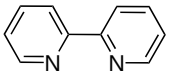
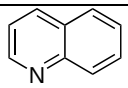
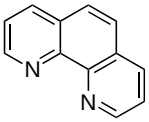
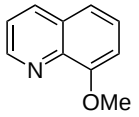
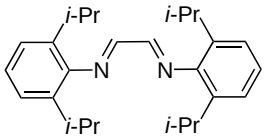
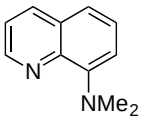
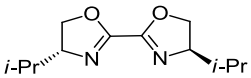
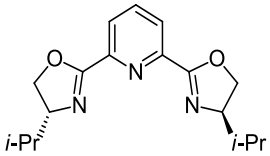
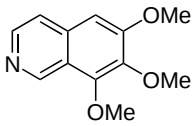
[a]Yield determined by integration of a gas chromatogram and comparison against undecane as a calibrated internal standard.

A similar trend was observed for the cobalt-catalyzed cross-coupling of electron-rich 2-chloro-5-(dimethylamino)pyridine (**1j**) with phenylmagnesium chloride (**2a**, Table 3). The use of 2,2'-bipyridine (**4c**), 1,10-phenanthroline (**4d**), the bis-imine **4e**, the bis-oxazoline **4f** or Pybox **4g** as additive significantly decelerated the cross-coupling, leading to conversions up to 13% only (entries 1-5). Contrary to the cross-coupling of 2-chloropyridine **1b**, the use of pyridine **4b** as ligand showed a positive effect on the reaction of the pyridine **1j** with the organomagnesium reagent **2a** (entry 6). Whereas all the quinolines **4h**, **4i** and **4j** and isoquinoline **4k** showed an improvement in the desired product formation (27-54%, entries 7-9 and 11), only isoquinoline (**4a**) appeared to largely increase the yield of this reaction. Indeed, 80% of the pyridine **3j** was formed under these reaction conditions (entry 10).

Table 3: Screening of various additives for the Co-catalyzed cross-coupling reaction of 2-chloro-5-(dimethylamino)pyridine (1j) with PhMgCl (2a).



1j **3j**

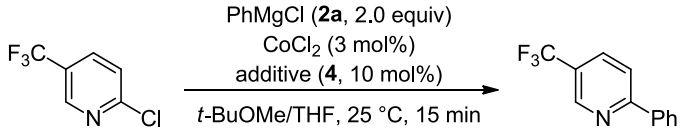
Entry	Additive	Yield **(%)**[a]	Entry	Additive	Yield **(%)**[a]
1	 **4c**	9	7	 **4h**	54
2	 **4d**	12	8	 **4i**	32
3	 **4e**	13	9	 **4j**	27
4	 **4f**	10	10	**4a**	**80**
5	 **4g**	1	11	 **4k**	40
6	 **4b**	41	12	No additive	22

[a]Yield determined by integration of a gas chromatogram and comparison against undecane as a calibrated internal standard.

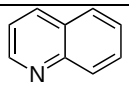
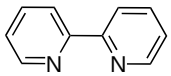
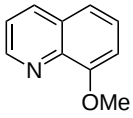
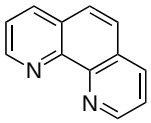
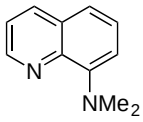
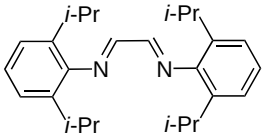
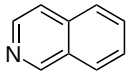
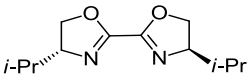
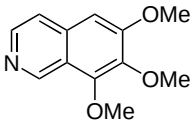
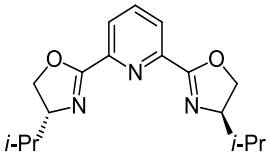
Remarkably, the cross-coupling of 2-chloro-5-(trifluoromethyl)pyridine (**1k**) with phenylmagnesium chloride (**2a**) in the presence of 3 mol% $CoCl_2$ showed a very different trend (Table 4). Except of the bis-oxazoline compound **4f** (entry 5), all tested additives showed either no effect or a positive one on the studied reaction, compared to the corresponding cross-coupling in absence of ligand (entry 12). Interestingly, 2,2'-bipyridine (**4c**) and 1,10-phenanthroline (**4d**) furnished the desired product in respectively 64 and 52% yield (entries 3 and 4). The substituted isoquinoline **4k** showed a similar effect on the cross-coupling reaction as isoquinoline (**4a**), and only 21% of the product **3k** was observed (entries 10 and 11). Quinoline (**4h**) and its electron-donating substituted derivatives had a positive influence on the cross-coupling reaction (entries 7-9). The use of 10 mol%

8-dimethylaminoquinoline **4j** showed an impressive rate-acceleration in this case, and 2-phenyl-5-(trifluoromethyl)pyridine (**3k**) was produced in 84% yield after 15 min at 25 °C (entry 9).

Table 4: Screening of various additives for the Co-catalyzed cross-coupling reaction of 2-chloro-5-(trifluoromethyl)pyridine (1k) with PhMgCl (2a).



1k **3k**

Entry	Additive	Yield **(%)**[a]	Entry	Additive	Yield **(%)**[a]
1	 **4b**	35	7	 **4h**	59
2	 **4c**	64	8	 **4i**	47
3	 **4d**	52	9	 **4j**	**84**[b]
4	 **4e**	25	10	 **4a**	22
5	 **4f**	14	11	 **4k**	21
6	 **4g**	19	12	No additive	16

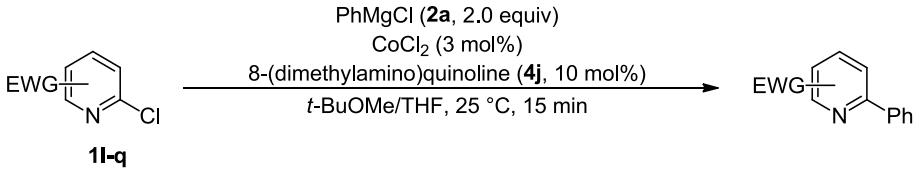
[a]Yield determined by integration of a gas chromatogram and comparison against undecane as a calibrated internal standard. [b] 79% isolated yield.

In conclusion, the comparison of the different ligand screenings showed that none of the tested additives presented a general rate-enhancement in the studied cobalt-catalyzed cross-coupling reactions. Indeed, in the case of 2-chloropyridine (**1b**, Table 2) and electron-rich 2-chloro-5-(dimethylamino)-pyridine (**1j**, Table 3), the best catalytic system proved to be 3 mol% cobalt(II)

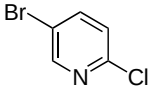
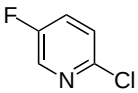
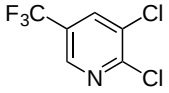
chloride in combination with 10 mol% isoquinoline (**4a**). In contrary, this ligand showed only a modest activity for the cross-coupling of electron-poor 2-chloro-5-(trifluoromethyl)pyridine (**1k**, Table 4) whereas electron-rich 8-dimethylaminoquinoline **4j** greatly contributed to a positive coordination with the cobalt center and led to a high yield in the product formation.

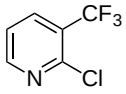
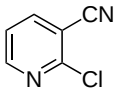
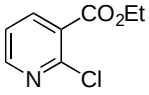
A study on the effect of 8-dimethylaminoquinoline **4j** on the cobalt-catalyzed cross-coupling of various 2-chloropyridines bearing at least one electron-withdrawing substituent was performed (Table 5). Subsequently, 3-bromo-2-chloropyridine (**1l**) was first coupled with phenylmagnesium chloride (**2a**) under the developed conditions (entry 1). Due to the selectivity lack of this reaction, only 11% yield in the desired 2-arylated pyridine was observed. Better result could be achieved with 2-chloro-3-fluoropyridine (**1m**), leading to 91% of the desired product. However, it is worth mentioning that this product was obtained in 72% yield without any ligand (entry 2). The cross-coupling of very electron-poor 2,3-dichloro-5-(trifluoromethyl)pyridine (**1n**) showed the same problem as 3-bromo-2-chloropyridine (**1l**): only 13% of the desired 2-arylated pyridine was produced by the unselective cross-coupling (entry 3). However, 2-chloro-3-(trifluoromethyl)pyridine (**1o**) was successfully cross-coupled in 83% yield under these reaction conditions. This shows a real improvement compared to the cross-coupling performed in the absence of ligand, which led only to 9% yield, or to the 13% yield obtained if isoquinoline (**4a**) was used as additive (entry 4). The cobalt-catalyzed cross-coupling reactions of both 2-chloronicotinonitrile (**1p**) and ethyl 2-chloronicotinate (**1q**) were unsuccessful due to the addition of the Grignard reagent respectively to the cyano and ester functions of the pyridine scaffold (entries 5 and 6).

Table 5: Co-catalyzed 8-dimethylaminoquinoline-assisted cross-coupling reaction of electron-poor pyridines.



1l-q

Entry	Starting material	Yield **(%)**[a]
1	 **1l**	11
2	 **1m**	91[b]
3	 **1n**	13

		
4	**1o**	83[c]
		
5	**1p**	0
		
6	**1q**	0

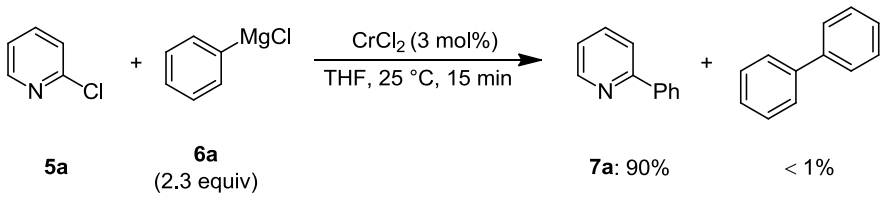
[a]Yield determined by integration of a gas chromatogram and comparison against undecane as a calibrated internal standard. [b]72% yield of the desired cross-coupling product was obtained if no ligand was added to the reaction mixture. [c]13% product was obtained if 10 mol% isoquinoline was added instead, and 9% yield was observed if no ligand was added to the reaction mixture.

2. CHROMIUM(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN CSP^2 CENTERS

In the search for alternative metal catalysts having a suitable low toxicity, the potential use of chromium salts have was studied.[117a-g, 86b, 117h-l] 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.[118]

2.1 PRELIMINARY EXPERIMENTS

Preliminary experiments showed that chromium-catalyzed cross-coupling reactions between Csp^2-centers proceed quite smoothly and led to significantly lower amounts of homo-coupling side-products compared to iron or cobalt.[119] Thus, the reaction of 2-chloropyridine (**5a**, 1.0 equiv) with PhMgCl (**6a**, 2.3 equiv) in THF in the presence of 3 % $CrCl_2$ (purity 99.99%) was complete within 15 min at 25 °C, affording the desired cross-coupling product **7a** in 90% yield (Scheme 60). GC-analysis of the crude reaction mixture indicated that less than 1% of homo-coupling product (biphenyl) was obtained. Performing the same reaction with 3% $FeBr_3$ or 3% $CoCl_2$ led to *ca.* 15% of homo-coupling product under optimized conditions.[115, 120] For all subsequent reactions, standard grade $CrCl_2$ (purity 97%) was used, since no difference was observed with $CrCl_2$ (purity 99.99%). Interestingly, performing the cross-coupling with 5% $MnCl_2$ led, under optimum conditions, to only 58% yield of **7a**[121] compared to 90% yield obtained with 3% $CrCl_2$. The performance of the cross-coupling using $CrCl_3$ instead of $CrCl_2$ was also possible, although a significant yield drop was observed (74% instead of 90 %), therefore $CrCl_2$ has been used for all further experiments.



Scheme 60: Chromium-catalyzed cross-coupling between 2-chloropyridine 5a and PhMgCl 6a.

A solvent screening (THF, *n*-hexane, toluene and *t*-BuOMe) indicated that THF was the optimal solvent. The optimization of the reaction stoichiometry showed that only a small excess of Grignard reagent (1.2 equiv) was required.

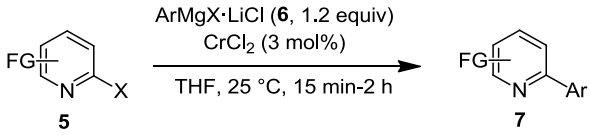
2.2 CROSS-COUPLING REACTIONS OF 2-HALOGENATED *N*-HETEROCYCLES WITH ARYL GRIGNARD REAGENTS

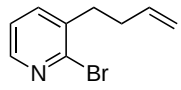
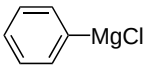
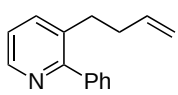
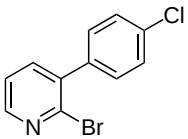
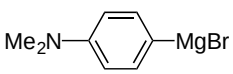
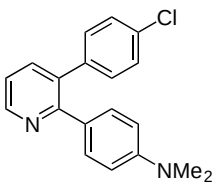
The reaction scope of this new cross-coupling proved to be quite broad. Thus, a range of *N*-heterocyclic chlorides and bromides could be readily used as electrophiles (Table 1). PhMgCl (**6a**) underwent a smooth cross-coupling with 2-bromo-3-(but-3-en-1-yl)pyridine (**5b**; 25 °C, 15 min), leading to the 2,3-disubstituted pyridine 7**b** in 95% yield (entry 1 of Table 6). Interestingly, no radical cyclization product was observed in this cross-coupling (similar iron and cobalt cross-couplings produced 20% of radical cyclization product).[120]

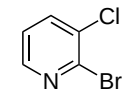
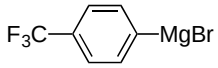
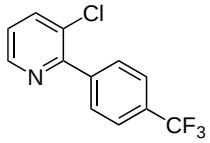
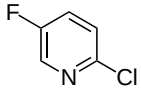
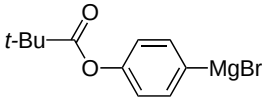
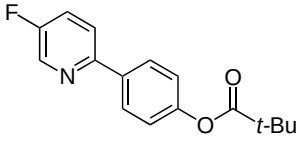
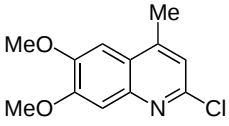
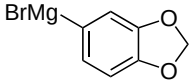
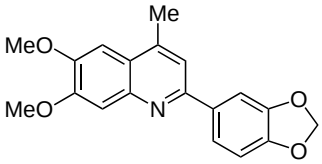
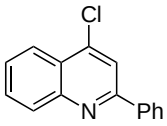
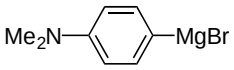
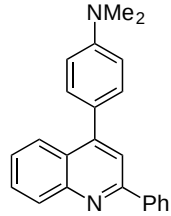
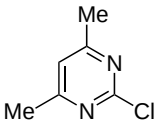
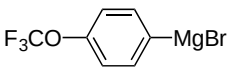
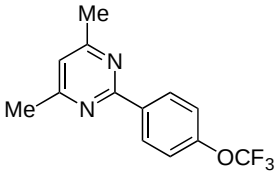
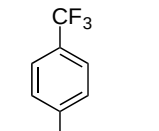
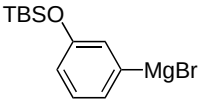
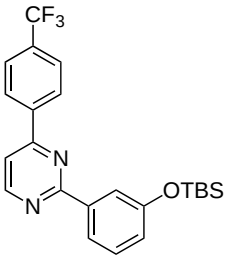
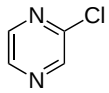
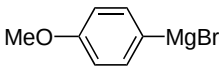
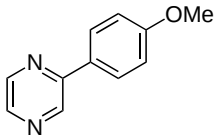
Both electron-rich and electron-poor Grignard reagents could be used for such cross-couplings.[122] Thus, the sterically hindered bromopyridine **5c** reacted with 4-*N*,*N*-dimethyl-aminophenylmagnesium bromide (**6b**) within 1.5 h at 25 °C, producing the 2,3-diarylated pyridine **7c** (80% yield; entry 2). Moreover, the electron-poor Grignard reagent **6c** reacted with 2-bromo-3-chloropyridine (**5d**) in 15 min at 25 °C, leading to the pyridine **7d** in 76% yield (entry 3). The similar cross-coupling performed with 3% of $FeBr_3$ gave only traces of product and significant amounts of homo-coupling. 2-Chloro-5-fluoropyridine (**5e**) also underwent the cross-coupling reaction with the sensitive ester-substituted Grignard reagent **6d** to give the pyridine **7e** in 66% yield (entry 4).

Further *N*-heterocyclic halides, such as the 2-chloroquinoline (**5f**) and the 4-chloroquinoline **5g**, reacted well with Grignard reagents **6e** and **6b**, affording the expected products **7f** and **7g** (74-78%; entries 5 and 6). In contrast, the corresponding iron-catalyzed cross-coupling with 4-chloroquinoline **5g** failed, indicating that this Cr(II)-catalyzed cross-coupling may have a broader reaction scope than the corresponding Fe- and Co-catalyzed cross-couplings.[115, 120] Halogenated diazenes, such as the 2-chloropyrimidines **5h-i** and the 2-chloropyrazine **5j**, rapidly reacted with the magnesium organometallics **6f-h** to provide the substituted diazenes **7h-j** in 71-85% yield (entries 7-9).

Table 6: Cr-catalyzed cross-coupling reactions between *N*-heterocyclic halides and arylmagnesium reagents at room-temperature.



Entry	Starting material	Grignard reagent	Product[a]
1	 **5b**	 **6a**	 **7b**: 95%; 15 min
			

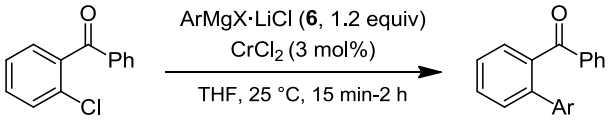
2	**5c**	**6b**	**7c**: 80%; 90 min
			
3	**5d**	**6c**	**7d**: 76%; 15 min
			
4	**5e**	**6d**	**7e**: 66%; 15 min
			
5	**5f**	**6e**	**7f**: 74%; 1 h
			
6	**5g**	**6b**	**7g**: 78%; 15 min
			
7	**5h**	**6f**	**7h**: 71%; 2 h
			
8	**5i**	**6g**	**7i**: 85%; 15 min
			
9	**5j**	**6h**	**7j**: 72%; 30 min
			

[a]Isolated yields of analytically pure products.

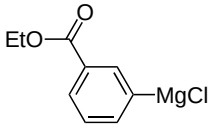
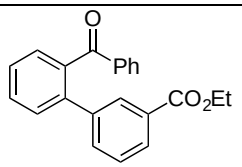
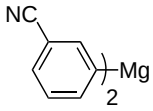
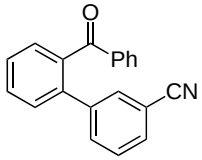
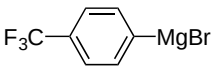
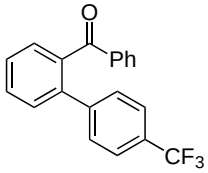
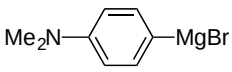
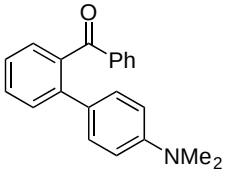
2.3 CROSS-COUPLING REACTIONS OF 2-HALOGENATED (HETERO)ARYL SUBSTITUTED KETONES WITH (HETERO)ARYL GRIGNARD REAGENTS

Remarkably, 2-halogenated aromatic ketones also underwent the chromium-catalyzed cross-coupling at room temperature within a time range of 15 min up to 2 h (Table 2).[123] Interestingly, the organomagnesium reagent did not attack the keto-function. Thus, 2-chlorobenzophenone (**8a**) reacted with a range of aryl- and heteroarylmagnesium reagents (**6b, 6c, 6i-k**) yielding the corresponding polyfunctional ketones **9a-e** (71-94%; entries 1-5 of Table 7).

Table 7: Cr-catalyzed cross-coupling reactions between 2-chlorobenzophenone (8a) and phenylmagnesium reagents.



8a **9**

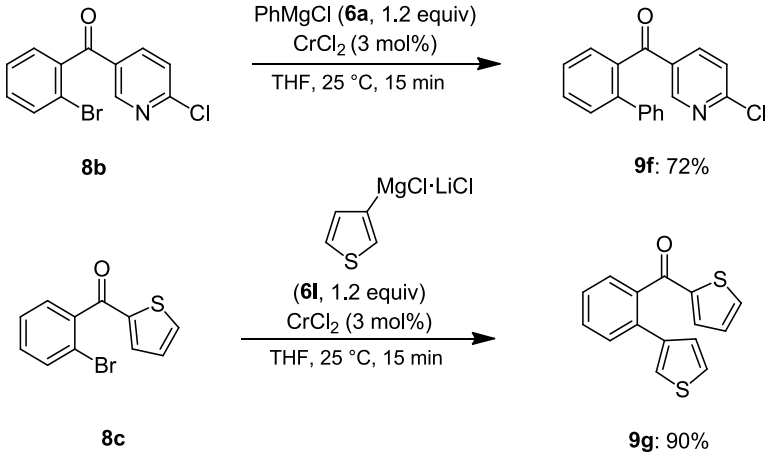
Entry	Grignard reagent	Product	Time	Yield[a]
				
1	**6i**	**9a**	15 min	79%
				
2[b]	**6j**	**9b**	2 h	71%
				
3	**6c**	**9c**	15 min	93%
				
4	**6b**	**9d**	15 min	94%

5	**6k**	**9e**	2 h	89%

[a] Isolated yields after purification by flash column chromatography. [b] 0.7 equiv of **2j** was used. [c] Reaction run at 50 °C for 2 h.

Interestingly, the (2-bromophenyl)(6-chloropyridin-3-yl)-methanone (**8b**) reacted with the Grignard reagent **6a** under complete regioselectivity (no chloride-substitution occurs) and furnishes the pyridylketone **9f** in 72% yield (Scheme 61).

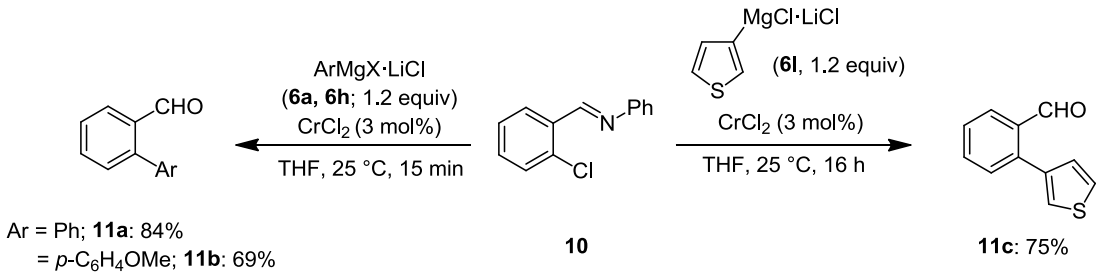
Heterocyclic ketones, such as **8c**, also cross-coupled well with 3-thienylmagnesium chloride **6l**, affording the new ketone **9g** in 90% yield (Scheme 61). These reactions showed a remarkable functional group tolerance, since ester, nitriles and ketones were compatible with this Cr-catalyzed cross-coupling methodology.[124]



Scheme 61: Cr-catalyzed cross-coupling reactions between heteroaryl-substituted ketones and Grignard reagents.

2.4 CROSS-COUPLINGS BETWEEN IMINE-PROTECTED ALDEHYDES AND ORGANOMAGNESIUM REAGENTS

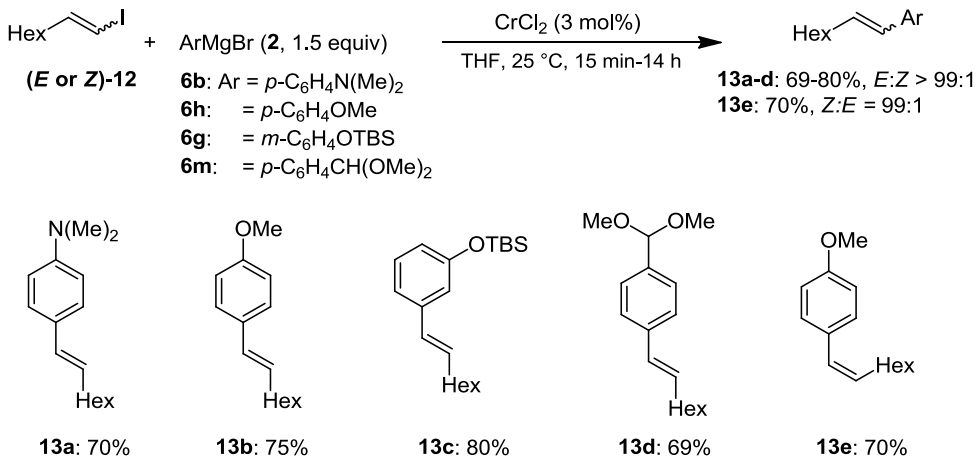
Interestingly, also the imine-protected 2-chlorobenzaldehyde **10** reacted readily under the $CrCl_2$-catalysis with various Grignard reagents (**6a, 6h, 6l**) at 25 °C. Acidic work-up provided the aldehydes **11a-c** in 69-84% yield (Scheme 62). The thiophene Grignard reagent **6l** required a considerably longer reaction time. After 16 h, **11c** was obtained in 75% yield. Thus, this cross-coupling constitutes a simple way for functionalizing aromatic aldehydes in *ortho*-position.



Scheme 62: Cr-catalyzed cross-coupling reactions between imine-protected aldehyde 10 and different Grignard reagents (6a, 6h, 6l).

2.5 CROSS-COUPLING REACTIONS OF ALKENYL IODIDES WITH ARYL GRIGNARD REAGENTS

Furthermore, alkenyl iodides, such as **(*E* or *Z*)-12**, underwent a stereoselective chromium-catalyzed arylation with a range of aryl Grignard reagents (**6b, 6g, 6h, 6m**), affording in all cases the functionalized styrenes **13a-e** in 69-80% yield (Scheme 63). For the alkenyl iodide **(*E*)-12**, the reactions were completed in 15 min at 25 °C (*E:Z* ratio > 99:1), whereas a reaction time of 14 h was required for the coupling of **(*Z*)-12** (*Z:E* ratio = 99:1). Since no loss of stereochemistry was observed, a single electron transfer mechanism implying radical intermediates could be excluded, confirming the results obtained with the radical clock substrate (**6b**, entry 1 of Table 6).



Scheme 63: Cr-catalyzed cross-coupling reactions between alkenyl iodide (*E* or *Z*)-12 and Grignard reagents 6.

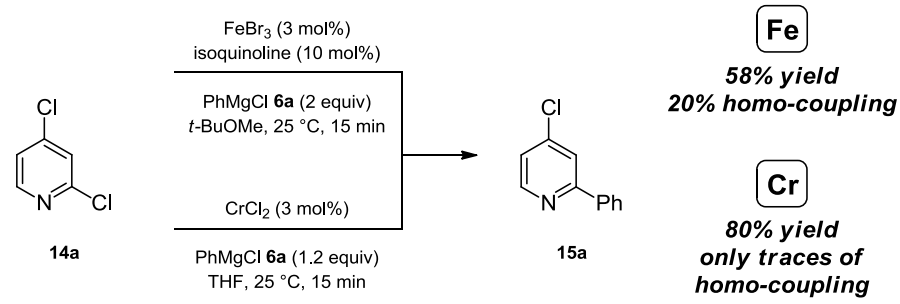
2.6 REGIOSELECTIVE CROSS-COUPLING REACTIONS OF DICHLORINATED HETEROAROMATICS

An effective strategy to obtain highly functionalized heteroaromatic structural motifs involves the use of polyhalogenated starting materials that can be subsequently functionalized. Challenges in product selectivity with such systems have been addressed by utilizing differentially halogenated rings.

Indeed, regioselective differentiation of a wide range of dichloropyridines, -quinolines, and -isoquinolines was studied in the context of biaryl coupling due to the prevalence of such motifs in drug discovery programs.

2.6.1 Regioselective Csp^2-Csp^2 cross-coupling reactions between dichlorinated pyridines and (hetero)aryl Grignard reagents

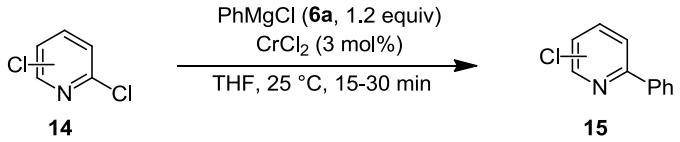
Initial work showed that the reaction of 2,4-dichloropyridine (**14a**) with PhMgCl (**6a**) *via* a previously optimized Fe-catalysis protocol[125, 114a] exclusively gave the 2-arylated product (**15a**) in 58% yield. In comparison, the chromium(II) chloride-catalyzed reaction using lower amount of **6a** (1.2 instead of 2 equiv) selectively furnished pyridine **15a** in even higher yield (80%; Scheme 64) with only trace amounts of the homocoupled product.[126]

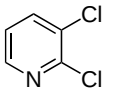
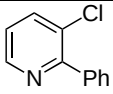
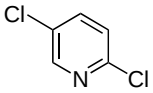
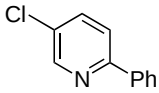
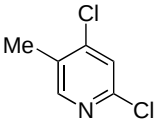
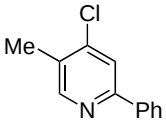
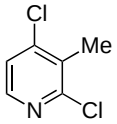
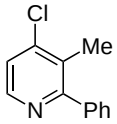
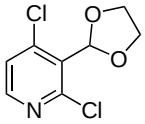
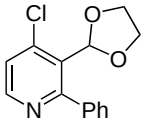
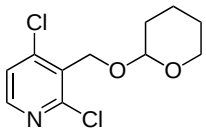
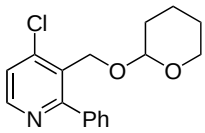


Scheme 64: Cross-coupling of 2,4-dichloropyridine (14a) with PhMgCl (6a): Fe *versus* Cr.

Evaluation of the scope of the regioselective chromium-catalyzed cross-coupling led to the arylation of a range of dichloro-*N*-heterocycles at room temperature (Table 8). Both 2,3-dichloropyridine (**14b**) and 2,5-dichloropyridine (**14c**) reacted with Grignard reagent **6a** within minutes to selectively form the 2-arylated products 15**b** (76% yield, entry 1) and **15c** (87% yield, entry 2) respectively. Methyl substitution on the pyridine ring also led to high levels of selectivity. Therefore, 2,4-dichloropyridines **14d**-**e** reacted rapidly with **6a** to afford phenylated products **15d**-**e** in high yields (85% for **15d** and 88% for **15e**, entries 3-4). The sterically more demanding and coordinating acetal-containing 2,4-dichloropyridines **14f**-**g** also reacted rapidly to furnish products **15f**-**g** in 67% and 76% yield, respectively (entries 5-6).

Table 8: Regioselective Csp^2-Csp^2 cross-coupling reactions between dichlorinated pyridines (14b-g) and PhMgCl.[a]



Entry	Grignard reagent	Product	Time (min)	Yield
				
1	**14b**	**15b**	15	76%
				
2	**14c**	**15c**	15	87%
				
3	**14d**	**15d**	15	85%
				
4	**14e**	**15e**	15	88%
				
5	**14f**	**15f**	30	67%
				
6	**14g**	**15g**	30	76%

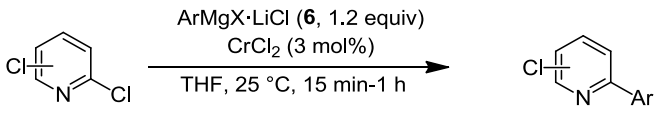
[a]Reaction conditions: PhMgCl (**6a**; 1.2 equiv), dichlorinated pyridine (1 equiv), $CrCl_2$ (3 mol %) in THF at 25 °C.

To further evaluate the utility of the regioselective chromium(II)-catalyzed cross-coupling reaction, various aromatic Grignard reagents were employed (Table 9).[127] Electron-rich Grignard reagents such as 3-(methoxyphenyl) magnesium bromide **6n** and methylenedioxyarylmagnesium bromide **6c** reacted with dihalogenated pyridines **14c** and **14a** resulting in the formation of the coupled products **15h-i** in 71-77% yield (entries 1 and 2). Notably, complete control in site-selectivity was obtained in these cross-coupling reactions. Heteroaromatic nucleophile 5-magnesiated indole **6o** reacted with 2,3-dichloro-5-(trifluoromethyl)pyridine (**14h**) within 1 h to give the 2-arylated coupling product **15j** in 56% yield (entry 3). Silyl-protected 3-hydroxyphenyl magnesium bromide **6g** and acetal-substituted arylmagnesium derivative **6p** participated in the $CrCl_2$-catalyzed cross-coupling reaction with dichlorinated pyridines **14b**, **14h** and **14g** selectively on C2 affording the desired products in 66-82% isolated yield (entries 4-6).

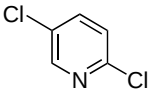
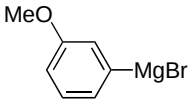
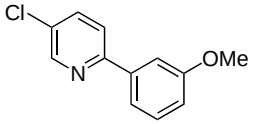
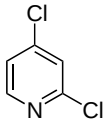
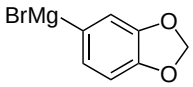
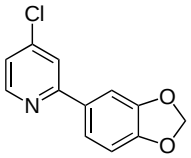
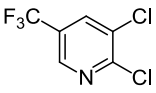
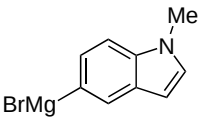
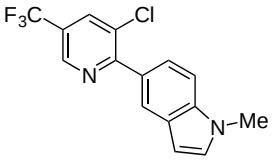
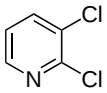
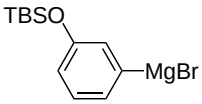
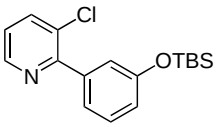
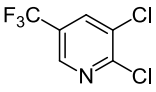
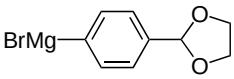
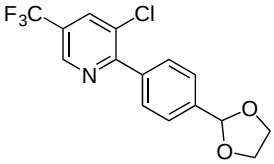
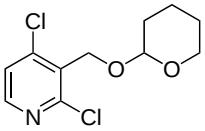
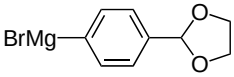
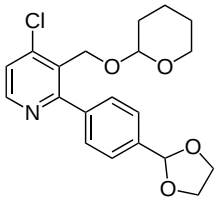
Electron-poor Grignard reagent 4-(trifluoromethyl)phenyl magnesium bromide (**6c**) was particularly effective in the Cr-catalyzed cross-coupling reaction. When this substrate was treated with pyridine **14a** in the presence of 3 mol% $CrCl_2$, the formation of heterocycle **15n** occurred in 92% yield (entry 7). Chloro-substituted Grignard reagent **6q** coupled with trifluoromethylated 2,3-dichloropyridine

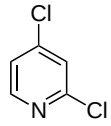
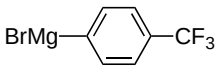
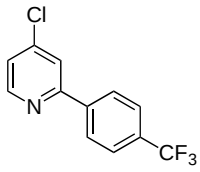
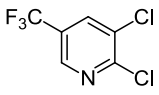
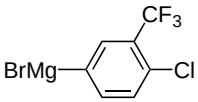
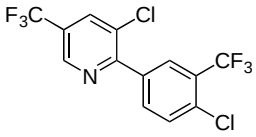
14h and furnished the desired product **15o** in 66% yield (entry 8).

Table 9: Regioselective Csp^2-Csp^2 cross-coupling reactions between dichlorinated pyridines and various Grignard reagents.[a]



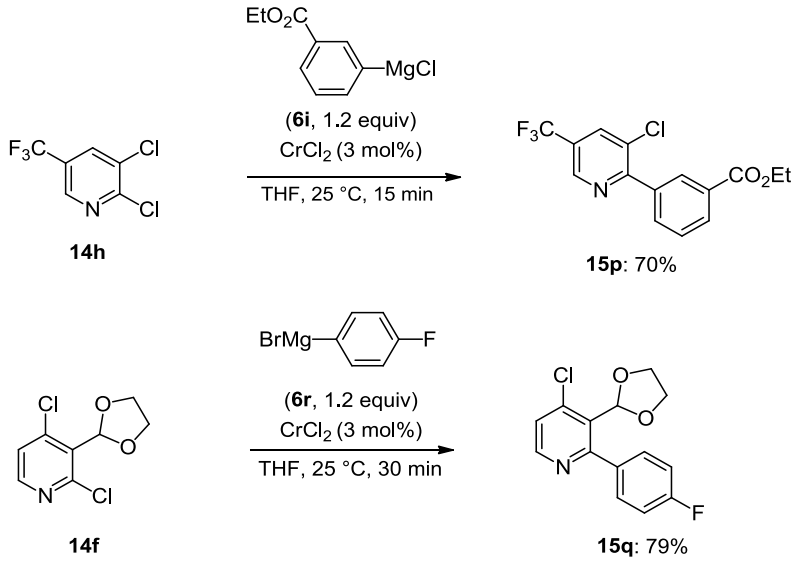
14 **15**

Entry	Substrate	Grignard reagent	Product
1	 **14c**	 **6n**	 **15h**: 71%; 30 min
2	 **14a**	 **6c**	 **15i**: 77%; 15 min
3[b]	 **14h**	 **6o**	 **15j**: 56%; 1 h
4	 **14b**	 **6g**	 **15k**: 82%; 15 min
5	 **14h**	 **6p**	 **15l**: 71%; 15 min
6	 **14g**	 **6p**	 **15m**: 66%; 30 min

7	 **14a**	 **6c**	 **15n**: 92%; 30 min
8	 **14h**	 **6q**	 **15o**: 66%; 30 min

[a]Reaction conditions: Grignard reagent (1.2 equiv), dichlorinated heterocycle of type **14** (1 equiv), $CrCl_2$ (3 mol %) in THF at room temperature. [b]The reaction was performed at 50 °C.

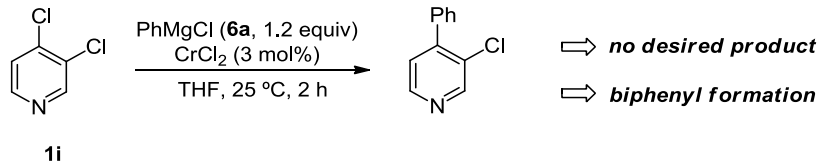
The ability to conduct these experiments at room temperature is a significant advantage. Thermally sensitive Grignard reagents, such as those containing an ester (**6i**) or 4-fluorophenylmagnesium bromide **6r**, underwent rapid cross-coupling reactions leading to trisubstituted pyridines **15p-q** in 70-79% yield (Scheme 65). It turned out that **14h** was particularly reactive in Cr-catalyzed arylations with electron-poor aromatic Grignard reagents, such as **6i**, probably due to the electron deficiency of this starting material. Ester **6i** has previously been used in Pd-catalyzed cross-coupling reactions on monohalogenated systems. Therefore, this method proves to be very practical to access heterobiaryls that are commonly found in bioactive pharmaceuticals.



Scheme 65: Regioselective Cr(II)-catalyzed cross-coupling reactions of pyridines 14h and 14f with thermally sensitive Grignard reagents 6i and 6r.

To rationalize the site-selectivity in this Cr-catalyzed cross-coupling methodology, a mechanism where the nitrogen of the pyridine ring directs the attack of the low-valent phenyl-chromium organometallic onto the dihaloaromatic was postulated.[128] To support the notion of a directed delivery of the aryl nucleophile, treatment of 3,4-dichloropyridine **1i** (where a ring nitrogen is not

proximal to the C–Cl bond) with Grignard reagent **6a** in the presence of 3 mol% chromium chloride led to the exclusive formation of biphenyl, and no cross-coupled product was observed (Scheme 66). The formation of a chromium-aryl species is proposed in analogy to recent studies on the formation of an iron-aryl species that can oxidatively add into 2-chloropyridine.[129] Furthermore, high selectivity for aryl incorporation proximal to the nitrogen with various 2,4- and 2,5-dichloropyridines supports the hypothesis of an *N*–directed addition.

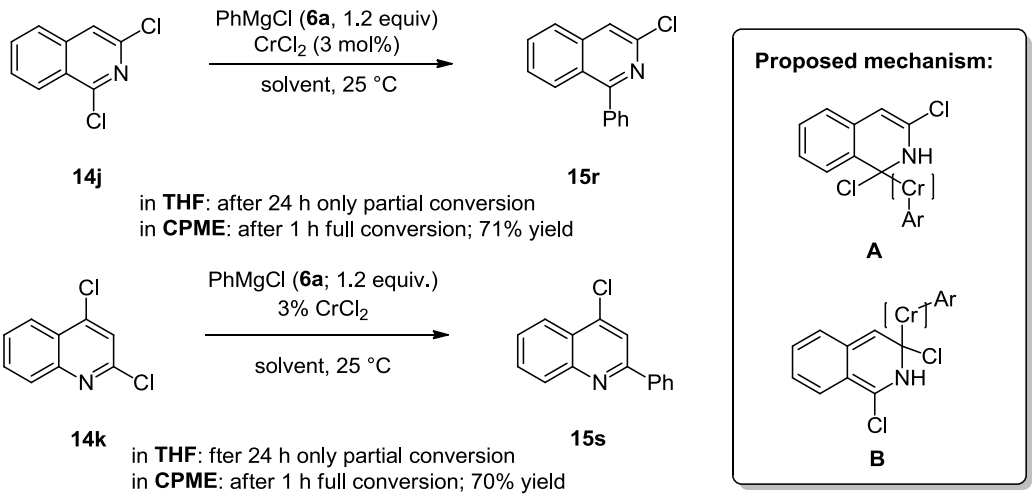


1i

Scheme 66: Evidence for N-directed site selectivity.

2.6.2 Use of cyclopentyl methyl ether as solvent for the Cr(II)-catalyzed cross-coupling reactions of chloroquinolines and -isoquinolines

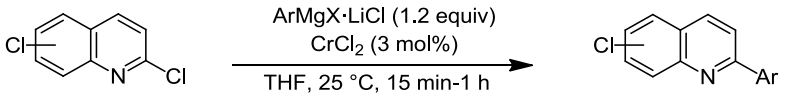
Chromium-catalyzed biaryl formation on 1,3-dichloroisoquinoline **14j** and 2,4-dichloroquinoline **14k** proved to be very challenging. Although selective, the optimal conditions illustrated in
Table 9 resulted in attenuated reactivity. Evaluation of coordinating and non-coordinating solvents with these fused aromatics revealed the superiority of CPME (cyclopentyl methyl ether) in the $CrCl_2$-catalyzed cross-coupling reaction. The desired coupling product **15r** was obtained in 71% yield after only 1 h reaction time at room temperature, using 3 mol% of $CrCl_2$ in CPME as solvent. The phenylation regioselectivity of **14j** at C1 can be explained by formation of the more stable intermediate **A** that retains aromaticity. The competing arylation at C3 does not occur because of loss of aromaticity in intermediate **B**. Analogously, the regioselective coupling between quinoline **14k** and Grignard reagent **6a** afforded the desired 2-arylated quinoline **15s** in 70% yield using CPME (Scheme 67).

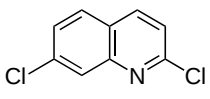
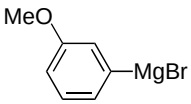
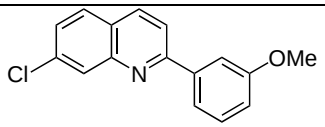
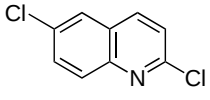
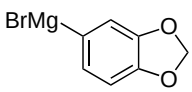
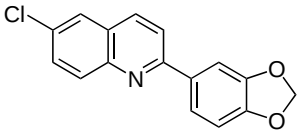
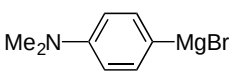
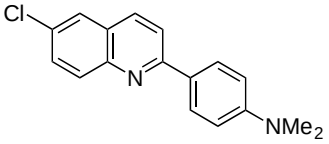


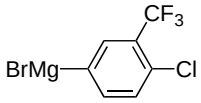
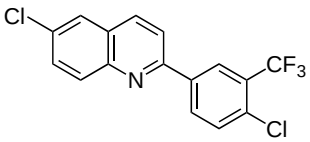
Scheme 67: Cr(II)-catalyzed cross-coupling reactions using CPME as solvent and mechanistic aspects.

Regioselective cross-coupling reactions of other chlorinated quinolines could also be improved by the use of CPME as solvent. 2,7-Dichloroquinoline **14l** reacted well with the electron-rich Grignard **6n**, leading to the 2-substituted desired quinoline **15t** in 72% yield after 2 h (Table 10, entry 1). Both electron-rich and -poor Grignard reagents (**6e**, **6b** and **6q**) could be successfully coupled with 2,6-dichloro-quinoline **14m** under chromium(II)-catalysis in 71-87% yield (entries 2-4).

Table 10: Regioselective Csp^2-Csp^2 cross-coupling reactions between dichlorinated quinolines and various aryl Grignard reagents.[a]



Entry	Substrate	Grignard reagent	Product
1	 **14l**	 **6n**	 **15t**: 72%; 2 h
2	 **14m**	 **6e**	 **15u**: 82%; 1 h
3[b]	**14m**	 **6b**	 **15v**: 71%; 3 h

4	**14m**		**6q**		**15w**: 87%; 1 h

[a]Reaction conditions: Grignard reagent (1.2 equiv), dichlorinated heterocycle of type **14** (1 equiv), $CrCl_2$ (3 mol %) in CPME at room temperature. [b]The reaction was performed in THF.

2.7 REMOVAL OF THE CHROMIUM CATALYST

After demonstrating the wide substrate scope, the removal of the chromium salt needed to be investigated. Despite the low toxicity of chromium(III) picolinate,[37q] the reduction of the overall chromium content from the reaction mixture prior to chromatography was considered. Employing 2,4-dichloropyridine **14a** as a prototype, treatment with PhMgCl **6a** in the presence of 3 mol% $CrCl_2$, quenching unreacted Grignard reagent with an aqueous solution of ammonium chloride, separation and treatment of the organic layer using various solid supports was evaluated. Chromium concentration of the untreated organic layer after aqueous work-up was 34 ppm. As illustrated in Figure 4, several scavengers resulted in high recovery of arylated pyridine **15a** with remarkably low levels of chromium thereby enhancing the utility of this methodology for pharmaceutical applications where low levels of concerning metals are crucial.

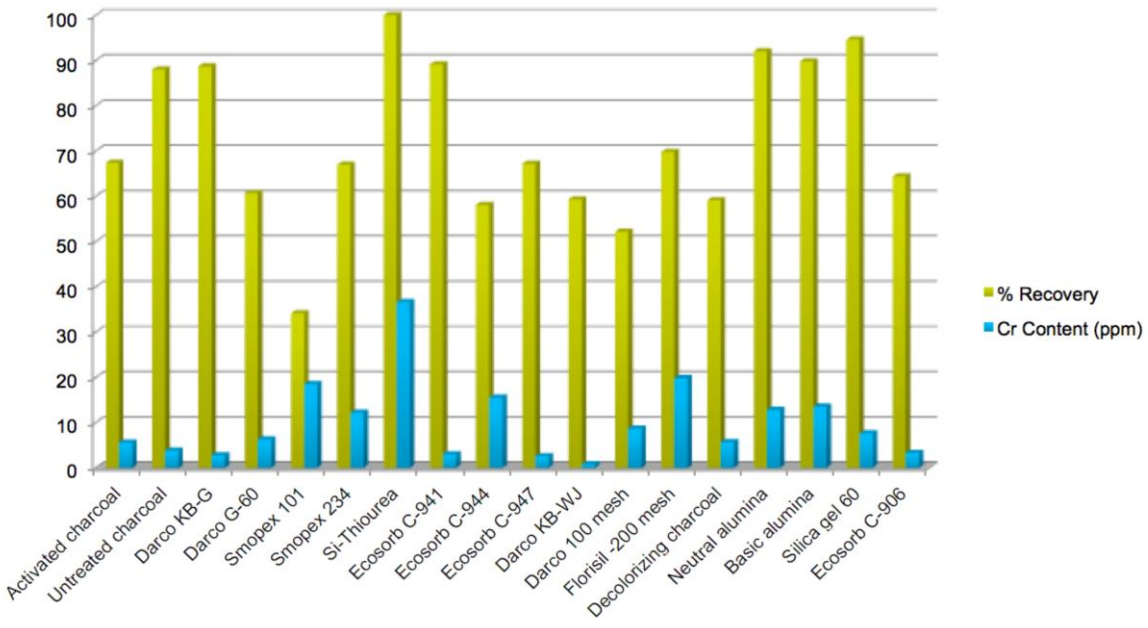


Figure 4: Scavenger treatment to evaluate recovery and chromium levels prior to chromatography.

3. CHROMIUM(II)-CATALYZED AMINATION OF *N*-HETEROCYCLIC CHLORIDES WITH MAGNESIUM AMIDES

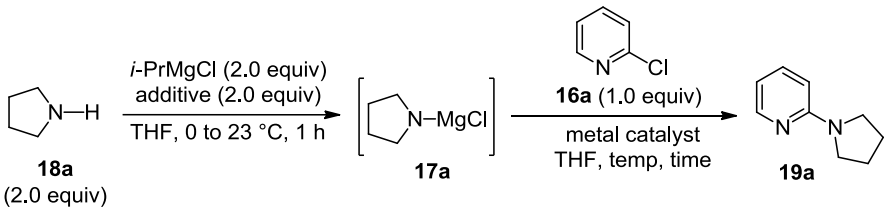
With the objective of replacing cost-intensive palladium and sensitive phosphine ligands generally used in the Buchwald-Hartwig amination methodoly, economic, low toxic and readily available transition metal catalysts for amination reactions were considered.
Therefore, a chromium(II)-catalyzed amination of *N*-heterocyclic chlorides with magnesium amides was studied, affording a range of aminated pyridines, quinolines and quinoxalines.

3.1 OPTIMIZATION OF THE REACTION CONDITIONS

In preliminary experiments, the transition metal-catalyzed amination of 2-chloropyridine (**16a**) with magnesium chloride pyrrolidin-1-ide (**17a**) was investigated. **17a** was prepared by deprotonation of pyrrolidine (**18**) with *i*-PrMgCl in THF at 0 °C and subsequently warmed up to 23 °C over 1 h (Table 11). The resulting magnesium amide showed a high thermic stability and a good solubility under the reaction conditions.
In absence of any catalyst, only 13% of the aminated product (**19a**) was observed at 23 °C after 20 h reaction time (entry 1). However, when the Grignard reagent was prepared with an equimolar amount of lithium chloride as additive (by using *i*-PrMgCl·LiCl),[127a, 130] the conversion was increased and 27% of the pyridine **19a** was detected by calibrated GC analysis (entry 2).
The use of 3% $FeBr_3$ or 3% $CoCl_2$ under the same conditions did not improve the amination (14–12%, entries 3 and 4). Interestingly, in the presence of 3% $CrCl_2$, **19a** was obtained in 72% yield, which could be improved to 77% by using 10% of catalyst (entries 5 and 6). Performing the latter experiment without lithium chloride led to the formation of noticeably less product (64%, entry 7). In an attempt to further accelerate the reaction, the amination was then performed at 50 °C with 10 mol% of chromium(II) chloride. In the presence of 2.0 equivalents of LiCl, the aminated product **19a** was isolated in 95% yield, whereas **19a** was obtained in only 60% yield without additive (entries 8 and 9). Other chromium catalysts [$CrCp_2$,[131] $Cr(acac)_3$, $CrBr_2$[132]] led to somewhat lower yields (45–81%, entries 10–12). Indeed, the air-stable and cheap $Cr(acac)_3$ could be used in these aminations but led to either similar or, in most cases, to lower yields and/or longer reaction times. The mechanism of this amination method may be a result of the Lewis-acidity of Cr(II) as well as the higher ligand rate exchange of Cr(II)-complexes compared to Cr(III)-salts.

Performing this reaction at 50 °C for three hours without catalyst in the presence of LiCl produced the aminated pyridine **19a** in 43% yield and, without LiCl, in 27% yield, confirming the importance of this salt (entries 13 and 14). However, it is worth mentioning that a longer reaction time (20 h at 50 °C) also led to full conversion. Replacing 2-chloropyridine with the corresponding 2-bromopyridine led to slower substitution rates and incomplete conversion.

Table 11: Optimization of the reaction conditions.[a]



Entry	Catalyst	Amount (mol%)	Additive	Temp. (°C)	Time (h)	Yield (%)[b]
1	-	-	-	23	20	13
2	-	-	LiCl	23	20	27
3	$CoCl_2$	3	LiCl	23	20	14
4	$FeBr_3$	3	LiCl	23	20	12
5	$CrCl_2$	3	LiCl	23	24	72
6	$CrCl_2$	10	LiCl	23	20	77
7	$CrCl_2$	10	-	23	20	64
8	**$CrCl_2$**	**10**	**LiCl**	**50**	**3**	**95**
9	$CrCl_2$	10	-	50	3	60
10	$CrCp_2$	10	LiCl	50	3	45
11	$Cr(acac)_3$	10	LiCl	50	3	81
12	$CrBr_2$	10	LiCl	50	3	70
13	-	-	LiCl	50	3	43
14	-	-	-	50	3	27

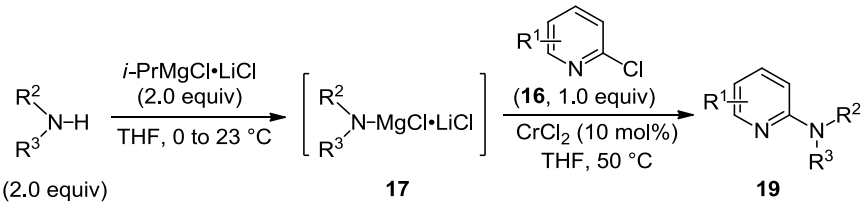
[a]Reaction conditions: deprotonation of pyrrolidine **18** (2.0 mmol) with *i*-PrMgCl (with or without LiCl; 2.0 mmol) in THF at 0 to 23 °C in 1 h. Amination of 2-chloropyridine (**16a**; 1.0 mmol) with the prepared magnesium amide **17a** in THF at 23 or 50 °C with or without $CrCl_2$. [b]Yield determined by integration of a gas chromatogram and comparison against undecane as a calibrated internal standard.

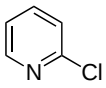
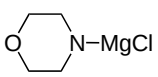
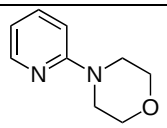
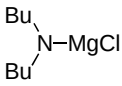
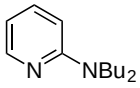
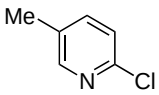
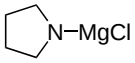
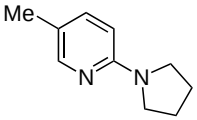
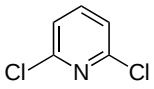
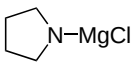
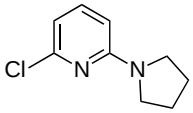
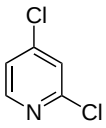
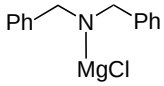
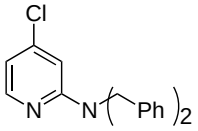
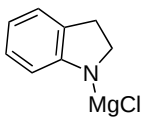
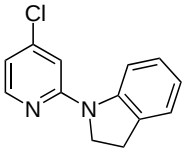
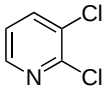
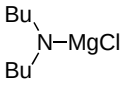
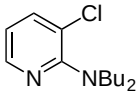
3.2 CHROMIUM-CATALYZED AMINATION OF SUBSTITUTED 2-CHLOROPYRIDINES

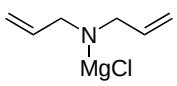
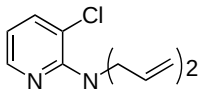
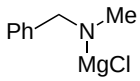
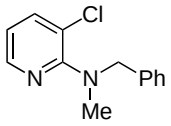
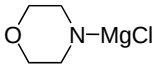
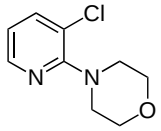
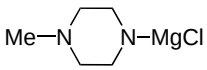
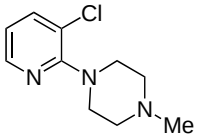
The reaction scope of this amination was studied by using various magnesium amides (Table 12). First, 2-chloropyridine (**16a**) underwent an amination with magnesium chloride morpholin-4-ide (**17b**) or magnesium chloride dibutylamide (**17c**), respectively leading to the formation of the aminated pyridines **19b** and **19c** in 75% yield after 5-12 h reaction time (entries 1-2). Substituted pyridines such as 2-chloro-5-methylpyridine (**16b**) usually reluctantly undergo amination with magnesium chloride pyrrolidin-1-ide (**17a**) and full conversion was not observed even after 3 d at 50 °C without catalyst. In the presence of 10% $CrCl_2$, the aminated product **19d** was isolated in 96% after 24 h (entry 3). A selective monoamination of 2,6-dichloropyridine (**16c**) with magnesium chloride pyrrolidin-1-ide (**17a**) was selectively achieved after 7 h to give the pyridine **19e** in 81% yield (entry 4). 2,4-Dichloropyridine (**16d**) showed complete regioselectivity for the C2 position of the pyridine ring. Performing this amination reaction either with magnesium chloride dibenzylamide (**17d**) or with magnesium chloride indolin-1-ide (**17e**) led to the corresponding aminated pyridines **19f** and **19g** in 50-54% yield after 3 h (entries 5-6), showing the limits of this chromium-catalysis.

In the same way, 2,3-dichloropyridine (**16e**) underwent the desired selective amination with a range of aliphatic (**17c**), allylic (**17f**), benzylic (**17g**) and saturated heterocyclic (**17b**, **17h**) magnesium amides to provide the aminated pyridines **19h-l** in 71-86% yield (entries 7-11). In any case, no diamination product was observed in the aminations involving **16c**, **16d**, and **16e**.

Table 12: Cr(II)-catalyzed amination of the 2-chloropyridines (16a-i) with magnesium amides (17a-k).[a]



Entry	Substrate	Magnesium amide[b]	Product
			
1	**16a**	**17b**	**19b**: 75%; 12 h
			
2	**16a**	**17c**	**19c**: 75%; 5 h
			
3	**16b**	**17a**	**19d**: 96%; 24 h
			
4	**16c**	**17a**	**19e**: 81%; 7 h
			
5	**16d**	**17d**	**19f**: 50%; 3 h
			
6	**16d**	**17e**	**19g**: 54%; 3 h
			
7	**16e**	**17c**	**19h**: 71%; 5 h

			
8	**16e**	**17f**	**19i**: 82%; 5 h
			
9	**16e**	**17g**	**19j**: 83%; 3 h
			
10	**16e**	**17b**	**19k**: 86%; 4 h
			
11	**16e**	**17h**	**19l**: 71%; 5 h

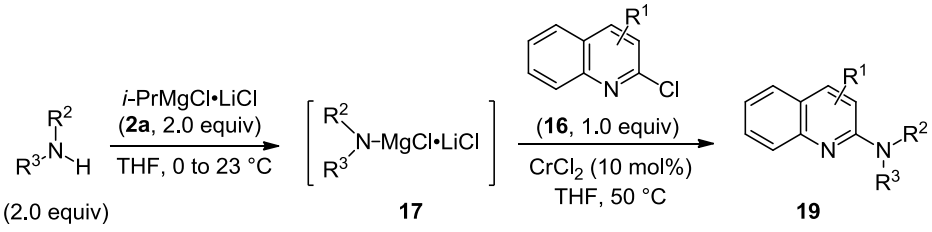
[a]Reaction conditions: $CrCl_2$ (10 mol%), chlorinated heterocycle (**16a-e**, 1.0 equiv), magnesium amide (**2a-h**, 2.0 equiv) in THF at 50 °C. [b]LiCl was omitted for clarity.

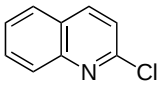
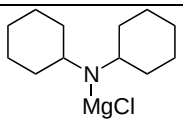
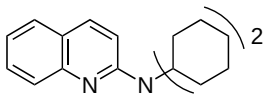
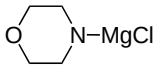
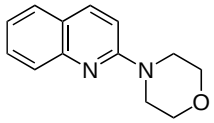
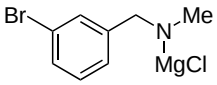
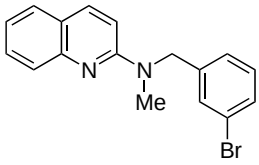
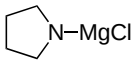
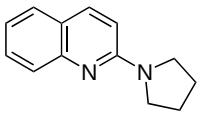
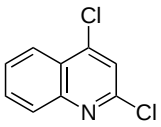
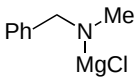
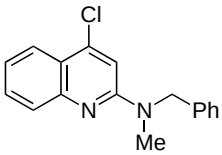
3.3 CHROMIUM-CATALYZED AMINATION OF SUBSTITUTED 2-CHLOROQUINOLINES, 1-CHLOROISOQUINOLINE AND 2,3-DICHLOROQUINOXALINE

The amination of various other 2-chlorinated *N*-heterocycles was also examined. 2-Chloroquinoline (**16f**) was aminated with diverse saturated cyclic (**17i**) or heterocyclic (**17b**) magnesium amides, as well as with the magnesiated substituted benzylic amide **17j**, to afford the desired *N*-substituted quinolines **19m-o** in 85-95% yield after 6-23 h (Table 13, entries 1-3). Also, the use of chromium(II) chloride dramatically increased the reaction rate and efficiency of 2-chloroquinoline (**16f**) with magnesium chloride pyrrolidin-1-ide (**17a**). Without catalyst, only 65% of the aminated quinoline **19p** was obtained after 2 d whereas 95% of **19p** was isolated after 10 h in the presence of 10% $CrCl_2$ (entry 4).

Regioselective amination of 2,4-dichloroquinoline (**16g**) with the benzylic magnesium amide **17g** led selectively to the aminated heterocycle **19q** (50 °C, 5 h) in 54% yield (entry 5).

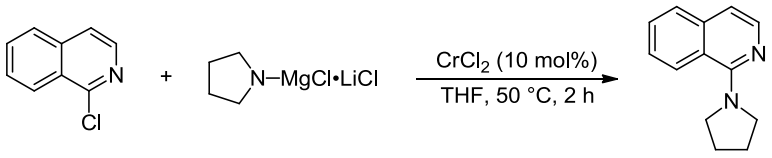
Table 13: Cr(II)-catalyzed amination of the 2-chloroquinoline 16f-g with magnesium amides 17.[a]



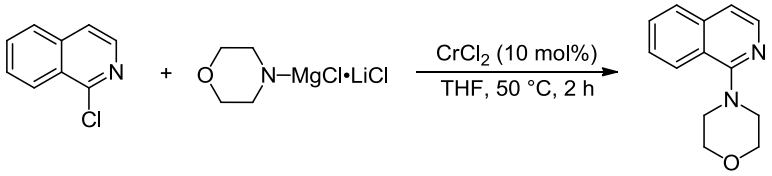
Entry	Substrate	Magnesium amide[b]	Product
			
1	**16f**	**17i**	**19m**: 85%; 23 h
			
2	**16f**	**17b**	**19n**: 85%; 8 h
			
3	**16f**	**17j**	**19o**: 95%; 6 h
			
4	**16f**	**17a**	**19p**: 90%; 10 h
			
5	**16g**	**17g**	**19q**: 54%; 5h

[a]Reaction conditions: $CrCl_2$ (10 mol%), chlorinated heterocycle (**16**, 1.0 equiv), magnesium amide (**17**, 2.0 equiv) in THF at 50 °C. [b]LiCl was omitted for clarity.

The amination on the C1 position of 1-chloroisoquinoline (**16h**) could be realized efficiently by using the saturated heterocyclic magnesium amides **17a** and **17b**, which led to the isoquinolines **19r** and **19s** after 2 h at 50 °C in 89-93% yield (Scheme 68).



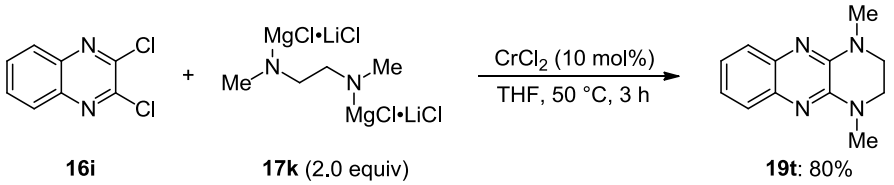
16h **17a** (2.0 equiv) **19r**: 93%



16h **17b** (2.0 equiv) **19s**: 89%

Scheme 68: Cr(II)-catalyzed amination of 1-chloroisoquinoline 16h with magnesium amides (17a-b).[a]

Noteworthy, the annelation of the quinoxaline scaffold was achieved by diamination of 2,3-dichloroquinoxaline (**16i**) with the bis-magnesium amide **17k** leading to the hydropyrazino[2,3-*b*]quinoxaline **19t** in 80% (Scheme 69).



16i **17k** (2.0 equiv) **19t**: 80%

Scheme 69: $CrCl_2$-catalyzed diamination of 2,3-dichloroquinoxaline (16i).

4. SYNTHESIS OF PYRIDO[3,2-*F*][1,7]NAPHTHYRIDINE AND RELATED HETEROCYCLES

Six-membered *N*-heterocyclic molecules have found numerous applications due to their biological or physical properties. Annelated six-membered *N*-heteroaromatics bearing one nitrogen atom per ring such as naphthyridines **20**, triazaanthracenes **21** and triazaphenanthrenes **22** are much less studied. In particular, the applications of pyridonaphthyridines – azaphenanthrenes resulting from the fusion of three pyridines – could be of high interest due to their favorable geometry for coordination (Figure 5).

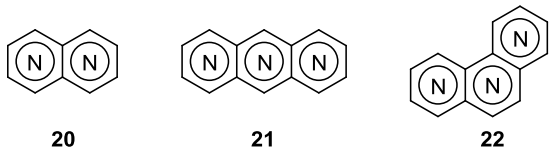


Figure 5: Fused six-membered *N*-heteroaromatics.

In total, among the 16 possible regioisomers, the syntheses of only 6 different pyridonaphthyridines have been reported so far. The methodologies developed for their synthesis appear to be inefficient, inconvenient and not very general. Except of the method described by Rault *et al*.,[109] none of them are applicable in medicinal chemistry.

A general synthesis of new pyrido[3,2-*f*][1,7]naphthyridine **23** using Negishi cross-coupling with polyfunctional zinc intermediates, as well as the study of their reactivity was envisioned (Figure 6).

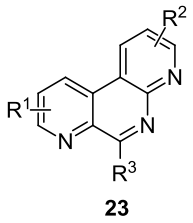
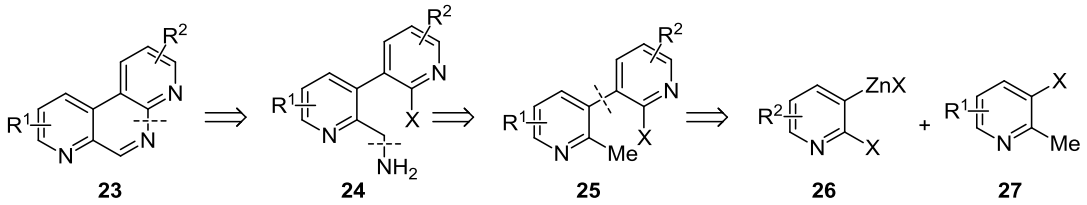


Figure 6: New pyrido[3,2-*f*][1,7]naphthyridine 23.

4.1 RETROSYNTHETIC ANALYSIS

The retrosynthesis proposed involved as final ring closure an intramolecular *N*-arylation of bis-pyridine **24** possibly catalyzed by transition metals.[18a, 53a, 16g, 14c] This aminopyridine **24** could be readily prepared from the bis-pyridine **25** by selective halogenation and amination of the methyl substituent. The polyfunctional bis-pyridine **25** would be finally synthesized *via* a Negishi cross-

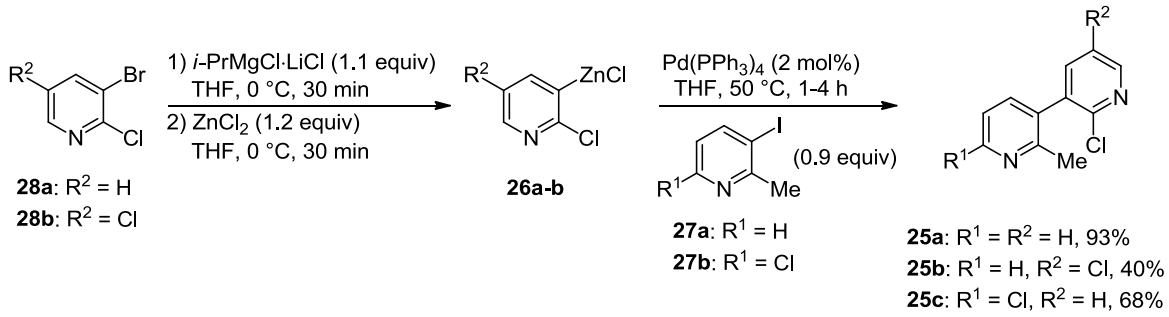
coupling of the 3-zincated 2-chloropyridine **26** with the 3-halogenated 2-picoline **27** (Scheme 70).



Scheme 70: Retrosynthetic analysis.

4.2 MULTI-STEP SYNTHESIS OF PYRIDO[3,2-*F*][1,7]NAPHTHYRIDINE AND DERIVATIVES

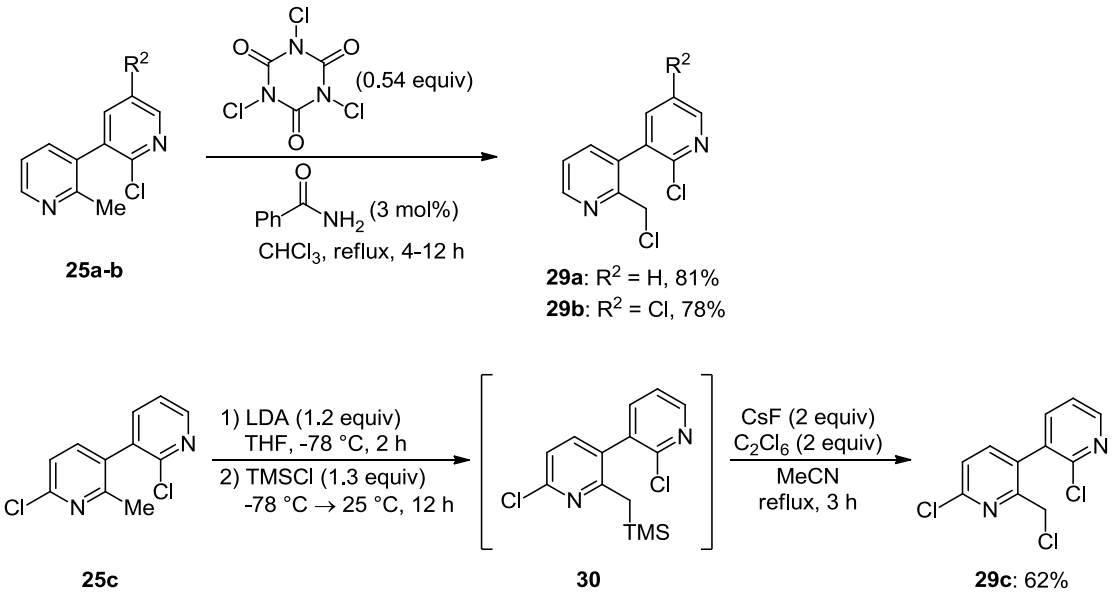
First, the polyfunctional zinc reagents of type **26** required from the retrosynthetic analysis were prepared from the corresponding 3-bromo-2-chloropyridines **28a-b** by a bromine/magnesium exchange using *i*-PrMgCl·LiCl followed by transmetallation with $ZnCl_2$. These pyridylzinc reagents underwent a Negishi cross-coupling with the iodopicolines **27a-b** in THF in the presence of 2% $Pd(PPh_3)_4$. Interestingly, a number of catalyst systems were screened and $Pd(PPh_3)_4$ gave the best results in most cases. However, for the cross-coupling of **26a** with **27b**, better yields were obtained by using 2% $Pd(OAc)_2$/4 % SPhos. These cross-couplings were usually completed within 1-5 h at 50 °C. As expected, the presence of electron-withdrawing substituents on the pyridylzinc reagents **26** lowered significantly the cross-coupling efficiency (Scheme 71).



Scheme 71: Negishi cross-coupling towards the synthesis of the bis-pyridines (25a-c).

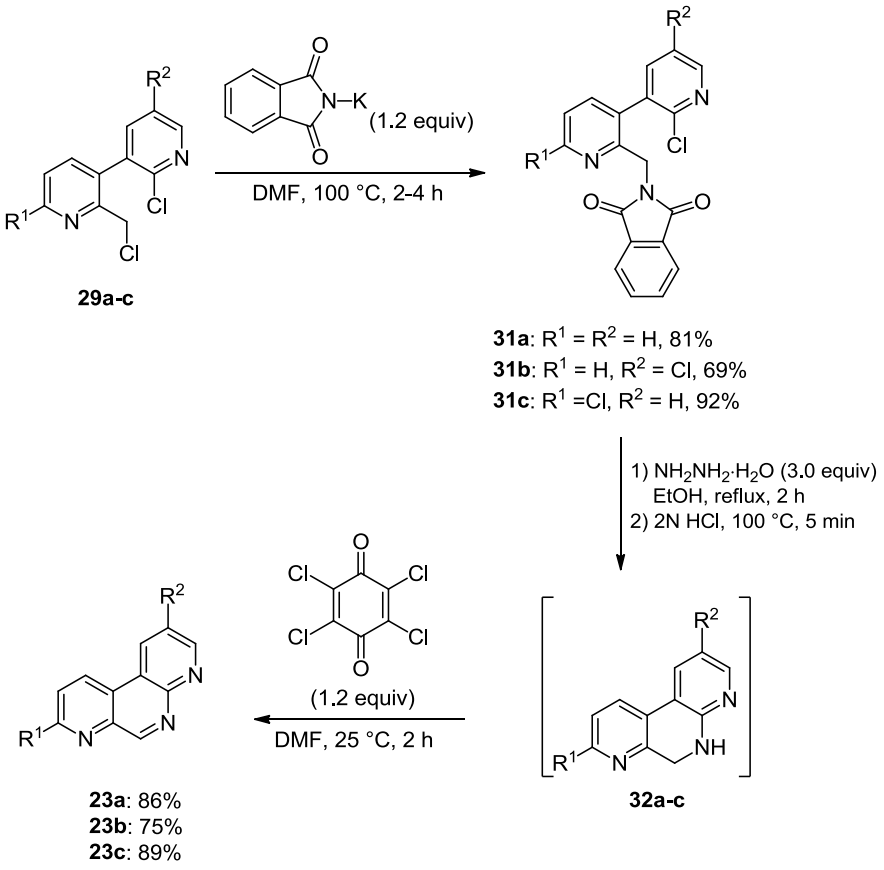
Subsequently, the introduction of an amino function was achieved by the convertion of the 2-methyl substituent into a chloromethyl group, followed by a Gabriel reaction.[133] This chlorination was achieved by two methods. The most convenient procedure consisted of the treatment of the bis-pyridines **25a-b** with trichloroisocyanuric acid in chloroform in the presence of 3% $PhCONH_2$ (60 °C, 4-12 h), leading to the chloromethyl bis-pyridines 2**9a-b** in 78-81% yield.[134] This electrophilic substitution did not proceed if the methyl substituent was attached to a pyridyl ring bearing an electron-withdrawing chlorine substituent. In this case, the intermediate trimethylsilylmethyl derivative **30** was prepared by deprotonation with LDA (1.2 equiv, -78 °C, 2 h), followed by trapping with TMSCl. Intermediate **30** was smoothly chlorinated by the method of Fraser,[135] using C_2Cl_6 and

CsF in acetonitrile (reflux, 3 h), affording the chloromethyl derivative **29c** in 62% yield (Scheme 72).



Scheme 72: Chlorination of the picolyl derivatives (25a-c).

Gabriel reaction using potassium phthalimide (DMF, 100 °C, 2-5 h) provided the phthalimides (**31a-c**) in 69-92% yield. Deprotection of the phthalimides **31a-c** using hydrazine hydrate in ethanol gave aminomethyl intermediates of type **24**. Unexpectedly, those aminated compounds underwent a spontaneous ring closure under the reaction conditions, providing the dihydrotriazaphenanthrenes (**32a-c**). Treatment with chloranil in DMF (25 °C, 2 h) led to the aromatized target molecules (**23a-c**) in 75-89% yield (Scheme 73).



Scheme 73: Gabriel substitution and corresponding deprotection leading to the azaphenanthrenes (23a-c).

4.3 FUNCTIONALIZATION OF PYRIDO[3,2-*F*][1,7]NAPHTHYRIDINE BY ORGANOLITHIUMS ADDITION

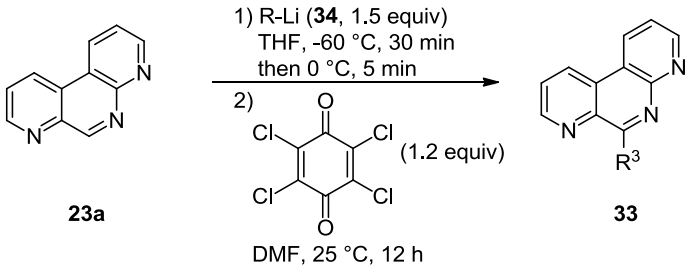
Additionally, the reactivity and further functionalization of these new *N*-heterocycles was studied.

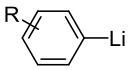
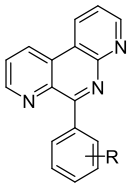
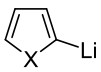
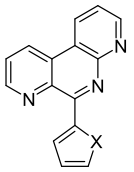
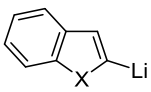
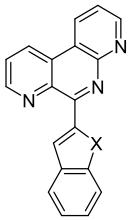
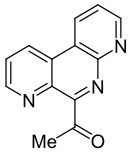
Although metalations using various TMP-bases (TMPLi, $TMP_2Mg·2LiCl$, TMPMgCl·LiCl, $TMP_2Zn·2LiCl$, TMPZnCl·LiCl)[136] led to complex mixtures, the treatment of **23a** with a range of organolithiums at -60 °C for 0.5 h followed by a rearomatization with chloranil (DMF, 25 °C) furnished the functionalized triazaphenanthrenes (**33a-j**) in 34-93% yield (Table 14).

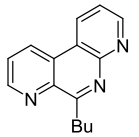
A range of aryllithium reagents (**34a-d**) bearing electron-donating (**34b**) and -withdrawing groups (**34c-d**) react well with **23a**, leading to the azaphenanthrenes (**33a-d**) in 62-93% yields after rearomatization (entries 1-4). Also, heterocyclic lithium derivatives smoothly added to the pyridonaphthyridine (**23a**). Thus, 2-lithiofuran (**34e**), 2-lithiothiophene (**34f**), as well as 2-lithiobenzofuran (**34g**) and 2-lithiobenzothiophene (**34h**), led to azaphenanthrenes (**33e-h**) in 32-80% yield (entries 5-8). Interestingly, 1-lithio-1-ethoxyethene (**34i**) reacted well with **4a** under these reaction conditions, and the keto-azaphenanthrene derivative (**33i**) was produced in 90% yield (entry 9). Surprisingly, alkyllithium reagents such as *n*-BuLi (**34j**) underwent a similar addition on the

azaphenanthrene core without competitive metalation, affording the butyl-substituted azaphenanthrene (**33j**) in 76% yield (entry 10).

Table 14: Functionalization of azaphenanthrene (23a) with organolithium reagents leading to substituted pyridonaphthyridines of type 33.



Entry	Organolithium reagent	Product[a]
		
1	**34a**: R = H	**33a**: 93%
2	**34b**: R = *p*-OMe	**33b**: 87%
3	**34c**: R = *p*-CF_3	**33c**: 68%
4	**34d**: R = *m*-F	**33d**: 62%
		
5	**34e**: X = O	**33e**: 80%
6	**34f**: X = S	**33f**: 46%
		
7	**34g**: X = O	**33g**: 32%
8	**34h**: X = S	**33h**: 51%
		
9	**34i**	**33i**: 90%

		n-BuLi	
10	**34j**		**33j**: 76%

[a]Isolated yields of analytically pure product.

5. SUMMARY AND OUTLOOK

Nitrogen-containing heterocyclic compounds are of significant interest for the pharmaceutical and agrochemical industry. Transition-metal-catalyzed cross-coupling reactions have become a cornerstone in the functionalization of such compounds, and are among the most used C-C bond forming reactions in organic chemistry. In general, cross-coupling reactions employ Pd- or Ni-salts as catalyst, while palladium is certainly by far the most used metal. However, the high cost of palladium and the comparable high toxicity of nickel salts have motivated the development of new cross-coupling methods employing economically reasonable, environmentally friendly, and readily available less toxic transition metals.

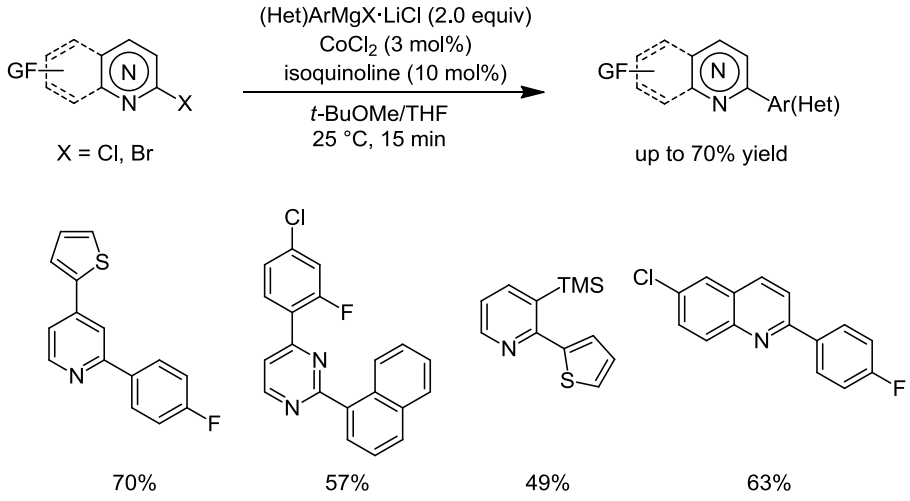
This work focused on the search for alternative metals to replace palladium- and nickel-catalysts by the development of new cobalt(II)- and chromium(II)-catalyzed cross-coupling methodologies. Furthermore, an effective strategy to obtain highly functionalized structural heterocyclic motifs involves the use of polyhalogenated starting materials that can be subsequently functionalized. For this purpose, the use of $CrCl_2$ in highly regioselective cross-coupling reactions of dichlorinated heteroaromatics was demonstrated. Attention was also paid to the effective purging of chromium salts from the desired product by demonstrating the use of various solid supports for the removal of remaining metal traces. Besides the C-C bond formation, this work focused on the replacement of the cost-intensive palladium salt associated with sensitive phosphine ligands in the Buchwald-Hartwig amination reaction. Therefore, the chromium(II)-chloride catalyzed amination of *N*-heterocyclic chlorides with a range of magnesium amides was developed.

Besides, particular attention was paid to the synthesis and functionalization of unexplored annelated six-membered *N*-heterocycles having potential use in medicinal and/or material applications: pyrido[3,2-*f*][1,7]naphthyrdine.

5.1 COBALT(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN *N*-HETEROCYCLIC HALIDES AND ARYL OR HETEROARYL MAGNESIUM REAGENTS

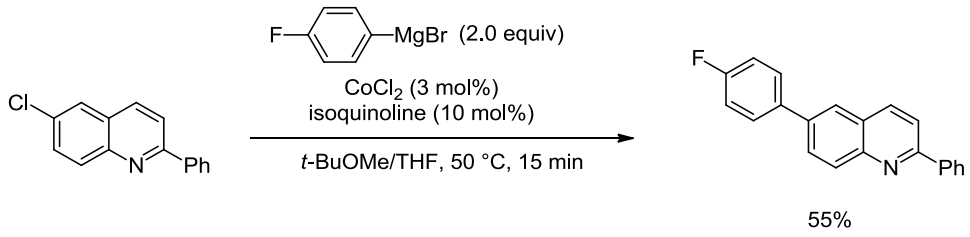
The reaction scope of cobalt-catalyzed cross-coupling reactions in the presence of isoquinoline in the solvent mixture *t*-BuOMe/THF was further investigated.

Various 2-halogenated pyridine, pyrimidine, and quinoline derivatives were arylated under mild reaction conditions in high yields (Scheme 74).



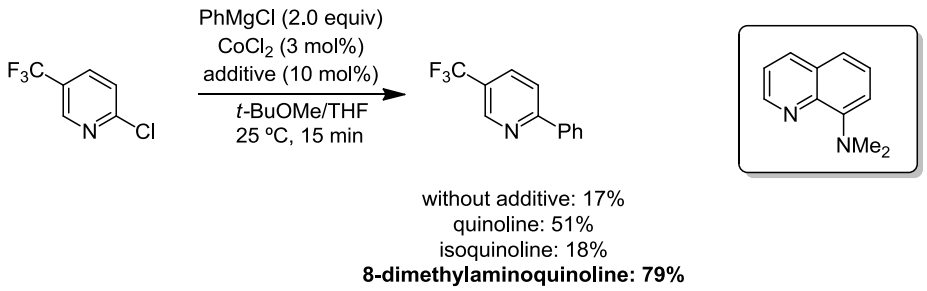
Scheme 74: Cobalt(II)-catalyzed cross-coupling reactions of 2-halogenated *N*-heterocycles.

The developed catalytic system of the cobalt(II) complex associated with isoquinoline allows, not only to perform cross-coupling reactions at the 2-position of the haloquinoline, but also to achieve the more challenging cross-coupling at the 6-position of 6-chloro-2-phenylquinoline with electron poor
4-fluorophenylmagnesium bromide (Scheme 75).



Scheme 75: $CoCl_2$-catalyzed cross-coupling of 6-chloro-2-phenylquinoline with 4-fluorophenylmagnesium bromide.

Furthermore, it was found that the use of 10% 8-dimethylaminoquinoline increases greatly the yields of some Co-catalyzed cross-coupling reactions with chloropyridines bearing electron-withdrawing substituents, *e.g*. for 2-chloro-5-(trifluoromethyl)pyridine (Scheme 76).



Scheme 76: Co-catalyzed cross-coupling reaction between 2-chloro-5-(trifluoromethyl)pyridine and PhMgCl utilizing 8-dimethylaminoquinoline as ligand.

Upcoming work could focus on the optimization of this ligand system, since it is lacking from generality. Future heterocyclic ligands should involve the following features:

1. General catalysis with all different types of halogenated heterocycles, regardless the electron-withdrawing or -donating nature of its substituents.
2. Easily accessible, either by a very short synthesis or, in best case, an inexpensive commercially available compound.

Future extensions could involve cross-coupling reactions with non-activated aromatic halides instead of *N*-heterocyclic halides.

5.2 CHROMIUM(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN CSP^2 CENTERS

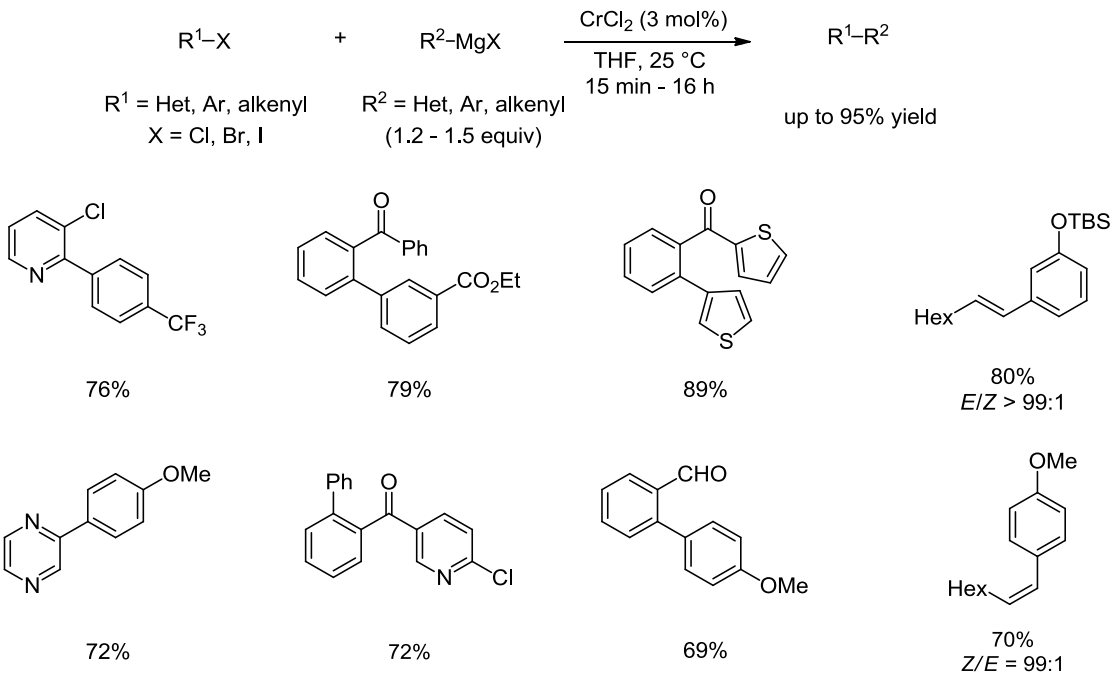
Against common wisdom, toxicological data has proven the low toxicity of $CrCl_2$, in contrary to high-valent Cr(VI) complexes. It is worth noting that, analogous to other commonly used salts such as $PdCl_2$, $NiCl_2$ or even $CoCl_2$, chromium(II) chloride exhibits a lower toxicity. Therefore, $CrCl_2$ is sold as a low-toxic chemical by major international suppliers.

In this work it was shown that, unexpectedly, $CrCl_2$ can undergo very efficiently cross-coupling reactions of C–X bonds with a wide range of Grignard reagents, which allow the effective construction of C–C bonds with a fast conversion rate under ambient conditions.
The simple procedure does not require any additional ligand or additive for coupling reactions to proceed at room temperature in the presence of 3 mol% of chromium(II) chloride.

Remarkably, much lower amounts of homo-coupling side products are obtained compared to related iron, cobalt, or manganese cross-couplings.

Using this novel methodology, various unsymmetrical (hetero)biaryls can be formed from (hetero)arylmagnesium reagents with *N*-heterocyclic halides and aromatic halogenated ketones (Scheme 77). Imino-protected 2-chlorobenzaldehyde, as well as alkenyl iodides, are also suitable partners for the efficient coupling with a range of (hetero)aromatic Grignard reagents. A variety of functionalities, such as electron-withdrawing halogens, ester, trifluoromethyl or cyano groups, as

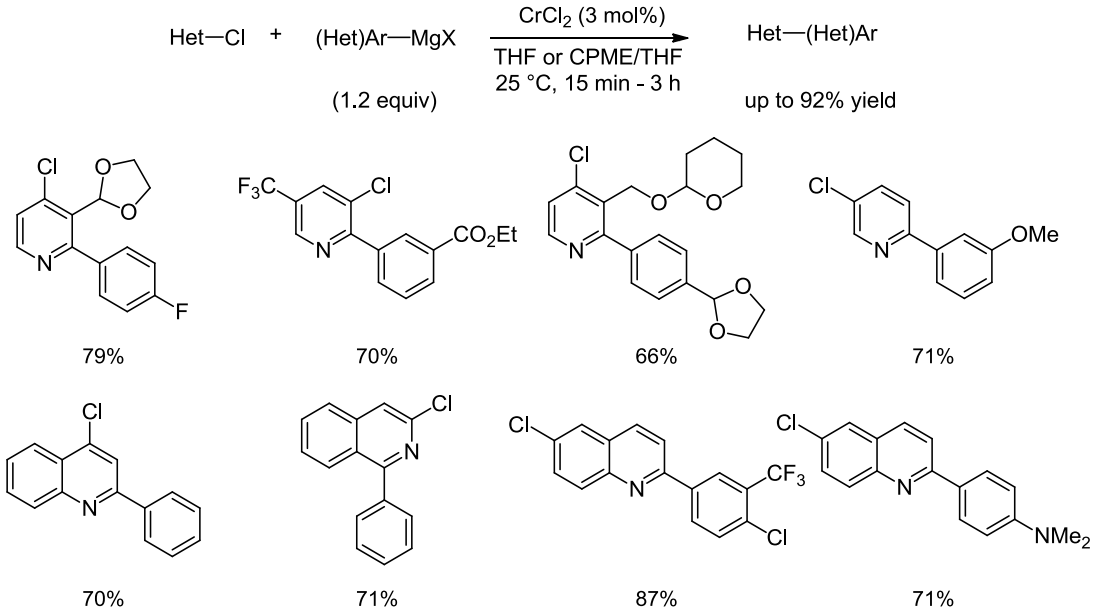
well as electron-donating methoxy and amino group, are compatible with this catalytic system.



Scheme 77: Cr-catalyzed cross-coupling reaction at room-temperature.

Moreover, a further study of this cross-coupling method led to a broadened substrate scope by regio- and chemoselectively coupling of a wide range of substituted dichloropyridines to aromatic Grignard reagents (Scheme 78).

Furthermore, it was found that previously challenging electron-rich quinolines and isoquinolines undergo the selective Cr-catalyzed cross-coupling much faster in CPME (cyclopentyl methyl ether) than in THF as solvent.



Scheme 78: Regioselective Cr-catalyzed cross-couplings of dichlorinated heteroaromatics.

The unexpected discovery that $CrCl_2$ can catalyze cross-coupling reactions led to various studies as extension for the scope of this methodology.

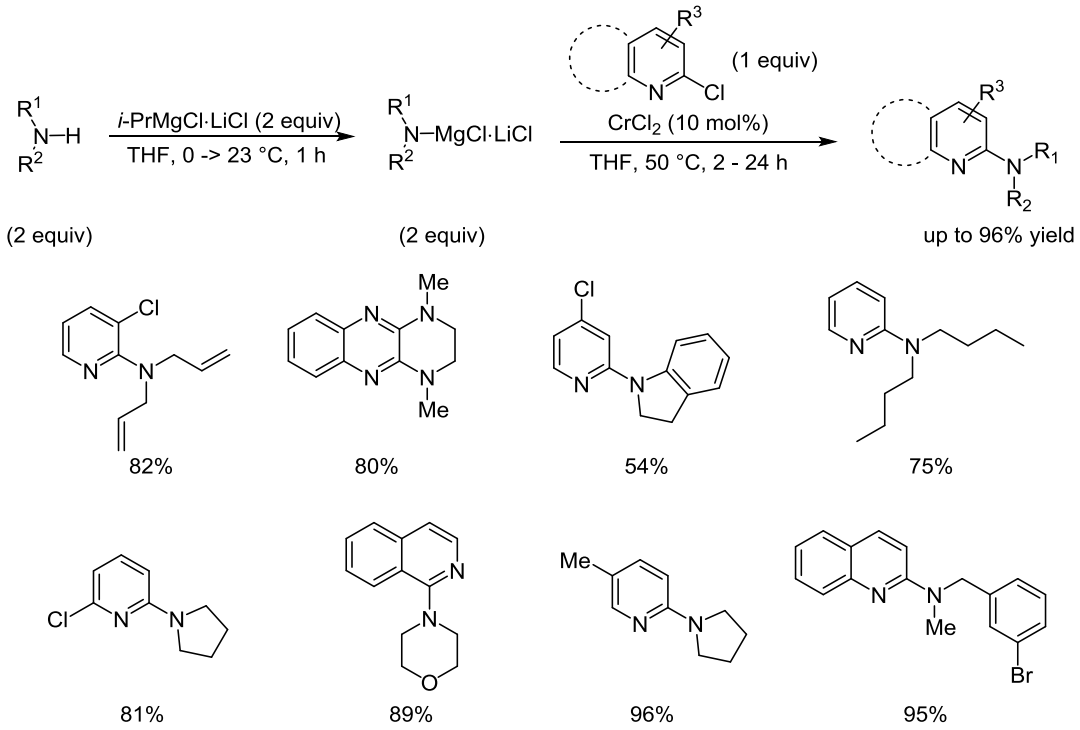
The cross-coupling methodology was pushed further by demonstrating the chromium(II)-catalyzed direct C-H arylation of pyridines, aryl oxazolines, and imines with arylmagnesium reagents.[137]

Furthermore, also aryl alkyl ethers in the presence of aryl and alkyl Grignard reagents could successfully provide the desired regioselective Cr-catalyzed cross-coupling products.[138]

5.3 CHROMIUM(II)-CATALYZED AMINATION OF *N*-HETEROCYCLIC CHLORIDES WITH MAGNESIUM AMIDES

After studying the effect of chromium(II) salts in cross-couplings, its possible use in amination reactions as an alternative to the palladium-catalyzed Buchwald-Hartwig reaction was investigated.

For this reason, the ligand-free chromium(II)-catalyzed amination reaction of various *N*-heterocyclic chlorides was found. $CrCl_2$ regioselectively catalyzes the reaction of chloro- and dichloropyridines, -quinolines, -isoquinolines and -quinoxalines with a range of aliphatic, allylic, benzylic and saturated (hetero)cyclic magnesium amides in the presence of lithium chloride as additive (Scheme 79). The reactions have been performed at 50 °C in THF and led to the desired aminated products in 56-96% yield.



Scheme 79: Cr(II)-catalyzed amination of N-heterocyclic chlorides with magnesium amides.

Using chromium(II) salts, future work could focus on extending the scope of chromium-catalysis to other potential reactions like carbometalation, borylation or trifluoromethylation reactions.

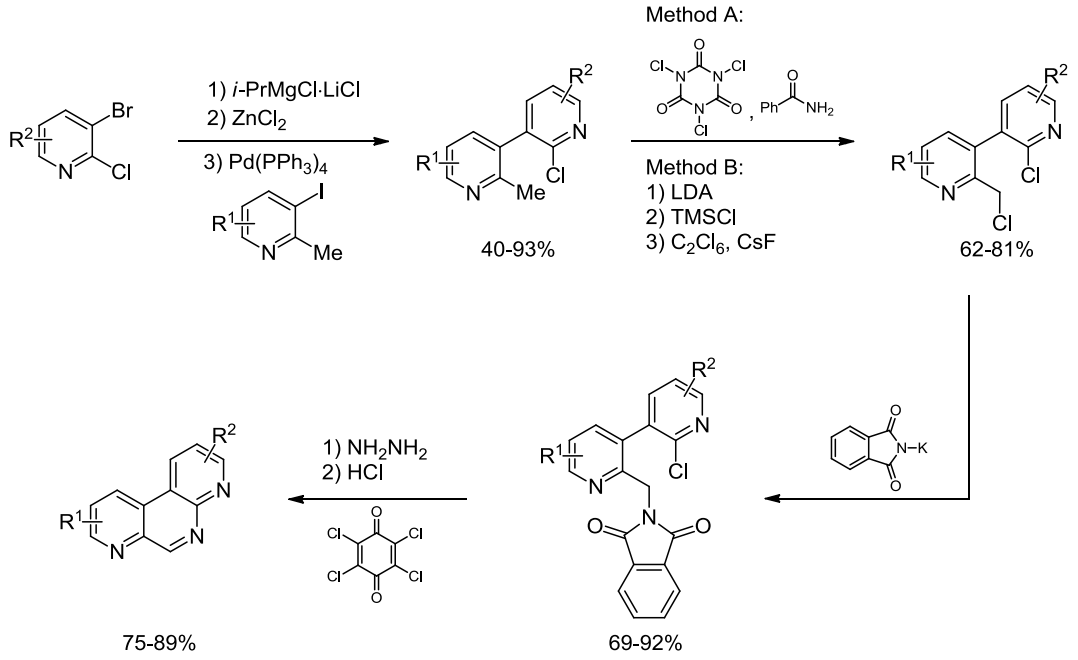
5.4 SYNTHESIS OF PYRIDO[3,2-F][1,7]NAPHTHYRIDINE AND RELATED HETEROCYCLES

N-heterocycles play an important role in medicinal chemistry and material science. However, the synthesis of complex six-membered *N*-heteroaromatics still remains an under-explored field. Due to their great potential as ligand, drug or fluorescent probe for instance, pyrido[3,2-*f*][1,7]naphthyridines were studied. A general synthesis based on metal-catalyzed cross-coupling and amination reactions was envisioned (Scheme 80).

First, Negishi cross-coupling of polyfunctional pyridylzinc reagents furnished the desired bis-pyridines in moderate to excellent yields under tetrakis(triphenylphosphine)palladium-catalysis, and no expensive ligand was needed in most cases.

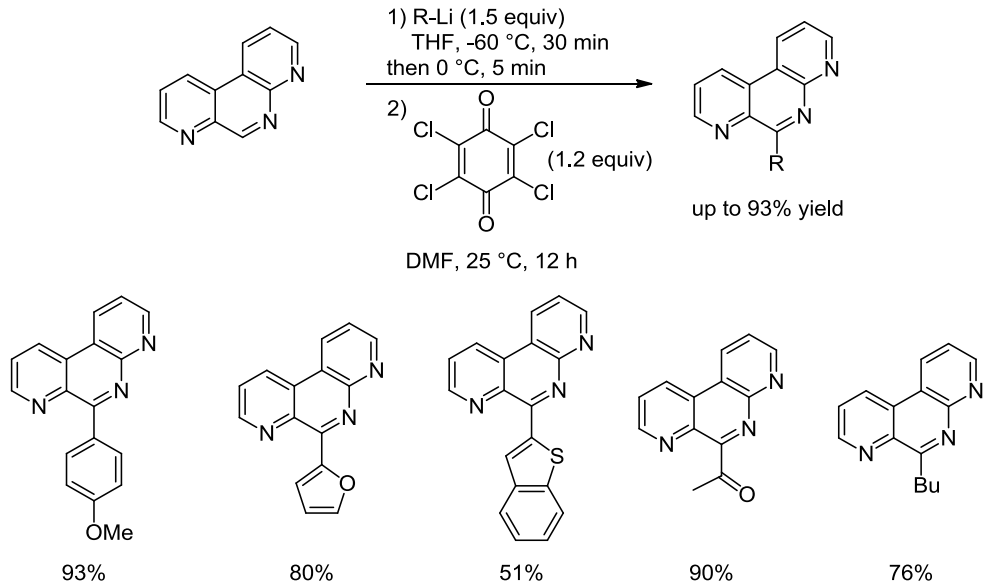
Furthermore, in order to generate the required amino-pyridine, selective halogenation and further amination was envisioned. Chlorination was performed using two different methods depending on the electron-density of the substrate. Whereas electrophilic chlorination was achieved using trichloroisocyanuric acid, metalation by LDA, followed by TMS trapping and halogenation led to the chloromethyl intermediates in good yield.

Gabriel substitution and subsequent deprotection under Manske-Ing conditions furnished the desired amino-pyridines, which underwent spontaneous ring closure. Hence, the final substituted pyrido[3,2-*f*][1,7]naphthyridines were obtained in high yield after aromatization.



Scheme 80: General synthesis of pyrido[3,2-*f*][1,7]naphthyridines.

Furthermore, the reactivity of pyrido[3,2-*f*][1,7]naphthyridines was also studied. It could be shown that these molecules are readily functionalized by the addition of organolithium reagents. A wide range of aryl-, heteroaryl- and alkyllithiums could add successfully and led to the 6-substituted azaphenanthrene after smooth rearomatization (Scheme 81).



Scheme 81: Functionalization of azaphenanthrene with organolithium reagents.

At the moment, the potential application of these complex *N*-heterocycles as fluorescence markers is investigated.

Furthermore, upcoming work should continue with the functionalization of the pyridinonaphthyridines in order to generate a broader variety of interesting new molecules. Besides metalations, also other methods such as C-H-functionalization or amination reactions could be considered.

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 pre-dried over $CaCl_2$ and distilled from CaH_2.

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

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

Toluene was pre-dried over $CaCl_2$ and distilled from CaH_2.

Solvents for column chromatography were distilled prior to use.

1.2 REAGENTS

All reagents were obtained from commercial sources and used without further purification unless otherwise stated.

$CoCl_2$ was dried under high vacuum at 200 °C for 2 min prior to reactions (until the color turned blue).

$CrCl_2$ was dried under high vacuum at 200 °C for 2 min prior to reactions (until the color turned white-grey).

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

PhMgCl solution in THF was purchased from Rockwood Lithium GmbH.

$ZnCl_2$ 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.

$(i\text{-Pr})_2NH$ was distilled under Ar prior to use.

***n*-BuLi** was purchased as a solution in hexane from Rockwood Lithium.

1.3 CONTENT DETERMINATION OF ORGANOMETALLIC REAGENTS

Organzinc and organomagnesium reagents were titrated against I_2 in THF. [139]

Organolithium reagents were titrated against *i*-PrOH using 1,10-phenanthroline as indicator in THF.[140]

1.4 CHROMATOGRAPHY

Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) from Merck.
Thin layer chromatography was performed using SiO_2 pre-coated aluminium plates (Merck 60, F-254). The chromatograms were examined under UV light at 254 nm and/or by staining of the TLC plate with one of the solutions given below followed by heating with a heat gun:

- $KMnO_4$ (3.0 g), 5 drops of conc. H_2SO_4 in water (300 mL).
- Phosphomolybdic acid (5.0 g), $Ce(SO_4)_2$ (2.0 g) and conc. H_2SO_4 (12 mL) in water (230 mL).
- Ninhydrin (0.3 g) and AcOH (3.0 mL) in butanol (100 mL).

1.5 ANALYTICAL DATA

^{1}H-NMR and **^{13}C-NMR** spectra were recorded on VARIAN Mercury 200, BRUKER ARX 300, VARIAN VXR 400 S and BRUKER AMX 600 instruments. Chemical shifts are reported as δ-values in ppm relative to tetramethylsilane. The following abbreviations were used to characterize signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), spt (septet), m (multiplet) as well as br (broadened).

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 ionization energy of 70 eV.

For coupled gas chromatography/mass spectrometry, a HEWLETT-PACKARD HP 6890/MSD 5973 GC/MS system was used. Molecular fragments are reported starting at a relative intensity of 10%.

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. Wavenumbers are reported in cm^{-1} starting at an absorption of 10%.

Melting points (m.p.) were determined on a BÜCHI B-540 melting point apparatus and are uncorrected. Compounds decomposing upon melting are indicated by (decomp.).

2. COBALT(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN *N*-HETEROCYCLIC HALIDES AND ARYL OR HETEROARYL MAGNESIUM REAGENTS

2.1 STARTING MATERIALS SYNTHESIS

Grignard reagents were prepared according to a literature procedure.[122]

Starting materials **1a, b, c, f, 1k** are commercially available.
Starting material **1d** was prepared according to a procedure described in the literature.[141]
Starting material **1e** was prepared according to a procedure described in the literature.[142]
Starting material **1g** was prepared according to a procedure described in the literature.[114a]
Starting material **1h** was prepared according to a procedure described in the literature.[143]
Starting material **1j** was prepared according to a procedure described in the literature.[144]

Ligand **4a-h** are commercially available.
Ligand **4i** was prepared according to a procedure described in the literature.[145]
Ligand **4j** was prepared according to a procedure described in the literature.[146]
Ligand **4k** was prepared according to a procedure described in the literature.[147]

2.2 GENERAL PROCEDURES

2.2.1 Typical procedure for the Co-catalyzed cross-coupling reaction with isoquinoline as ligand (**TP1**)

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 $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), isoquinoline (6.5 mg, 0.05 mmol, 0.10 equiv), and the aryl halide (0.5 mmol, 1.0 equiv) in *t*-BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for the indicated time before being quenched with 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 25 °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, leading to the final compound as an analytically pure substance.

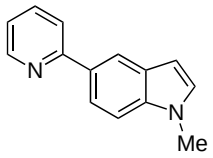
2.2.2 Typical procedure for the ligand screening of the Co-catalyzed cross-coupling reaction of chloropyridines (**TP2**)

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 $CoCl_2$ (1.9 mg, 0.015 mmol, 0.03 equiv), the appropriate ligand (0.05 mmol, 0.10 equiv), and the aryl halide (0.5 mmol, 1.0 equiv) in *t*-BuOMe (2.5 mL) at 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched with sat. aq. $NaHCO_3$ and extracted with ethyl acetate. The organic phase was injected to a gas chromatography apparatus and the yields were determined by integration of the gas chromatogram and comparison against undecane as a calibrated internal standard.

2.3 PREPARATION OF THE SYNTHESIZED *N*-HETEROCYCLIC COMPOUNDS

Synthesis of 1-methyl-5-(pyridin-2-yl)-1H-indole (3c) according to TP1:



According to **TP1**, the substituted pyridine **3c** was prepared from 0.5 mmol of **1c** with 1.0 mmol of **2b** at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 3:1 + 0.5% NEt_3) furnished **3c** as brown solid (64 mg, 61%).

m.p.: 66.8 – 68.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.82 (s, 3 H), 6.58 (d, *J*=3.04 Hz, 1 H), 7.09 (d, *J*=3.04 Hz, 1 H), 7.14 - 7.20 (m, 1 H), 7.41 (d, *J*=8.57 Hz, 1 H), 7.68 - 7.82 (m, 2 H), 7.94 (dd, *J*=8.57, 1.66 Hz, 1 H), 8.29 (d, *J*=1.11 Hz, 1 H), 8.71 (d, *J*=4.70 Hz, 1 H).

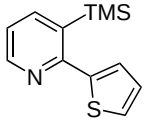
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 32.9, 101.9, 109.4, 119.7, 120.3, 120.9, 121.0, 128.8, 129.6, 131.0, 136.6, 137.3, 149.5, 158.8.

MS (70 eV, EI) m/z (%): 209 (13), 208 (100), 207 (26), 166 (4), 104 (5), 43 (10).

IR ATR ν (cm^{-1}): 3084, 2998, 2923, 1615, 1584, 1558, 1513, 1461, 1420, 1339, 1304, 1271, 1245, 1184, 1149, 1104, 1081, 968, 884, 819, 775, 760, 729, 686.

HRMS (EI) for **$C_{14}H_{12}N_2$** (208.1000) $[M]^+$: 289.0993.

Synthesis of 2-(thiophen-2-yl)-3-(trimethylsilyl)pyridine (3d) according to TP1:



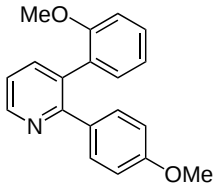
According to **TP1**, the substituted pyridine **3d** was prepared from 0.5 mmol of **1d** with 1.0 mmol of **2c** at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 4:1 + 0.5% NEt_3) furnished **3d** as brown oil (81 mg, 49%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.18 (s, 9 H), 7.07 (dd, *J*=4.84, 3.73 Hz, 1 H), 7.17 - 7.28 (m, 2 H), 7.41 (d, *J*=4.98 Hz, 1 H), 7.91 (dd, *J*=7.60, 1.80 Hz, 1 H), 8.61 (dd, *J*=4.84, 1.80 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 0.1, 121.6, 126.6, 126.8, 127.4, 133.9, 143.4, 145.6, 149.2, 158.3.

MS (70 eV, EI) m/z (%): 233 (22), 220 (15), 219 (23), 218 (100), 202 (9), 188 (14).
IR ATR ν (cm^{-1}): 3028, 2953, 2897, 1560, 1548, 1439, 1391, 1264, 1249, 1214, 1129, 1044, 972, 835, 781, 749, 697, 658.
HRMS (EI) for **$C_{12}H_{15}NSSi$** (233.0694) $[M]^+$: 233.0684.

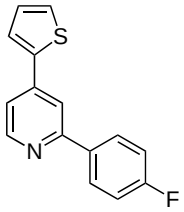
Synthesis of 3-(2-methoxyphenyl)-2-(4-methoxyphenyl)pyridine (3e) according to TP1:



According to **TP1**, the substituted pyridine **3e** was prepared from 0.5 mmol of **1e** with 1.0 mmol of **2d** at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 7:1) furnished **3e** as colourless oil (100 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.42 (s, 3 H), 3.75 (s, 3 H), 6.61 - 6.86 (m, 3 H), 6.95 (t, *J*=7.46 Hz, 1 H), 7.14 (dd, *J*=7.46, 1.66 Hz, 1 H), 7.17 - 7.42 (m, 4 H), 7.66 (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: 55.1, 111.2, 113.0, 120.8, 121.3, 129.1, 129.3, 130.1, 131.2, 132.5, 133.6, 139.1, 148.2, 156.2, 157.6, 159.1.
MS (70 eV, EI) m/z (%): 291 (100), 276 (30), 275 (26), 260 (48), 204 (18), 108 (11), 61 (15), 41 (82).
IR ATR ν (cm^{-1}): 3044, 3001, 2956, 2934, 2835, 1607, 1580, 1576, 1513, 1494, 1460, 1418, 1296, 1240, 1174, 1124, 1104, 1041, 1023, 998, 935, 836, 797, 780, 752, 677.
HRMS (EI) for **$C_{19}H_{17}NO_2$** (291.1259) $[M]^+$: 291.1257.

Synthesis of 2-(4-fluorophenyl)-4-(thiophen-2-yl)pyridine (3f) according to TP1:

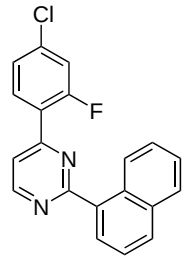


According to **TP1**, the substituted pyridine **3f** was prepared from 0.5 mmol of **1f** with 1.0 mmol of **2e** at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 4:1 + 0.5% NEt_3) furnished **3f** as yellow oil (89 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.95 - 7.24 (m, 3 H), 7.32 - 7.49 (m, 2 H), 7.56 (d, *J*=3.59 Hz, 1 H), 7.85 (s, 1 H), 8.03 (dd, *J*=8.71, 5.39 Hz, 2 H), 8.65 (d, *J*=5.25 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 115.5, 115.8, 116.6, 118.4, 126.9 (d, J=230.31 Hz), 127.2, 128.8 (d, *J*=8.26 Hz), 135.4 (d, *J*=3.13 Hz), 141.4, 142.3, 150.2, 157.3, 162.0, 165.3.
MS (70 eV, EI) m/z (%):255 (100), 254 (49), 86 (11), 84 (17), 70 (10), 61 (15), 45 (14), 43 (92).
IR ATR ν (cm^{-1}): 3106, 3073, 2924, 2852, 1600, 1591, 1541, 1510, 1471, 1431, 1416, 1388, 1343,

1296, 1222, 1156, 1096, 1050, 1013, 989, 879, 836, 819, 761, 747, 696.
HRMS (EI) for **$C_{15}H_{10}FNS$** (255.0518) $[M]^+$: 255.0511.

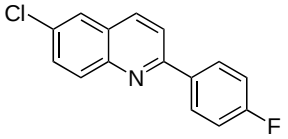
Synthesis of 4-(4-chloro-2-fluorophenyl)-2-(naphthalen-1-yl)pyrimidine (3g) according to TP1:



According to **TP1**, the substituted pyrimidine **3g** was prepared from 0.5 mmol of **1g** with 1.0 mmol of **2f** at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 19:1 + 0.5% NEt_3) furnished **3g** as white solid (95 mg, 57%).

m.p.: 119 - 121 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.19 - 7.36 (m, 2 H), 7.48 - 7.67 (m, 3 H), 7.81 (dd, *J*=5.39, 1.80 Hz, 1 H), 7.90 - 8.05 (m, 2 H), 8.17 (dd, *J*=7.19, 0.83 Hz, 1 H), 8.34 (t, *J*=8.57 Hz, 1 H), 8.67 - 8.80 (m, 1 H), 8.99 (d, *J*=5.25 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 117.2 (d, *J*=26.42 Hz) 117.4, 118.2 (d, *J*=12.81 Hz), 123.5 (d, *J*=10.25 Hz), 125.2, 125.4 (d, *J*=3.42 Hz), 125.8, 125.9, 126.9, 128.5, 129.6, 130.7, 131.1, 131.8 (d, *J*=3.42 Hz), 134.2, 135.8, 137.7 (d, *J*=10.82 Hz), 157.9, 159.1 (d, *J*=2.85 Hz), 161.4 (d, *J*=256.22 Hz), 167.1.
MS (70 eV, EI) m/z (%):336 (21), 335 (39), 334 (55), 333 (100), 205 (7), 153 (10), 149 (5), 126 (5).
IR ATR ν (cm^{-1}): 3078, 3040, 2922, 2263, 1927, 1713, 1605, 1562, 1544, 1511, 1482, 1465, 1423, 1398, 1315, 1285, 1255, 1236, 1164, 1133, 1056, 856, 825, 809, 795, 786, 770, 760.
HRMS (EI) for **$C_{20}H_{11}ClFN_2$** (333.0595) $[M-H]^+$: 333.0588.

Synthesis of 6-chloro-2-(4-fluorophenyl)quinoline (3h) according to TP1:



According to **TP1**, the substituted quinoline **3h** was prepared from 0.5 mmol of **1h** with 1.0 mmol of **2e** at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 20:1) furnished **3h** as white solid (80 mg, 63 %).

m.p.: 148.4 - 149.5 °C
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.11 - 7.27 (m, 2 H), 7.64 (dd, *J*=8.98, 2.35 Hz, 1 H), 7.73 - 7.89 (m, 2 H), 7.98 - 8.23 (m, 4 H).
^{13}C NMR (75.5 MHz, $CDCl_3$) δ/ppm: 115.8 (d, *J*=21.60 Hz), 119.3, 126.1, 127.6, 129.3 (d, *J*=8.41 Hz),

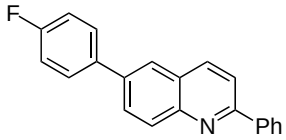
130.7, 131.2, 132.0, 135.3 (d, *J*=3.08 Hz), 135.9, 146.6, 156.4, 162.4 (d, *J*=249.64 Hz).

MS (70 eV, EI) m/z (%): 257 (100), 222 (30), 111 (45), 75 (7).

IR ATR ν (cm^{-1}): 3054, 1595, 1551, 1513, 1487, 1414, 1372, 1335, 1318, 1296, 1276, 1242, 1215, 1189, 1164, 1127, 1106, 1089, 1073, 1050, 1010, 972, 946, 881, 843, 828, 811, 789.

HRMS (EI) for $C_{15}H_9ClFN$ (257.0408) $[M]^+$: 257.0404.

Synthesis of 6-(4-fluorophenyl)-2-phenylquinoline (3i) according to TP1:



According to **TP1**, the substituted quinoline **3i** was prepared from 0.5 mmol of **1i** with 1.0 mmol of **2e** at 50 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 25:1) furnished **3i** as white solid (83 mg, 55 %).

m.p.: 206.2 - 209.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm: 7.18 (t, *J*=8.57 Hz, 2 H), 7.43 - 7.59 (m, 3 H), 7.68 (dd, *J*=8.43, 5.39 Hz, 2 H), 7.83 - 7.99 (m, 3 H), 8.21 (dd, *J*=16.59, 7.74 Hz, 4 H).

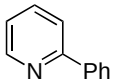
^{13}C NMR (75.5 MHz, $CDCl_3$): δ/ppm: 162.7 (d, *J*=247.71 Hz), 157.3, 147.3, 139.5, 138.0, 136.9, 136.5 (d, *J*=3.02 Hz), 130.2, 129.4, 129.2, 129.0, 128.9 (d, *J*=8.32 Hz), 127.5, 127.3, 125.0, 119.4, 115.8 (d, *J*=21.92 Hz).

MS (70 eV, EI) m/z (%): 299 (100), 298 (29), 204 (4), 150 (7), 139 (5).

IR ATR ν (cm^{-1}): 3048, 2953, 2924, 2853, 1600, 1515, 1488, 1414, 1396, 1333, 1312, 1232, 1140, 1104, 1076, 1053, 1026, 956, 890, 761.

HRMS (EI) for $C_{21}H_{14}FN$ (299.1110) $[M]^+$: 299.1107.

Synthesis of 2-phenyl-pyridine (3b) according to TP2:



According to **TP2**, the substituted pyridine **3b** was prepared from 0.5 mmol of **1b** with 1.0 mmol of **2a** at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 6:1 + 0.5% NEt_3) furnished **3b** as colorless oil (70 mg, 90 %).

^{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, 2H), 8.70 (d, J=4.7 Hz, 1 H).

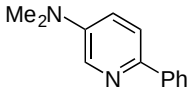
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.6, 122.1, 126.9, 128.7, 129.0, 136.8, 139.2, 149.5, 157.4.

MS (70 eV, EI) m/z (%): 155 (100), 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 N,N-dimethyl-6-phenylpyridin-3-amine (3j) according to TP2:



According to **TP2**, the substituted pyridine **3j** was prepared from 0.5 mmol of **1j** with 1.0 mmol of **2a** at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 95:5 + 0.5% NEt_3) furnished **3j** as yellow solid (77 mg, 78 %).

m.p.: 117.8 - 120.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 8.24 (d, J=3.09 Hz, 1H), 7.94 – 7.91 (m, 2H), 7.60 (dd, J=8.79, 0.71 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.34 – 7.29 (m, 1H), 7.05 (dd, J=8.78, 3.10 Hz, 1H), 3.01 (s, 6H).

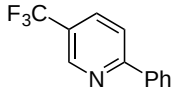
^{13}C NMR (75.5 MHz, $CDCl_3$) δ/ppm**:** 145.3, 144.9, 139.4, 134.4, 128.4, 127.2, 125.6, 120.1, 119.2, 77.2, 77.2, 76.8, 76.5, 39.9.

MS (70 eV, EI) m/z (%): 199 (13), 198 (100), 197 (66), 182 (12), 115 (12).

IR ATR ν (cm^{-1}): 3061, 2921, 2853, 1894, 1587, 1488, 1442, 1364, 1219, 1066, 826, 774, 730, 691.

HRMS (EI) for $C_{12}H_8F_3N$ (198.1157) $[M]^+$: 198.1151.

Synthesis of 2-phenyl-5-(trifluoromethyl)pyridine (3k) according to TP2:



According to **TP2**, the substituted pyridine **3k** was prepared from 0.5 mmol of **1k** with 1.0 mmol of **2a** at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 95:5 + 0.5% NEt_3) furnished **3k** as white solid (88 mg, 79 %).

m.p.: 90.1 - 91.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.26 (s, 1 H), 7.44 - 7.55 (m, 2 H), 7.85 (d, *J*=8.29 Hz, 1 H), 7.91 - 8.15 (m, 3 H), 8.95 (s, 1 H).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ/ppm**:** 119.9, 123.7 (q, J=271.80 Hz), 124.0, 124.6, 125.0, 127.2, 128.9, 130.0, 137.94, 133.9 (q, J=7.28 Hz), 146.6 (q, *J*=8.13 Hz), 160.7.

MS (70 eV, EI) m/z (%): 224 (27), 223 (100), 222 (50), 204 (15).

IR ATR ν (cm^{-1}): 2945, 2925, 2854, 1601, 1566, 1482, 1449, 1388, 1326, 1294, 1273, 1167, 1116, 1085, 1073, 1011, 940, 862, 838, 789, 739, 692, 652, 614.

HRMS (EI) for $C_{12}H_8F_3N$ (223.0609) $[M]^+$: 223.0603.

3. CHROMIUM(II)-CATALYZED CROSS-COUPLING REACTIONS BETWEEN CSP^2 CENTERS

3.1 STARTING MATERIALS SYNTHESIS

Grignard reagents **6a-h**, **6k, 6m-q** were prepared via LiCl-assisted Mg-insertion into the corresponding aromatic halides according to a literature procedure.[122]
Grignard reagents **6i-j**, **6l** and **6r** were prepared via halogen-magnesium exchange reaction.[124]

Starting materials **5a, 5d-h, 5j, 8a, (Z)-12, 14a-l** are commercially available.
The syntheses of compounds **5b**, **5c** and **5i** are described in the literature.[114a]
The syntheses of compounds **8b** and **8c** are described in the literature.[148]
The synthesis of compound **10** is described in the literature.[149]
The synthesis of compound **(Z)-12** is described in the literature.[130a]

3.2 GENERAL PROCEDURES

3.2.1 Typical procedure for the Cr-catalyzed cross-coupling reactions in THF (**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 25 °C. The suspension was stirred at 25 °C for the indicated time before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield the final compound as an analytically pure substance.

3.2.2 Typical procedure for the Cr-catalyzed cross-coupling reactions with imine **10** (**TP4)**

A solution of the appropriate Grignard reagent (concentration in THF varying depending on the nature of the Grignard reagent, 1.2 mmol, 1.2 equiv) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and the aryl halide (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for the indicated time before being quenched with 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.

3.2.3 Typical procedure for the Cr-catalyzed cross-coupling reactions with alkenyl iodide **(E or Z)-8** (**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 the E or Z aryl halide (1 mmol, 1.0 equiv) in THF (5 mL) at 25 °C. The suspension was stirred at 25 °C for the indicated time before being quenched with brine and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to yield the crude compound, which was purified by column chromatography to yield the final compound as an analytically pure substance.

3.2.4 Typical procedure for the Cr-catalyzed cross-coupling reactions in CPME (**TP6**)

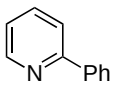
A solution of the appropriate Grignard reagent (concentration in THF varying depending on the nature of the Grignard reagent, 1.2 mmol, 1.2 equiv) was added dropwise to a suspension of anhydrous $CrCl_2$ (3.7 mg, 0.03 mmol, 0.03 equiv; 97% purity) and the aryl halide (1 mmol, 1.0 equiv) in CPME (5 mL)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

3.2.5 Typical procedure for the evaluation of recovery and chromium levels prior to chromatography, using various scavengers (**TP7**)

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 25 °C. The suspension was stirred at 25 °C for 15 min before being quenched by addition of a saturated aqueous solution of NH_4Cl and the mixture was extracted using EtOAc. The organic phase was poured into the solid support and it was agitated on a mechanic shaker for 24 h. The mixture was filtered and the solvent was evaporated to give the crude product, which was sent for analysis to "Intertek Pharmaceutical Services" (Whitehouse, New Jersey, USA).

3.3 PRODUCT SYNTHESIS ACCORDING TO THE GENERAL PROCEDURES

<u>Synthesis of 2-phenylpyridine (7a) according to TP3:</u>

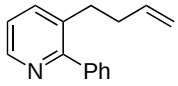


According to **TP3**, the substituted pyridine **7a** was prepared from 1.0 mmol of **6a** with 1.2 mmol of **5a** (1.61 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 6:1 + 0.5% NEt_3)

furnished **7a** as colorless oil (140 mg, 90%).

Other analytical data can be found in part C/2.3 of this dissertation.

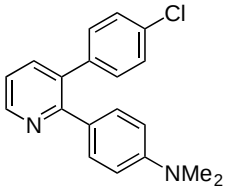
Synthesis of 3-(but-3-en-1-yl)-2-phenylpyridine (7b) according to TP3:



According to **TP3**, the substituted pyridine **7b** was prepared from 1.0 mmol of **5b** with 1.2 mmol of **6a** (1.61 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 6:1 + 0.5% NEt_3) furnished **7b** as colorless oil (199 mg, 95%).

^{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*=7.8, 4.8 Hz, 1 H), 7.32 - 7.54 (m, 5 H), 7.57 - 7.64 (m, 1 H), 8.53 (dd, *J*=4.9, 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.

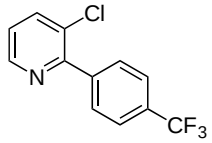
Synthesis of 4-(3-(4-chlorophenyl)pyridin-2-yl)-N,N-dimethylaniline (7c) according to TP3:



According to **TP3**, the substituted pyridine **7c** was prepared from 1.0 mmol of **5c** with 1.2 mmol of **6b** (1.12 M) at 25 °C for 90 min. Flash column chromatography (dichloromethane/ethyl acetate 9:1 + 0.5% NEt_3) furnished **7c** as light yellow oil (247 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.95 (s, 6 H), 6.59 (d, *J*=8.9 Hz, 2 H), 7.08 - 7.35 (m, 7 H), 7.61 (dd, *J*=7.8, 1.66 Hz, 1 H), 8.65 (dd, *J*=4.7, 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 (7d) according to TP3:



According to **TP3**, the substituted pyridine **7d** was prepared from 1.0 mmol of **5d** with 1.2 mmol of **6c** (0.93 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 8:1 + 0.5% NEt_3) furnished **7d** as white solid (195 mg, 76%).

m.p.: 53.0 - 54.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.27 (dd, *J*=8.0, 4.7 Hz, 1 H), 7.69 - 7.78 (m, 2 H), 7.79 - 7.92 (m, 3 H), 8.62 (dd, *J*=4.7, 1.66 Hz, 1 H).

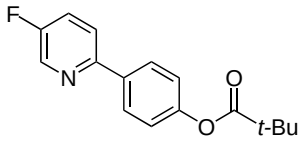
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 123.7, 124.0 (q, *J*=272.1 Hz), 125.0 (q, *J*=3.9 Hz), 129.8, 130.3, 130.8 (q, *J*=32.5 Hz), 138.3, 141.6, 147.8, 155.1.

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 (7e) according to TP3:



According to **TP3**, the substituted pyridine **7e** was prepared from 1.0 mmol of **5e** with 1.2 mmol of **6d** (0.78 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 6:1 + 0.5% NEt_3) furnished **7e** as white solid (180 mg, 66%).

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*=8.4, 3.3 Hz, 1 H), 7.69 (dd, *J*=8.9, 4.42 Hz, 1 H), 7.95 (m, 2 H), 8.53 (d, *J*=2.8 Hz, 1 H).

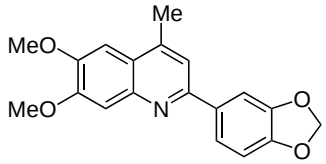
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.1, 39.1, 121.1, 121.2, 121.8, 123.5, 123.7, 127.8, 135.8, 137.5, 137.8, 151.8, 152.9, 152.9, 157.1, 160.5, 176.9.

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 (7f) according to TP3:



According to **TP3**, the substituted quinoline **7f** was prepared from 1.0 mmol of **5f** with 1.2 mmol of **6e** (1.11 M) at 25 °C for 1 h. Flash column chromatography (*i*-hexane/ethyl acetate 3:1 + 0.5% NEt_3) furnished **7f** as yellow solid (239 mg, 74%).

m.p.: 195 - 221 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.67 (s, 3 H), 4.04 (d, *J*=5.5 Hz, 6 H), 6.02 (s, 2 H), 6.92 (d, *J*=8.3 Hz, 1 H), 7.13 (s, 1 H), 7.50 (d, *J*=5.8 Hz, 2 H), 7.59 (dd, *J*=8.2, 1.8 Hz, 1 H), 7.65 (d, *J*=1.9 Hz, 1 H).

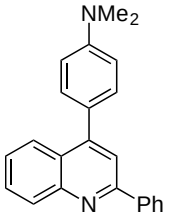
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 19.2, 56.0, 56.1, 101.2, 101.5, 107.7, 108.4, 108.6, 117.9, 121.3, 122.2, 134.3, 143.0, 144.8, 148.2, 148.4, 149.3, 152.2, 154.5.

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 (7g) according to TP3:



According to **TP3**, the substituted quinoline **7g** was prepared from 1.0 mmol of **5g** with 1.2 mmol of **6b** (1.12 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 8:1 + 0.5% NEt_3) furnished **7g** as red solid (253 mg, 78%).

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).

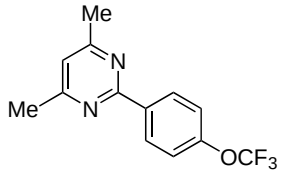
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 40.4, 112.2, 113.1, 119.1, 125.9, 126.1, 127.0, 127.6, 128.8, 129.2, 129.3, 130.0, 130.6, 139.9, 148.9, 149.5, 150.6, 156.9.

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 (7h) according to TP3:



According to **TP3**, the substituted pyrimidine **7h** was prepared from 1.0 mmol of **5h** with 1.2 mmol of **6f** (0.80 M) at 25 °C for 2 h. Flash column chromatography (*i*-hexane/ethyl acetate 6:1 + 0.5% NEt_3) furnished **7h** as white solid (190 mg, 71%).

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*=8.3 Hz, 2 H), 8.48 (d, *J*=8.6 Hz, 2 H).

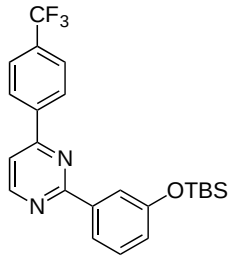
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 24.1, 118.2, 120.5, 120.5 (q, *J*=257.6 Hz), 129.9, 136.6, 150.9, 162.8, 166.9.

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 (7i) according to TP3:



According to **TP3**, the substituted pyrimidine **7i** was prepared from 1.0 mmol of **5i** with 1.2 mmol of **6g** (1.00 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 8:1 + 0.5% NEt_3) furnished **7i** as light yellow oil (344 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.29 (s, 6 H), 1.05 (s, 9 H), 7.02 (dd, *J*=7.6, 2.1 Hz, 1 H), 7.40 (t, *J*=7.9 Hz, 1 H), 7.63 (d, *J*=5.3 Hz, 1 H), 7.81 (m, 2 H), 8.08 (dd, *J*=2.2, 1.7 Hz, 1 H), 8.17 - 8.22 (m, 1 H), 8.33 (m, 2 H), 8.90 (d, *J*=5.25 Hz, 1 H).

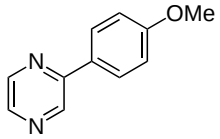
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.3, 18.3, 25.7, 107.6, 108.4, 112.6, 114.8, 119.9, 121.4, 122.9, 123.9 (q, *J*=272.6 Hz), 125.9 (q, *J*=3.9 Hz), 127.6, 129.6, 129.9, 132.4, 140.3, 156.1, 156.7, 158.0, 162.5, 164.5.

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 (7j) according to TP3:



According to **TP3**, the substituted pyrazine **7j** was prepared from 1.0 mmol of **5j** with 1.2 mmol of **6h** (1.34 M) at 25 °C for 30 min. Flash column chromatography (*i*-hexane/ethyl acetate 6:1 + 0.5% NEt_3) furnished **7j** as white solid (134 mg, 72%).

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*=2.5 Hz, 1 H), 8.58 (dd, *J*=2.5, 1.4 Hz, 1 H), 8.97 (d, *J*=1.4 Hz, 1 H).

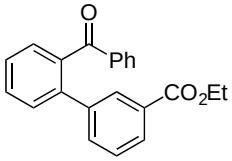
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.4, 114.5, 128.3, 128.8, 141.5, 141.9, 144.0, 152.5, 161.2.

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 (9a) according to TP3:



According to **TP3**, the substituted benzophenone **9a** was prepared from 1.0 mmol of **8a** with 1.2 mmol of **6i** (0.81 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/diethyl ether 9:1) furnished **9a** as white solid (261 mg, 79%).

m.p.: 65.1 - 66.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.33 (t, *J*=7.1 Hz, 3 H), 4.32 (q, *J*=7.2 Hz, 2 H), 7.23 - 7.32 (m, 3 H), 7.38 – 7.69 (m, 8 H), 7.85 (dt, *J*=7.8, 1.5 Hz, 1 H), 7.98 (t, *J*=1.7 Hz, 1 H).

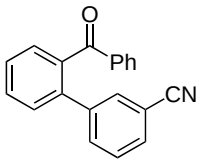
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.2, 60.9, 127.4, 128.1, 128.2, 128.4, 128.9, 129.8, 129.9, 130.1, 130.5, 130.5, 132.9, 133.3, 137.3, 138.9, 140.2, 140.3, 166.1, 198.3.

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.

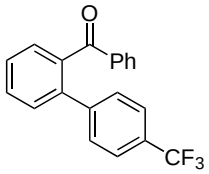
Synthesis of 2'-benzoyl-[1,1'-biphenyl]-3-carbonitrile (9b) according to TP3:



According to **TP3**, the substituted benzophenone **9b** was prepared from 1.0 mmol of **8a** with 0.7 mmol of **6j** (0.51 M) at 25 °C for 2 h. Flash column chromatography (*i*-hexane/ethyl acetate 95:5) furnished **9b** as colorless oil (261 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.22– 7.39 (m, 3H), 7.41– 7.50 (m, 4H), 7.51– 7.68 (m, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 112.5, 118.5, 128.0, 128.4, 129.0, 129.2, 130.1, 130.8, 130.9, 132.2, 133.3, 133.4, 137.2, 138.8, 138.9, 141.5, 197.8.
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.

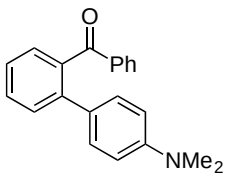
Synthesis of phenyl(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)methanone (9c) according to TP3:



According to **TP3**, the substituted benzophenone **9c** was prepared from 1.0 mmol of **8a** with 1.2 mmol of **6c** (0.93 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 96:4) furnished **9c** as colorless oil (305 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.26 - 7.42 (m, 4 H), 7.43 - 7.65 (m, 7 H), 7.66 - 7.71 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 124.1 (q, *J*=272.1 Hz), 125.2 (q, *J*=3.9 Hz), 127.7, 128.3, 128.9, 129.3, 129.4 (q, *J*=32.5 Hz), 129.9, 130.1, 130.6, 133.2, 137.3, 138.9, 139.9, 143.9, 198.1.
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 (9d) according to TP3:



According to **TP3**, the substituted benzophenone **9d** was prepared from 1.0 mmol of **8a** with 1.2

mmol of **6b** (1.12 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 97:3 + 4% Et_3N) furnished **9d** as orange solid (282 mg, 94%).

m.p.: 112.4 - 113.8 °C.

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

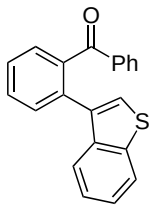
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 40.4, 112.3, 126.0, 128.1, 128.1, 128.6, 129.8, 129.8, 129.9, 130.2, 132.7, 137.5, 138.6, 141.2, 149.7, 199.3.

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 (9e) according to TP3:



According to **TP3**, the substituted benzophenone **9e** was prepared from 1.0 mmol of **8a** with 1.2 mmol of **6k** (0.96 M) at 50 °C for 2 h. Flash column chromatography (*i*-hexane/ethyl acetate 96:4) furnished **9e** as red solid (305 mg, 89%).

m.p.: 121.2 - 123.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.05 - 7.13 (m, 2 H), 7.18 (s, 1 H), 7.20 - 7.38 (m, 3 H), 7.49 - 7.75 (m, 8 H).

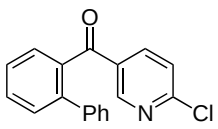
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 122.5, 122.7, 124.3, 124.3, 126.0, 127.7, 127.8, 129.1, 129.1, 130.3, 130.4, 132.4, 134.5, 135.6, 137.2, 138.3, 139.9, 140.1, 198.5.

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 (9f) according to TP3:



According to **TP3**, the substituted benzophenone **9f** was prepared from 1.0 mmol of **8b** with 1.2 mmol of **6a** (1.61 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/diethyl ether 2:1)

furnished **9f** as white crystals (211 mg, 72%).

m.p.: 108.6 - 111.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.12 - 7.24 (m, 6 H), 7.48 - 7.68 (m, 4 H), 7.81 (dd, *J*=8.3, 2.5 Hz, 1 H), 8.42 (dd, *J*=2.5, 0.6 Hz, 1 H).

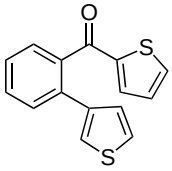
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 123.8, 127.7, 127.8, 128.6, 129.0, 129.1, 130.1, 131.4, 131.8, 137.6, 138.9, 139.6, 141.2, 151.2, 154.8, 196.3.

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 (9g) according to TP3:



According to **TP3**, the substituted benzophenone **9g** was prepared from 0.68 mmol of **8c** with 0.82 mmol of **6l** (0.79 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/diethyl ether 9:1) furnished **9g** as light brown solid (165 mg, 90%).

m.p.: 68.8 - 70.2 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.94 (dd, *J*=4.8, 3.7 Hz, 1 H), 7.09 (dd, *J*=4.8, 1.5 Hz, 1 H), 7.17 - 7.28 (m, 3 H), 7.38 - 7.45 (m, 1 H), 7.47 - 7.65 (m, 4 H).

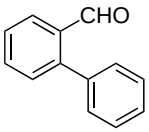
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 123.4, 125.9, 127.0, 127.9, 128.1, 128.2, 129.7, 130.3, 134.7, 134.8, 135.2, 138.7, 140.5, 144.5, 190.8.

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.

Synthesis of [1,1'-biphenyl]-2-carbaldehyde (11a) according to TP4:

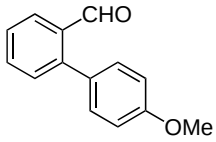


According to **TP4**, the substituted benzaldehyde **11a** was prepared from 1 mmol of **10** with 1.2 mmol of **6a** (1.61 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/diethyl ether 9:1)

furnished **11a** as yellow oil (152 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.37 - 7.41 (m, 2 H), 7.43 - 7.52 (m, 5 H), 7.64 (td, J=7.5, 1.5 Hz, 1 H), 8.04 (dd, J=7.7, 1.4 Hz, 1 H), 10.00 (d, J=0.8 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 127.6, 127.8, 128.1, 128.4, 130.1, 130.8, 133.5, 133.7, 137.7, 146.0, 192.4.
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.

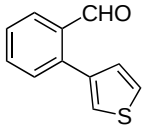
Synthesis of 4'-methoxy-[1,1'-biphenyl]-2-carbaldehyde (11b) according to TP4:



According to **TP4**, the substituted benzaldehyde **11b** was prepared from 1 mmol of **10** with 1.2 mmol of **6h** (1.34 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/diethyl ether 95:5) furnished **11b** as yellow oil (152 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.87 (d, *J*=0.8 Hz, 3 H), 6.97 - 7.04 (m, 2 H), 7.25 - 7.34 (m, 2 H), 7.40 - 7.49 (m, 2 H), 7.57 - 7.65 (m, 1 H), 8.00 (dt, *J*=7.8, 0.7 Hz, 1 H), 10.00 (t, *J*=0.7 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.4, 113.9, 127.3, 127.6, 130.0, 130.8, 131.3, 133.5, 133.8, 145.6, 159.7, 192.6.
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 (11c) according to TP4:



According to **TP4**, the substituted benzaldehyde **11c** was prepared from 1 mmol of **10** with 1.2 mmol of **6l** (0.79 M) at 25 °C for 16 h. Flash column chromatography (*i*-hexane/diethyl ether 95:5) furnished **11c** as yellow oil (140 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.17 - 7.21 (m, 1 H), 7.29 (dd, *J*=2.9, 1.2 Hz, 1 H), 7.42 - 7.51 (m,

3 H), 7.58 - 7.65 (m, 1 H), 7.97 - 8.03 (m, 1 H), 10.10 (d, *J*=0.6 Hz, 1 H).

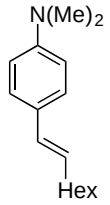
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 125.0, 126.3, 127.6, 127.8, 129.3, 130.6, 133.6, 134.0, 138.3, 140.4, 192.3.

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.

Synthesis of (*E*)-*N*,*N*-dimethyl-4-(oct-1-en-1-yl)aniline (13a) according to TP5:



According to **TP5**, the substituted styrene **13a** was prepared from 1 mmol of **(E)-12** with 1.5 mmol of **6b** (1.12 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 9:1) furnished **13a** as light yellow oil (162 mg, 70%).

^{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*=16.0 Hz, 1 H), 6.66 - 6.74 (m, 2 H), 7.21 - 7.29 (m, 2 H).

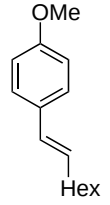
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.1, 22.7, 28.9, 29.7, 31.8, 33.1, 40.7, 112.8, 126.7, 127.2, 129.4, 149.6.

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 (13b) according to TP5:



According to **TP5**, the substituted styrene **13b** was prepared from 1 mmol of **(E)-12** with 1.5 mmol of **6h** (1.34 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 20:1) furnished **13b** as colorless oil (164 mg, 75%).

^{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,

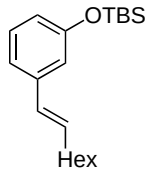
130.8, 158.6.

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 (13c) according to TP5:



According to **TP5**, the substituted styrene **13c** was prepared from 1 mmol of **(E)-12** with 1.5 mmol of **6g** (1.00 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane) furnished **13c** as colorless oil (255 mg, 80%).

^{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*=7.3 Hz, 2 H), 6.15 - 6.26 (m, 1 H), 6.30 - 6.38 (m, 1 H), 6.70 (dd, *J*=8.0, 2.2 Hz, 1 H), 6.94 - 7.00 (m, 1 H), 7.12 - 7.28 (m, 2 H).

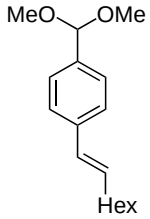
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.4, 14.1, 18.2, 22.6, 25.7, 28.9, 29.3, 31.8, 33.0, 117.5, 118.5, 119.1, 120.1, 129.5, 131.3, 139.5, 155.8.

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 (13d) according to TP5:



According to **TP5**, the substituted styrene **13d** was prepared from 1 mmol of **(E)-12** with 1.5 mmol of **6m** (0.93 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 20:1) furnished **13d** as colorless oil (181 mg, 69%).

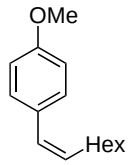
^{1}H NMR (300 MHz, DMSO) δ/ppm: 0.81 - 0.87 (m, 3 H), 1.23 - 1.32 (m, 6 H), 1.36 - 1.45 (m, 2 H), 2.15 (q, *J*=6.6 Hz, 2 H), 3.32 (s, 6 H), 5.33 (s, 1 H), 6.24 - 6.39 (m, 2 H), 7.28 (m, 2 H), 7.36 (m, 2 H).

^{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.

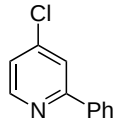
Synthesis of (*Z*) -1-methoxy-4-(oct-1-en-1-yl)benzene (13e) according to TP5:



According to **TP5**, the substituted styrene **13e** was prepared from 0.5 mmol of **(Z)-12** with 0.75 mmol of **6h** (0.79 M) at 25 °C for 14 h. Flash column chromatography (*i*-hexane) furnished **13e** as colorless oil (76 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.84 - 0.93 (m, 3 H), 1.26 - 1.56 (m, 8 H), 2.24 - 2.41 (m, 2 H), 3.82 (s, 3 H), 5.58 (dt, *J*=11.6, 7.2 Hz, 1 H), 6.28 - 6.40 (m, 1 H), 6.82 - 6.92 (m, 2 H,), 7.18 - 7.28 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.1, 22.6, 28.7, 29.1, 30.0, 31.7, 55.2, 113.5, 128.0, 129.9, 130.5, 131.7, 158.1.
MS (70 eV, EI) m/z (%): 218 (27), 148 (12), 147 (100), 134 (17), 121 (15), 115 (11), 91 (17), 43 (21).
IR ATR ν (cm^{-1}): 2955, 2924, 2871, 2854, 2836, 1608, 1510, 1464, 1301, 1247, 1174, 1113, 1037, 964, 837, 818, 752, 725.
HRMS (EI) for **$C_{15}H_{22}O$** (218.1671) $[M]^+$: 218.1662.

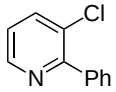
Synthesis of 4-chloro-2-phenylpyridine (15a) according to TP3:



According to **TP3**, the substituted pyridine **15a** was prepared from 1 mmol of **14a** with 1.2 mmol of **6a** (1.7 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 6:1 + 0.5% NEt_3) furnished **15a** as light yellow oil (152 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.21 - 7.29 (m, 1 H), 7.41 - 7.57 (m, 3 H), 7.74 (dd, *J*=1.94, 0.55 Hz, 1 H), 7.90 - 8.08 (m, 2 H), 8.59 (dd, *J*=5.25, 0.55 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 120.8, 122.3, 127.0, 128.9, 129.6, 138.1, 144.74, 150.5, 159.0
MS (70 eV, EI) m/z (%): 189 (51) $[M]^+$, 188 (14), 154 (27), 127 (12), 70 (11), 43 (100).
IR ATR ν (cm^{-1}): 3044, 2358, 1571, 1549, 1497, 1462, 1442, 1382, 1112, 1096, 1072, 1053, 872, 823, 802, 771, 728, 703, 690, 668, 659.
HRMS (EI) for **$C_{11}H_8ClN$** (189.0345) $[M]^+$: 189.0337.

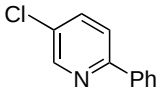
Synthesis of 3-chloro-2-phenylpyridine (15b) according to TP3:



According to **TP3**, the substituted pyridine **15b** was prepared from 1 mmol of **14b** with 1.2 mmol of **2a** (1.7 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 6:1 + 0.5% NEt_3) furnished **15b** as light yellow oil (144 mg, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.22 (dd, *J*=8.02, 4.70 Hz, 1 H), 7.43 - 7.53 (m, 3 H), 7.72 - 7.84 (m, 3 H), 8.61 (dd, *J*=4.70, 1.38 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 123.0, 128.0, 128.8, 129.3, 130.2, 138.1, 138.2, 147.6, 156.6.
MS (70 eV, EI) m/z (%): 189 (22), 154 (50), 61 (18), 43 (100).
IR ATR ν (cm^{-1}): 3057, 3042, 2362, 1570, 1553, 1496, 1450, 1431, 1415, 1222, 1181, 1131, 1089, 1075, 1031, 1016, 1002, 974, 918, 794, 786, 761, 737, 694, 681, 668, 659, 654.
HRMS (EI) for **$C_{11}H_8ClN$** (189.0345) $[M]^+$: 189.0344.

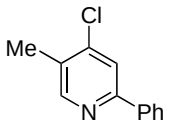
Synthesis of 5-chloro-2-phenylpyridine (15c) according to TP3:



According to **TP3**, the substituted pyridine **15c** was prepared from 1 mmol of **14c** with 1.2 mmol of **2a** (1.7 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 6:1 + 0.5% NEt_3) furnished **15c** as white crystals (165 mg, 87%).

m.p.: 65.8 - 67.8 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.42 - 7.52 (m, 3 H), 7.66 - 7.69 (m, 1 H), 7.71 - 7.74 (m, 1 H), 7.95 - 8.01 (m, 2 H), 8.65 (dd, *J*=2.34, 0.78 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 121.1, 126.8, 128.9, 129.3, 130.6, 136.5, 138.2, 148.5, 155.5.
MS (70 eV, EI) m/z (%): 191 (33), 189 (100), 154 (41), 127 (13).
IR ATR ν (cm^{-1}): 3062, 3037, 2360, 1574, 1554, 1460, 1456, 1442, 1436, 1419, 1365, 1290, 1136, 1112, 1074, 1022, 1007, 991, 979, 929, 920, 853, 834, 774, 755, 730, 707, 690, 676, 672, 668, 663, 658, 655, 653.
HRMS (EI) for **$C_{11}H_8ClN$** (189.0345) $[M]^+$: 189.0340.

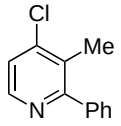
Synthesis of 4-chloro-5-methyl-2-phenylpyridine (15d) according to TP3:



According to **TP3**, the substituted pyridine **15d** was prepared from 1 mmol of **14d** with 1.2 mmol of **2a** (3.0 M) at 25 °C for 15 min. Flash column chromatography (0-40% MTBE/heptane) furnished **15d** as colorless oil (173 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.39 (s, 3H), 7.37 - 7.53 (m, 3H), 7.71 (s, 1H), 7.90 - 8.01 (m, 2H), 8.50 (s, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 16.5, 120.7, 126.7, 128.8, 129.2, 130.2, 138.2, 144.7, 151.1, 156.6.
MS (70 eV, EI) m/z (%): 217 (8), 206 (33), 204 (100), 202 (2).
HRMS (EI) for **$C_{12}H_{10}ClN$** (203.0502) $[M]^+$: 203.0505.

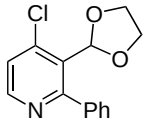
Synthesis of 4-chloro-3-methyl-2-phenylpyridine (15e) according to TP3:



According to **TP3**, the substituted pyridine **15e** was prepared from 1 mmol of **14e** with 1.2 mmol of **2a** (3.0 M) at 25 °C for 15 min. Flash column chromatography (0-40% MTBE/heptane) furnished **15e** as colorless oil (179 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.38 (s, 3H), 7.30 (d, J=5.3 Hz, 1H), 7.33 - 7.52 (m, 5H), 8.41 (d, J=5.3 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 17.2, 123.0, 128.2, 128.3, 129.0, 129.8, 140.1, 145.4, 147.0, 160.6.
MS (70 eV, EI) m/z (%): 225 (4), 206 (35), 204 (100).
HRMS (EI) for **$C_{12}H_{10}ClN$** (203.0502) $[M]^+$: 203.0512.

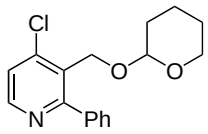
Synthesis of 4-chloro-3-(1,3-dioxolan-2-yl)-2-phenylpyridine (15f) according to TP3:



According to **TP3**, the substituted pyridine **15f** was prepared from 1 mmol of **14f** with 1.2 mmol of **2a** (1.7 M) at 25 °C for 30 min. Flash column chromatography (*i*-hexane/ethyl acetate 4:1 + 0.5% NEt_3) furnished **15f** as white solid (175 mg, 67%).

m.p.: 59.3 - 61.0 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.85 - 4.02 (m, 2 H), 4.02 - 4.20 (m, 2 H), 5.97 (s, 1 H), 7.30 - 7.67 (m, 6 H), 8.54 (d, *J*=5.25 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 65.8, 101.4, 125.0, 127.5, 128.0, 128.5, 129.4, 139.1, 145.2, 149.9, 162.1.
MS (70 eV, EI) m/z (%): 218 (30), 216 (89), 191 (33), 189 (100), 183 (26), 154 (47).
IR ATR ν (cm^{-1}): 2971, 2894, 2362, 1559, 1552, 1452, 1446, 1379, 1222, 1171, 1103, 1057, 1018, 973, 962, 938, 922, 862, 844, 838, 810, 792, 771, 763, 724, 707, 702, 685, 673, 668, 661, 656, 653.
HRMS (EI) for **$C_{14}H_{12}ClNO_2$** (261.0557) $[M]^+$: 261.0554.

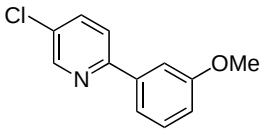
Synthesis of 4-chloro-2-phenyl-3-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)pyridine (15g) according to TP3:



According to **TP3**, the substituted pyridine **15g** was prepared from 1 mmol of **14g** with 1.2 mmol of **2a** (1.7 M) at 25 °C for 30 min. Flash column chromatography (*i*-hexane/ethyl acetate 4:1 + 0.5% NEt_3) furnished **15g** as colorless oil (231 mg, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.52 - 1.92 (m, 6 H), 3.46 - 3.55 (m, 1 H), 3.79 - 3.90 (m, 1 H), 4.39 (d, *J*=10.50 Hz, 1 H), 4.77 (t, *J*=3.04 Hz, 1 H), 4.83 (d, *J*=10.50 Hz, 1 H), 7.36 (d, *J*=5.25 Hz, 1 H), 7.41 - 7.51 (m, 3 H), 7.62 - 7.71 (m, 2 H), 8.52 (d, *J*=5.25 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 18.9, 25.4, 30.4, 61.7, 64.6, 99.0, 123.6, 128.1, 128.7, 129.2, 129.3, 139.4, 146.8, 149.3, 162.1.
MS (70 eV, EI) m/z (%): 219 (16), 204 (30), 202 (100), 167 (14), 85 (33).
IR ATR ν (cm^{-1}): 2940, 2894, 2362, 2338, 1560, 1548, 1496, 1452, 1438, 1410, 1378, 1348, 1200, 1182, 1174, 1131, 1118, 1103, 1076, 1068, 1055, 1037, 1022, 1001, 989, 962, 938, 922, 905, 890, 869, 843, 837, 818, 816, 810, 793, 779, 757, 732, 730, 724, 700, 686, 668, 653.
HRMS (EI) for **$C_{17}H_{18}ClNO_2$** (303.1026) $[M]^+$: 303.0949.

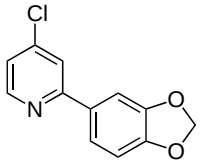
Synthesis of 5-chloro-2-(3-methoxyphenyl)pyridine (15h) according to TP3:



According to **TP3**, the substituted pyridine **15h** was prepared from 1 mmol of **14c** with 1.2 mmol of **6n** (1.24 M) at 25 °C for 30 min. Flash column chromatography (*i*-hexane/Et_2O 9:1 + 0.5% NEt_3) furnished **15h** as white solid (156 mg, 71%).

m.p.: 60.2 - 62.8 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.90 (s, 3 H), 6.99 (dd, *J*=8.16, 2.63 Hz, 1 H), 7.39 (t, *J*=8.02 Hz, 1 H), 7.49 - 7.59 (m, 2 H), 7.64 - 7.75 (m, 2 H), 8.64 (d, *J*=2.49 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.4, 112.0, 115.3, 119.1, 121.2, 129.8, 130.7, 136.4, 139.6, 148.4, 155.3, 160.1.
MS (70 eV, EI) m/z (%): 219 (66), 190 (50), 176 (11), 154 (50), 141 (36), 113 (17).
IR ATR ν (cm^{-1}): 3002, 2956, 2834, 2360, 2331, 1608, 1586, 1575, 1554, 1471, 1459, 1430, 1370, 1365, 1302, 1292, 1227, 1219, 1208, 1182, 1176, 1168, 1111, 1053, 1035, 1010, 894, 889, 885, 876, 858, 855, 848, 840, 836, 824, 791, 755, 749, 689, 668.
HRMS (EI) for **$C_{12}H_{10}ClNO$** (219.0451) $[M]^+$: 219.0435.

Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-6-chloroquinoline (15i) according to TP3:



According to **TP3**, the substituted pyridine **15i** was prepared from 1 mmol of **14a** with 1.2 mmol of **6c** (1.08 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 8:1 + 0.5% NEt_3) furnished **15i** as white solid (179 mg, 77%).

m.p.: 108.5 - 111.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.03 (s, 2 H), 6.90 (d, *J*=8.02 Hz, 1 H), 7.19 (dd, *J*=5.25, 1.94 Hz, 1 H), 7.45 - 7.53 (m, 2 H), 7.63 (d, *J*=1.94 Hz, 1 H), 8.53 (d, *J*=5.25 Hz, 1 H).

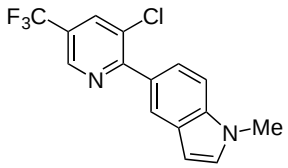
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 101.4, 107.3, 108.5, 120.2, 121.2, 121.8, 132.5, 144.6, 148.4, 149.0, 150.3, 158.4.

MS (70 eV, EI) m/z (%): 233 (100), 140 (19), 113 (13).

IR ATR ν (cm^{-1}): 2894, 2359, 1573, 1550, 1500, 1493, 1462, 1442, 1378, 1351, 1278, 1257, 1216, 1114, 1108, 1037, 934, 888, 869, 865, 861, 834, 815, 811, 780, 734, 719, 717, 701, 686, 684, 668.

HRMS (EI) for **$C_{12}H_8ClNO_2$** (233.0244) $[M]^+$: 233.0244.

Synthesis of 5-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-1-methyl-1H-indole (15j) according to TP3:



According to **TP3**, the substituted pyridine **15j** was prepared from 1 mmol of **14h** with 1.2 mmol of **6o** (1.02 M) at 50 °C for 1 h. Flash column chromatography (*i*-hexane/ethyl acetate 6:1 + 0.5% NEt_3) furnished **15j** as beige solid (174 mg, 56%).

m.p.: 83.9 - 85.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.85 (s, 3 H), 6.60 (d, *J*=3.04 Hz, 1 H), 7.13 (d, *J*=3.04 Hz, 1 H), 7.44 (d, *J*=8.57 Hz, 1 H), 7.68 (dd, *J*=8.85, 1.66 Hz, 1 H), 8.08 (dd, *J*=18.94, 2.07 Hz, 2 H), 8.87 (d, *J*=1.94 Hz, 1 H).

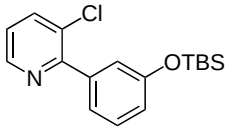
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 33.0, 102.1, 108.9, 122.8, 123.0, 123.0, 125.1 (q, J=33.59 Hz), 128.1, 128.2, 129.9, 130.1, 135.2 (q, J=3.42 Hz, 1 C), 137.2, 144.0 (q, J=3.99 Hz), 161.2.

MS (70 eV, EI) m/z (%): 310 (100), 275 (16), 111 (13), 97 (16), 85 (15).

IR ATR ν (cm^{-1}): 2923, 2853, 2357, 1596, 1485, 1455, 1443, 1437, 1325, 1310, 1293, 1288, 1280, 1271, 1243, 1232, 1220, 1202, 1188, 1181, 1153, 1133, 1118, 1109, 1093, 1066, 1027, 1004, 1003, 949, 941, 937, 931, 916, 899, 887, 884, 871, 848, 839, 825, 814, 809, 793, 783, 771, 766, 758, 752, 735, 730, 724, 718, 708, 693, 681, 676, 668, 660, 652.

HRMS (EI) for **$C_{15}H_{10}ClF_3N_2$** (310.0485) $[M]^+$: 310.0472.

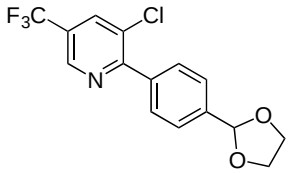
Synthesis of 2-(3-((tert-butyldimethylsilyl)oxy)phenyl)-3-chloropyridine (15k) according to TP3:



According to **TP3**, the substituted pyridine **15k** was prepared from 1 mmol of **14b** with 1.2 mmol of **6g** (1.11 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/Et_2O 9:1) furnished **15k** as colorless oil (262 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.24 (s, 6 H), 1.01 (s, 9 H), 6.93 (dt, *J*=7.26, 2.18 Hz, 1 H), 7.17 - 7.25 (m, 2 H), 7.28 - 7.38 (m, 2 H), 7.79 (dd, *J*=8.02, 1.66 Hz, 1 H), 8.59 (dd, *J*=4.56, 1.52 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: -4.38, 18.2, 25.7, 120.5, 121.1, 122.3, 123.0, 129.1, 130.1, 138.0, 139.5, 147.5, 155.2, 156.4.
MS (70 eV, EI) m/z (%): 319 (13), 264 (38), 262 (100), 226 (9).
IR ATR ν (cm^{-1}): 2955, 2928, 2857, 2360, 2338, 1602, 1581, 1570, 1486, 1471, 1462, 1439, 1419, 1415, 1406, 1306, 1272, 1259, 1251, 1243, 1227, 1199, 1130, 1029, 1001, 937, 884, 830, 816, 791, 778, 760, 723, 696, 685, 677, 668, 662.
HRMS (EI) for **$C_{17}H_{22}ClNOSi$** (319.1159) $[M]^+$: 319.1154.

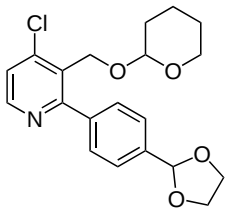
Synthesis of 2-(4-(1,3-dioxolan-2-yl)phenyl)-3-chloro-5-(trifluoromethyl)pyridine (15l) according to TP3:



According to **TP3**, the substituted pyridine **15l** was prepared from 1 mmol of **14h** with 1.2 mmol of **6p** (1.08 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 8:1 + 0.5% NEt_3) furnished **15l** as white solid (233 mg, 71%).

m.p.: 72.4 - 74.0 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 4.02 - 4.22 (m, 4 H), 5.92 (s, 1 H), 7.63 (m, 2 H), 7.80 (m, 2 H), 8.05 (d, *J*=1.36 Hz, 1 H), 8.85 (dd, *J*=2.05, 0.88 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 65.3, 103.2, 122.7 (q, J=272.93 Hz), 126.1 (q, J=33.59 Hz), 126.3, 129.5, 130.3, 135.3 (q, J=3.65 Hz), 137.7, 139.5, 144.2 (q, J=4.03 Hz), 159.5 (q, J=1.54 Hz).
MS (70 eV, EI) m/z (%): 329 (19), 328 (69), 286 (16), 271 (14), 257 (100), 222 (81), 73 (62).
IR ATR ν (cm^{-1}): 2899, 2361, 2339, 1599, 1380, 1324, 1309, 1216, 1153, 1119, 1093, 1081, 1069, 1028, 1014, 988, 981, 970, 957, 941, 911, 858, 843, 835, 824, 768, 735, 731, 695, 685.
HRMS (EI) for **$C_{15}H_{11}ClF_3NO_2$** (329.0430) $[M]^+$: 328.0355.

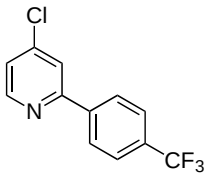
Synthesis of 2-(4-(1,3-dioxolan-2-yl)phenyl)-4-chloro-3-(((tetrahydro-2H-pyran-2-yl)oxy)-methyl)-pyridine (15m) according to TP3:



According to **TP3**, the substituted pyridine **15m** was prepared from 1 mmol of **14g** with 1.2 mmol of **6p** (1.08 M) at 25 °C for 30 min. Flash column chromatography (*i*-hexane/ethyl acetate 3:1 + 0.5% NEt_3) furnished **15m** as colorless oil (248 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.51 - 1.90 (m, 6 H), 3.45 - 3.60 (m, 1 H), 3.78 - 3.95 (m, 1 H), 3.99 - 4.22 (m, 4 H), 4.37 (d, *J*=10.78 Hz, 1 H), 4.73 - 4.91 (m, 2 H), 5.90 (s, 1 H), 7.36 (d, *J*=5.25 Hz, 1 H), 7.57 (m, 2 H), 7.71 (m, 2 H), 8.52 (d, *J*=5.25 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 19.0, 25.4, 30.4, 61.8, 64.5, 65.3, 99.0, 103.4, 123.6, 126.2, 129.3, 129.4, 138.5, 140.2, 146.9, 149.3, 161.7.
MS (70 eV, EI) m/z (%): 291 (25), 274 (40), 230 (13), 202 (36), 166 (16), 73 (100).
IR ATR ν (cm^{-1}): 2941, 2884, 2366, 2334, 1561, 1548, 1446, 1412, 1385, 1363, 1349, 1200, 1182, 1130, 1117, 1078, 1064, 1053, 1036, 1023, 989, 966, 941, 905, 890, 880, 869, 824, 816, 788, 775, 754, 729, 712, 710, 707, 693, 689, 687, 685, 681, 675, 668, 659, 658, 654.
HRMS (EI) for **$C_{20}H_{22}ClNO_4$** (375.1237) $[M]^+$: 374.1157.

Synthesis of 4-chloro-2-(4-(trifluoromethyl)phenyl)pyridine (15n) according to TP3:

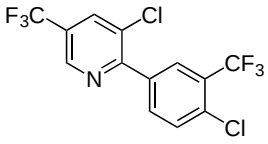


According to **TP3**, the substituted pyridine **15n** was prepared from 1 mmol of **14a** with 1.2 mmol of **6c** (0.98 M) at 25 °C for 30 min. Flash column chromatography (*i*-hexane/diethyl ether 9:1) furnished **15n** as white crystals (237 mg, 92%).

m.p.: 44.9 - 46.6 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.31 (dd, *J*=5.25, 1.11 Hz, 1 H), 7.69 - 7.80 (m, 3 H), 8.05 - 8.16 (m, 2 H), 8.62 (d, *J*=5.25 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 121.2, 123.1, 124.0 (q, J=272.35 Hz), 125.8 (q, J=3.65 Hz), 127.3, 131.4 (q, J=32.54 Hz), 141.4 (q, J=1.40 Hz), 145.0, 150.7, 157.3.
MS (70 eV, EI) m/z (%): 257 (100), 222 (50), 202 (12), 188 (15), 43 (47).
IR ATR ν (cm^{-1}): 2366, 2334, 1617, 1572, 1549, 1380, 1323, 1315, 1265, 1168, 1105, 1095, 1069, 1047, 1013, 988, 977, 956, 849, 840, 829, 818, 785, 765, 750, 739, 728, 706, 690, 668, 662.

HRMS (EI) for **$C_{12}H_7ClF_3N$:** (257.0219) $[M]^+$: 257.0211.

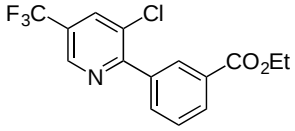
Synthesis of 3-chloro-2-(4-chloro-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)pyridine (15o) according to TP3:



According to **TP3**, the substituted pyridine **15o** was prepared from 1 mmol of **14h** with 1.2 mmol of **6q** (0.95 M) at 25 °C for 30 min. Flash column chromatography (*i*-hexane/ethyl acetate 15:1) furnished **15o** as colorless oil (239 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.65 (d, *J*=8.02 Hz, 1 H), 7.95 (dd, *J*=8.57, 2.21 Hz, 1 H), 8.09 (d, *J*=1.94 Hz, 1 H), 8.17 (d, *J*=1.94 Hz, 1 H), 8.88 (s, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 122.5 (q, J=273.20 Hz), 122.6 (q, J=273.48 Hz), 126.9 (q, J=33.94 Hz), 128.6 (q, J=31.70 Hz), 128.9 (q, J=5.33 Hz), 130.2, 131.3, 133.6, 133.9 (q, J=1.68 Hz), 135.6, 135.7 (q, J=3.65 Hz), 144.5 (q, J=3.93 Hz), 157.1 (q, J=1.68 Hz).
MS (70 eV, EI) m/z (%): 359 (81), 339 (14), 324 (100), 304 (17), 290 (12).
IR ATR ν (cm^{-1}): 2362, 2342, 1602, 1487, 1456, 1413, 1380, 1329, 1315, 1295, 1278, 1260, 1238, 1214, 1127, 1113, 1099, 1079, 1038, 1031, 910, 873, 836, 813, 766, 737, 718, 665.
HRMS (EI) for **$C_{13}H_5Cl_2F_6N$** (358.9703) $[M]^+$: 358.9690.

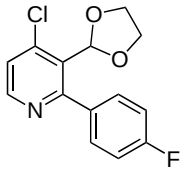
Synthesis of ethyl 3-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)benzoate (15p) according to TP3:



According to **TP3**, the substituted pyridine **15p** was prepared from 1 mmol of **14h** with 1.2 mmol of **6i** (0.61 M) at 25 °C for 15 min. Flash column chromatography (*i*-hexane/ethyl acetate 9:1 + 0.5% NEt_3) furnished **15p** as light yellow oil (231 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.41 (t, *J*=7.19 Hz, 3 H), 4.42 (q, *J*=7.19 Hz, 2 H), 7.59 (t, *J*=7.88 Hz, 1 H), 7.96 (dt, *J*=7.74, 1.52 Hz, 1 H), 8.07 (d, *J*=2.21 Hz, 1 H), 8.18 (dt, *J*=7.95, 1.42 Hz, 1 H), 8.46 (t, *J*=1.80 Hz, 1 H), 8.87 (d, *J*=1.11 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.3, 61.2, 122.6 (q, J=272.92 Hz), 126.4 (q, J=33.66 Hz), 128.3, 130.3, 130.6, 130.7, 130.7, 133.6, 135.4 (q, J=3.65 Hz), 137.2, 144.3 (q, J=3.39 Hz), 158.9 (q, J=1.40 Hz), 166.1
MS (70 eV, EI) m/z (%): 329 (33), 301 (22), 284 (100), 257 (55), 221 (15).
IR ATR ν (cm^{-1}): 2982, 2367, 2335, 1718, 1717, 1600, 1368, 1322, 1312, 1285, 1249, 1223, 1214, 1160, 1131, 1093, 1082, 1075, 1036, 1020, 1001, 912, 847, 820, 741, 710, 693, 668, 662.
HRMS (EI) for **$C_{15}H_{11}ClF_3NO_2$** (329.0430) $[M]^+$: 329.0419.

Synthesis of 4-chloro-3-(1,3-dioxolan-2-yl)-2-(4-fluorophenyl)pyridine (15q) according to TP3:



According to **TP3**, the substituted pyridine **15q** was prepared from 1 mmol of **14f** with 1.2 mmol of **6r** (1.0 M) at 25 °C for 30 min. Flash column chromatography (*i*-hexane/ethyl acetate 4:1 + 0.5% NEt_3) furnished **15q** as white crystals (221 mg, 79%).

m.p.: 76.2 - 79.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.88 - 4.13 (m, 4 H), 5.95 (s, 1 H), 7.06 - 7.20 (m, 2 H), 7.36 (d, *J*=5.25 Hz, 1 H), 7.45 - 7.60 (m, 2 H), 8.52 (d, *J*=5.25 Hz, 1 H).

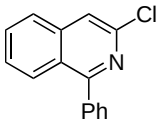
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 65.8, 101.3, 114.8, 115.1, 125.0, 127.5, 131.3, 131.4, 135.2, 135.2, 145.3, 149.8, 161.0, 161.4, 164.6.

MS (70 eV, EI) m/z (%): 236 (29), 234 (84), 220 (11), 207 (100), 183 (42), 171 (22), 144 (17).

IR ATR ν (cm^{-1}): 2983, 2899, 2360, 2344, 1603, 1564, 1556, 1511, 1457, 1381, 1234, 1224, 1213, 1179, 1159, 1154, 1102, 1096, 1057, 1019, 1013, 984, 971, 958, 940, 883, 846, 832, 821, 776, 726, 720, 691, 668.

HRMS (EI) for **$C_{14}H_{11}ClFNO_2$** (279.0462) $[M]^+$: 278.0372.

Synthesis of 3-chloro-1-phenylisoquinoline (15r) according to TP6:



According to **TP6**, the substituted isoquinoline **15r** was prepared from 1 mmol of **14j** with 1.2 mmol of **6a** (1.7 M) at 25 °C for 1 h. Flash column chromatography (*i*-hexane/ethyl acetate 3:1 + 0.5% NEt_3) furnished **15r** as light yellow solid (170 mg, 71%).

m.p.: 75.9 - 77.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.47 - 7.60 (m, 4 H), 7.67 - 7.75 (m, 4 H), 7.79 - 7.84 (m, 1 H), 8.10 (d, *J*=8.57 Hz, 1 H).

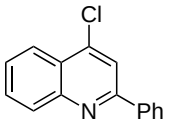
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 118.9, 125.5, 126.3, 127.3, 127.8, 128.4, 129.1, 130.0, 130.9, 138.2, 139.0, 144.8, 161.5.

MS (70 eV, EI) m/z (%): 239 (100), 202 (71), 176 (18), 151 (15), 101 (17).

IR ATR ν (cm^{-1}): 3054, 3028, 2363, 2331, 1616, 1572, 1570, 1560, 1558, 1542, 1489, 1443, 1430, 1396, 1385, 1376, 1359, 1319, 1307, 1269, 1215, 1147, 1077, 1069, 1028, 999, 978, 974, 964, 922, 874, 854, 850, 799, 766, 757, 749, 724, 698, 677, 668, 658, 653.

HRMS (EI) for **$C_{15}H_{10}ClN$** (239.0502) $[M]^+$: 239.0477.

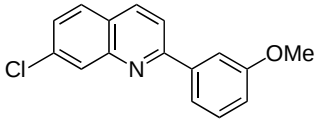
Synthesis of 4-chloro-2-phenylquinoline (15s) according to TP6:



According to **TP6**, the substituted quinoline **15s** was prepared from 1 mmol of **14k** with 1.2 mmol of **6a** (3.00 M) at 25 °C for 1 h. Flash column chromatography (0-80% ethyl acetate /heptane) furnished **15s** as white solid (167 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.43 - 7.68 (m, 4H), 7.77 (ddd, *J*=8.4, 6.9, 1.5 Hz, 1H), 7.96 (s, 1H), 8.07 - 8.28 (m, 4H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 119.1, 124.0, 125.3, 127.2, 127.5, 128.9, 129.8, 130.2, 130.6, 138.6, 143.1, 149.2, 157.3.
MS (70 eV, EI) m/z (%): 243 (5), 242 (32), 241 (18), 240 (100).
IR ATR ν (cm^{-1}): 3060, 3020, 2363, 2331, 1625, 1570, 1500, 1443, 1319, 1250, 1052, 1021, 982, 964, 920, 870, 854, 799, 677.
HRMS (EI) for **$C_{15}H_{10}ClN$** (239.0502) $[M]^+$: 239.0508.

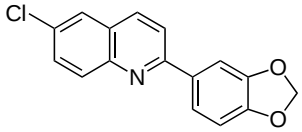
Synthesis of 7-chloro-2-(3-methoxyphenyl)quinoline (15t) according to TP3:



According to **TP3**, the substituted quinoline **15t** was prepared from 1 mmol of **14l** with 1.2 mmol of **6n** (1.24 M) at 25 °C for 2 h. Flash column chromatography (*i*-hexane/ethyl acetate 9:1 + 0.5% NEt_3) furnished **15t** as white solid (194 mg, 72%).

m.p.: 66.2 - 67.5 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.94 (s, 3 H), 7.04 (ddd, *J*=6.91, 1.66, 1.38 Hz, 1 H), 7.41 - 7.51 (m, 2 H), 7.68 - 7.80 (m, 3 H), 7.86 (d, *J*=8.29 Hz, 1 H), 8.12 - 8.22 (m, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 55.4, 112.7, 115.7, 119.2, 120.0, 125.6, 127.3, 128.6, 128.7, 129.8, 135.4, 136.5, 140.6, 148.6, 158.0, 160.2.
MS (70 eV, EI) m/z (%): 269 (71), 268 (100), 239 (45), 204 (12), 190 (16).
IR ATR ν (cm^{-1}): 2940, 2920, 2830, 2359, 1611, 1597, 1587, 1557, 1545, 1483, 1469, 1456, 1436, 1329, 1308, 1292, 1278, 1241, 1218, 1188, 1183, 1157, 1152, 1133, 1087, 1069, 1046, 1037, 997, 927, 880, 871, 849, 837, 806, 778, 766, 692, 674, 668, 659.
HRMS (EI) for **$C_{16}H_{12}ClNO$** (269.0607) $[M]^+$: 268.0524.

Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-6-chloroquinoline (15u) according to TP6:



According to **TP6**, the substituted quinoline **15u** was prepared from 1 mmol of **14m** with 1.2 mmol of **6e** (1.08 M) at 25 °C for 1 h. Flash column chromatography (*i*-hexane/ethyl acetate 8:1 + 0.5% NEt_3) furnished **15u** as white solid (232 mg, 82%).

m.p.: 159.2 - 160.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 6.05 (s, 2 H), 6.95 (d, *J*=8.02 Hz, 1 H), 7.64 (ddd, *J*=8.71, 2.35, 2.21 Hz, 2 H), 7.70 - 7.83 (m, 3 H), 8.06 (dd, *J*=8.71, 2.63 Hz, 2 H).

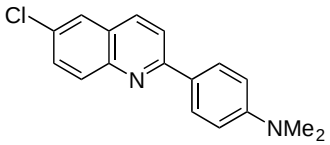
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 101.4, 107.8, 108.5, 119.3, 121.7, 126.1, 127.5, 130.5, 131.1, 131.6, 133.6, 135.7, 146.5, 148.4, 149.0, 156.8.

MS (70 eV, EI) m/z (%): 283 (100), 225 (14), 190 (25), 44 (20).

IR ATR ν (cm^{-1}): 2903, 2366, 2336, 1593, 1548, 1507, 1499, 1481, 1455, 1438, 1351, 1329, 1293, 1287, 1256, 1241, 1214, 1190, 1145, 1120, 1111, 1072, 1036, 948, 936, 924, 913, 894, 881, 861, 830, 824, 815, 809, 788, 775, 724, 706, 653.

HRMS (EI) for **$C_{16}H_{10}ClNO_2$** (283.0400) $[M]^+$: 283.0389.

Synthesis of 4-(6-chloroquinolin-2-yl)-N,N-dimethylaniline (15v) according to TP3:



According to **TP3**, the substituted quinoline **15v** was prepared from 1 mmol of **14m** with 1.2 mmol of **6b** (1.17 M) at 25 °C for 3 h. Flash column chromatography (*i*-hexane/ethyl acetate 8:1 + 0.5% NEt_3) furnished **15v** as beige solid (199 mg, 71%).

m.p.: 188.0 - 188.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.06 (s, 6 H), 6.84 (d, *J*=9.12 Hz, 2 H), 7.61 (dd, *J*=8.98, 2.35 Hz, 1 H), 7.75 (d, *J*=2.49 Hz, 1 H), 7.84 (d, *J*=8.85 Hz, 1 H), 7.97 - 8.15 (m, 4 H).

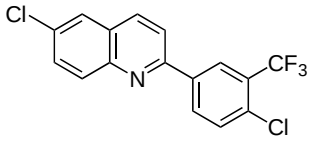
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 40.3, 112.2, 119.0, 126.0, 126.9, 127.2, 128.4, 130.2, 130.8, 130.8, 135.3, 146.8, 151.5, 157.5.

MS (70 eV, EI) m/z (%): 282 (100), 281 (47), 266 (9), 238 (11).

IR ATR ν (cm^{-1}): 2915, 2830, 2366, 1613, 1597, 1539, 1484, 1470, 1457, 1437, 1330, 1310, 1288, 1279, 1240, 1231, 1220, 1202, 1188, 1168, 1157, 1152, 1133, 1067, 1062, 1046, 1037, 949, 941, 930, 882, 871, 849, 838, 825, 809, 794, 778, 767, 760, 757, 693, 681, 675, 668.

HRMS (EI) for **$C_{17}H_{15}ClN_2$** (282.0924) $[M]^+$: 282.0921.

Synthesis of 6-chloro-2-(4-chloro-3-(trifluoromethyl)phenyl)quinoline (15w) according to TP6:



According to **TP6**, the substituted quinoline **15w** was prepared from 1 mmol of **14m** with 1.2 mmol of **6q** (0.95 M) at 25 °C for 1 h. Flash column chromatography (*i*-hexane/ethyl acetate 12:1 + 0.5% NEt_3) furnished **15w** as white solid (299 mg, 87%).

m.p.: 118.8 - 121.7 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 7.62 - 7.73 (m, 2 H), 7.82 (d, *J*=2.21 Hz, 1 H), 7.87 (d, *J*=8.57 Hz, 1 H), 8.10 (d, *J*=8.85 Hz, 1 H), 8.17 (d, *J*=8.29 Hz, 1 H), 8.26 (dd, *J*=8.29, 2.21 Hz, 1 H), 8.54 (d, *J*=2.21 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 118.9, 122.8 (q, J=273.30 Hz), 126.2, 126.5 (q, J=5.41 Hz), 127.9, 128.7, 128.9 (q, J=31.60 Hz), 131.0, 131.3, 131.9, 132.7, 133.5 (q, J=1.71 Hz), 136.3, 137.9, 146.5, 154.5.

MS (70 eV, EI) m/z (%): 341 (100), 308 (10), 306 (28), 286 (14), 272 (12).

IR ATR ν (cm^{-1}): 2926, 2860, 2360, 2331, 1595, 1476, 1411, 1328, 1321, 1315, 1276, 1259, 1251, 1236, 1164, 1155, 1133, 1123, 1113, 1075, 1056, 1034, 948, 904, 899, 874, 848, 827, 811, 781, 775, 729, 675, 668, 664, 658.

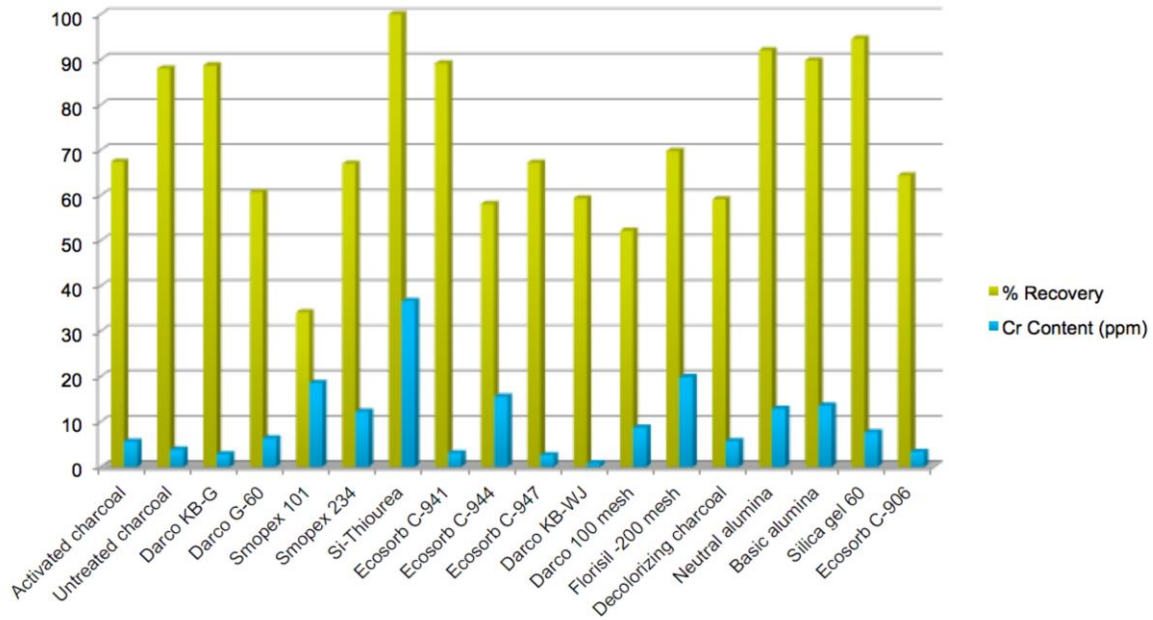
HRMS (EI) for **$C_{16}H_8Cl_2F_3N$:** (340.9986) $[M]^+$: 340.9969.

3.4 TREATMENT OF PYRIDINE 14A WITH SCAVENGERS TO EVALUATE RECOVERY AND CHROMIUM LEVELS PRIOR TO CHROMATOGRAPHY

A constant volume of the organic layer (50 µL) from the crude reaction mixture or the solution containing the scavenger-treated organic layer was diluted into 10 mL (1:1 acetonitrile: water) and HPLC area under the curve (AUC) was recorded. Recovery was based on the ratio of the AUC for the treated material to the untreated material.

Scavenger	HPLC AUC	AUC Treated/ AUC Crude	% Recovery **3a**	Cr Content (ppm)
Activated charcoal	600	0,67	67	5,6
Untreated charcoal	783	0,88	88	3,8
Darco KB-G	789	0,89	89	2,8
Darco G-60	540	0,61	61	6,3
Smopex 101	304	0,34	34	18,5
Smopex 234	596	0,67	67	12,2
Si-Thiourea	890	1,00	100	36,6

Ecosorb C-941	793	0,89	89	3
Ecosorb C-944	517	0,58	58	15,5
Ecosorb C-947	598	0,67	67	2,6
Darco KB-WJ	528	0,59	59	0,8
Darco 100 mesh	464	0,52	52	8,7
Florisil -200 mesh	621	0,70	70	19,8
Decolorizing charcoal	526	0,59	59	5,7
Neutral alumina	819	0,92	92	12,8
Basic alumina	799	0,90	90	13,5
Silica gel 60	842	0,95	95	7,6
Ecosorb C-906	573	0,64	64	3,3
Crude Reaction	890	1,00		



4. CHROMIUM(II)-CATALYZED AMINATION OF *N*-HETEROCYCLIC CHLORIDES WITH MAGNESIUM AMIDES

4.1 STARTING MATERIALS SYNTHESIS

Starting materials **16a-i** are commercially available.
Amines **18a-k** are commercially available and were previously distilled and stored under argon before use.

4.2 GENERAL PROCEDURES

4.2.1 Typical procedure for the formation of magnesium amides (**TP8**)

A dry and argon flushed Schlenk-tube was charged with the appropriate amine (2 equiv) and *i*-PrMgCl·LiCl (2 equiv, 1.2 M solution in THF) was added dropwise at 0 °C. This reaction mixture was warmed to room temperature (23 °C) and stirred for approximately 1 h at this temperature in order to get full conversion to the magnesium amide.

4.2.2 Typical procedure for the Cr-catalyzed amination with $CrCl_2$ (**TP9**)

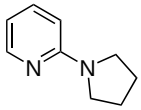
The solution of the magnesium amide previously prepared according to **TP8** was transferred via syringe to a second dry and argon-flushed Schlenk-tube, containing the *N*-heterocyclic halide in THF (1 equiv, 2 M in THF) and water-free $CrCl_2$ (0.1 equiv) at 23 °C. The resulting reaction mixture was stirred at 50 °C until the *N*-heterocyclic halide was consumed. The solvent was evaporated *in* vacuo and the crude product was purified on silica gel to afford the desired product.

4.2.3 Typical procedure for the Cr-catalyzed amination with $Cr(acac)_3$ (**TP10**)

The solution of the magnesium amide previously prepared according to **TP8** was transferred via syringe to a second dry and argon-flushed Schlenk-tube, containing the *N*-heterocyclic halide in THF (1 equiv, 2 M in THF) and $Cr(acac)_3$ (0.1 equiv) at 23 °C. The resulting reaction mixture was stirred at 50 °C until the *N*-heterocyclic halide was consumed. The solvent was evaporated *in* vacuo and the crude product was purified on silica gel to afford the desired product.

4.3 PREPARATION OF THE SYNTHESIZED AMINATED *N*-HETEROCYCLES

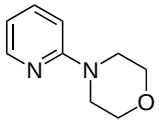
Synthesis of 2-(pyrrolidin-1-yl)pyridine (19a) according to TP9:



According to **TP9**, the substituted pyridine **19a** was prepared from 1 mmol of **16a** (113 mg) with 2 mmol of **17a** (1 M from 142 mg of pyrrolidine) at 50 °C for 3 h. Flash column chromatography (*i*-hexane/diethyl ether 8:2 + 2% NEt_3) furnished **19a** as colorless oil (140 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.97 - 2.04 (m, 4 H), 3.40 - 3.50 (m, 4 H), 6.30 - 6.38 (m, 1 H), 6.46 - 6.54 (m, 1 H), 7.37 - 7.46 (m, 1 H), 8.11 - 8.20 (m, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 25.5 (2 C), 46.6 (2 C), 106.4, 111.1, 136.8, 148.1, 157.2.
MS (70 eV, EI) m/z (%): 148 (30), 120 (33), 119 (100), 93 (12), 79 (20), 78 (24), 70 (18).
IR ATR ν (cm^{-1}): 2968, 2851, 2361, 1707, 1598, 1555, 1499, 1484, 1444, 1385, 1347, 1300, 1242, 1155, 993, 769, 733, 668, 467.
HRMS (EI) for **$C_9H_{12}N_2$** (148.1000) $[M]^+$: 148.1003.

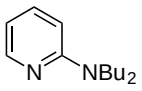
Synthesis of 4-(pyridin-2-yl)morpholine (19b) according to TP9:



According to **TP9**, the substituted pyridine **19b** was prepared from 1 mmol of **16a** (113 mg) with 2 mmol of **17b** (1 M from 174 mg of morpholine) at 50 °C for 12 h. Flash column chromatography (*i*-hexane/diethyl ether 8:2 + 2% NEt_3) furnished **19b** as brown oil (123 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.50 (t, *J*=5,0 Hz, 4 H), 3.83 (t, *J*=5,0 Hz, 4 H), 6.60 - 6.70 (m, 2 H), 7.50 (ddd, *J*=8.7, 7.1, 1.9 Hz, 1 H), 8.18 - 8.24 (m, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 45.6 (2 C), 66.7 (2C), 106.9, 113.8, 137.5, 147.9, 159.5.
MS (70 eV, EI) m/z (%): 164 (86), 163 (53), 134 (14), 133 (89), 119 (29), 107 (50), 106(14), 79 (100), 78 (27).
IR ATR ν (cm^{-1}): 2922, 2854, 1591, 1479, 1435, 1311, 1241, 1116, 1069, 1029, 980, 942, 773, 733.
HRMS (EI) for **$C_9H_{12}N_2O$** (164.0950) $[M]^+$: 164.0937.

Synthesis of N,N-dibutylpyridin-2-amine (19c) according to TP9:



According to **TP9**, the substituted pyridine **19c** was prepared from 1 mmol of **16a** (113 mg) with 2 mmol of **17c** (1 M from 259 mg of dibutylamine) at 50 °C for 5 h. Flash column chromatography (*i*-hexane/diethyl ether 9:1 + 0,5% NEt_3) furnished **19c** as colorless oil (155 mg, 75%).

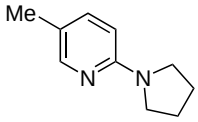
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.97 (t, *J*=7.2 Hz, 6 H), 1.27 - 1.44 (m, 4 H), 1.52 - 1.66 (m, 4 H), 3.44 (dd, *J*=7.5 Hz, 4 H), 6.38 - 6.49 (m, 2 H), 7.38 (ddd, *J*=8.7, 7.0, 1.9 Hz, 1 H), 8.10 - 8.18 (m, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 13.9 (2 C), 20.3 (2 C), 29.8 (2 C), 48.3 (2 C), 105.4, 110.5, 136.7, 148.0, 157.9.

MS (70 eV, EI) m/z (%): 206 (31), 183 (28), 163 (100), 149 (28), 127 (25), 121 (71), 112 (34), 111 (32), 107 (42), 97 (25), 85 (23), 83 (39), 78 (25), 71 (40), 70 (25). 57 (51), 41 (41).

IR ATR ν (cm^{-1}): 2956, 2930, 2872, 2861, 1594, 1558, 1492, 1466, 1439, 1429, 1372, 1324, 1292, 1225, 1189, 1159, 1094, 976, 927, 765, 730.

HRMS (EI) for **$C_{13}H_{22}N_2$** (206.1783) $[M]^+$: 206.1764.

Synthesis of 5-methyl-2-(pyrrolidin-1-yl)pyridine (19d) according to TP9:



According to **TP9**, the substituted pyridine **19d** was prepared from 1 mmol of **16b** (128 mg) with 2 mmol of **17a** (1 M from 142 mg of pyrrolidine) at 50 °C for 24 h. Flash column chromatography (*i*-hexane/diethyl ether 8:2 + 2% NEt_3) furnished **19d** as yellow oil (156 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.93 - 2.02 (m, 4 H), 2.16 (s, 3 H), 3.35 - 3.46 (m, 4 H), 6.27 (d, *J*=8.3 Hz, 1 H), 7.19 - 7.29 (m, 1 H), 7.96 (s, 1 H).

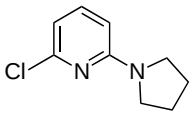
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 17.3, 25.5 (2 C), 46.7 (2 C), 106.1, 119.5, 137.9, 147.7, 155.9.

MS (70 eV, EI) m/z (%): 162 (44), 161 (14), 134 (32), 133 (100), 120 (12), 107 (15), 93 (17), 92 (15), 65 (13).

IR ATR ν (cm^{-1}): 2965, 2854, 1612, 1557, 1503, 1483, 1461, 1406, 1379, 1369, 1347, 1339, 1300, 1239, 1181, 1162, 1016, 984, 802.

HRMS (EI) for **$C_{10}H_{14}N_2$** (162.1157) $[M]^+$: 162.1150.

Synthesis of 2-chloro-6-(pyrrolidin-1-yl)pyridine (19e) according to TP9:



According to **TP9**, the substituted pyridine **19e** was prepared from 1 mmol of **16c** (148 mg) with 2 mmol of **17a** (1 M from 142 mg of pyrrolidine) at 50 °C for 7 h. Flash column chromatography (*i*-hexane/diethyl ether 9:1 + 0,5% NEt_3) furnished **19e** as yellow solid (148 mg, 81%).

m.p.: 70.4 - 72.0 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.88 - 2.12 (m, 4 H), 3.43 (t, *J*=6.6 Hz, 4 H), 6.20 (d, *J*=8.3 Hz, 1 H), 6.49 (d, *J*=7.5 Hz, 1 H), 7.21 - 7.43 (m, 1 H).

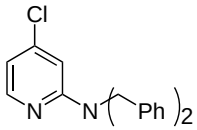
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 25.4 (2 C), 46.7 (2 C), 104.2, 109.9, 138.9, 149.6, 157.1.

MS (70 eV, EI) m/z: 184 (7), 182 (29), 97 (42), 83 (35), 71 (35), 69 (41), 57 (29), 56 (29), 47 (31).

IR ATR ν (cm^{-1}): 2969, 2858, 1591, 1486, 1454, 1410, 1384, 1164, 1124, 1001, 969, 769, 720, 705.

HRMS (EI) for **$C_9H_{11}ClN_2$** (182.0611) $[M]^+$: 182.0590.

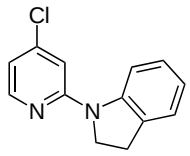
Synthesis of N,N-dibenzyl-4-chloropyridin-2-amine (19f) according to TP9:



According to **TP9**, the substituted pyridine **19f** was prepared from 1 mmol of **16d** (148 mg) with 2 mmol of **17d** (0.94 M from 395 mg of dibenzylamine) at 50 °C for 3 h. Flash column chromatography (*i*-hexane/diethyl ether 9:1 + 0,5% NEt_3) furnished **19f** as colorless oil (154 mg, 50%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 4.78 (s, 4 H), 6.46 - 6.51 (m, 1 H), 6.61 (dd, *J*=5.5, 1.4 Hz, 1 H), 7.20 - 7.36 (m, 10 H), 8.10 (d, *J*=5.5 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 50.9 (2 C), 105.5, 112.8, 127.0 (2 C), 127.1 (2 C), 128.7 (2 C), 137.7, 144.9, 148.8 (2 C), 159.6.
MS (70 eV, EI) m/z: 308 (5), 219 (34), 217 (100), 91 (42), 65 (18).
IR ATR ν (cm^{-1}): 3062, 3028, 2907, 1588, 1575, 1541, 1488, 1451, 1425, 1355, 1230, 1106, 974, 953, 823, 790, 728, 694.
HRMS (EI) for **$C_{19}H_{17}ClN_2$** (308.1080) $[M]^+$: 308.1077.

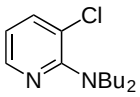
Synthesis of 1-(4-chloropyridin-2-yl)indoline (19g) according to TP9:



According to **TP9**, the substituted pyridine **19g** was prepared from 1 mmol of **16d** (148 mg) with 2 mmol of **17e** (1 M from 238 mg of indoline) at 50 °C for 3 h. Flash column chromatography (*i*-hexane/diethyl ether 9:1 + 0,5% NEt_3) furnished **19g** as white solid (125 mg, 54%).

m.p.: 119.8 - 121.7 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.23 (t, *J*=8.6 Hz, 2 H), 4.01 (t, *J*=8.6 Hz, 2 H), 6.71 - 6.81 (m, 2 H), 6.86 - 6.97 (m, 1 H), 7.15 - 7.26 (m, 2 H), 8.24 (d, *J*=6.1 Hz, 2 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 27.6 (2 C), 49.3 (2 C), 108.2, 114.1, 114.6, 121.1, 124.6, 127.3, 131.4, 144.4, 144.5, 148.8, 156.2.
MS (70 eV, EI) m/z: 232 (26), 231 (20), 230 (67), 229 (50), 118 (100), 117 (29), 91 (18).
IR ATR ν (cm^{-1}): 2960, 2925, 2882, 2857, 1572, 1548, 1487, 1478, 1456, 1433, 1107, 1020, 983, 814, 786, 748, 722, 706.
HRMS (EI) for **$C_{13}H_{11}ClN_2$** (230.0611) $[M]^+$: 230.0610.

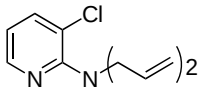
Synthesis of N,N-dibutyl-3-chloropyridin-2-amine (19h) according to TP9:



According to **TP9**, the substituted pyridine **19h** was prepared from 1 mmol of **16e** (148 mg) with 2 mmol of **17c** (1 M from 259 mg of dibutylamine) at 50 °C for 5 h. Flash column chromatography (*i*-hexane/diethyl ether 9:1 + 0,5% NEt_3) furnished **19h** as yellow oil (171 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 0.90 (t, *J*=7.3 Hz, 6 H), 1.23 - 1.38 (m, 4 H), 1.48 - 1.61 (m, 4 H), 3.33 (dd, *J*=7.7, 7.2 Hz, 4 H), 6.70 (dd, *J*=7.7, 4.7 Hz, 1 H), 7.52 (dd, *J*=7.7, 1.1 Hz, 1 H), 8.13 (dd, *J*=4.7, 1.1 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 14.0 (2 C), 20.3 (2 C), 30.2 (2 C), 50.6 (2 C), 116.1, 121.7, 138.8, 145.3, 158.1.
MS (70 eV, EI) m/z (%): 240 (18), 199 (40), 197 (100), 183 (19), 157 (23), 155 (84), 143 (20), 141 (69).
IR ATR ν (cm^{-1}): 2957, 2930, 2872, 2862, 1577, 1476, 1466, 1460, 1455, 1428, 1374, 1287, 1219, 1118, 1099, 1074, 1031, 927, 778, 743.
HRMS (EI) for **$C_{13}H_{21}ClN_2$** (240.1393) $[M]^+$: 240.1399.

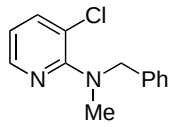
Synthesis of N,N-diallyl-3-chloropyridin-2-amine (19i) according to TP9:



According to **TP9**, the substituted pyridine **19i** was prepared from 1 mmol of **16e** (148 mg) with 2 mmol of **17f** (1 M from 194 mg of diallylamine) at 50 °C for 5 h. Flash column chromatography (*i*-hexane/diethyl ether 9:1 + 0,5% NEt_3) furnished **19i** as yellow oil (171 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 4.00 (d, *J*=5.8 Hz, 4 H), 5.13 - 5.27 (m, 4 H), 5.94 (dddd, *J*=16.9, 10.6, 6.0, 5.8 Hz, 2 H), 6.75 (dd, *J*=7.7, 4.7 Hz, 1 H), 7.55 (dd, *J*=7.8, 1.4 Hz, 1 H), 8.14 (dd, *J*=4.6, 1.4 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 52.2 (2 C), 116.7 (2 C), 117.2 (2 C), 121.3, 135.0, 139.0, 145.4, 157.6.
MS (70 eV, EI) m/z: 208 (5), 168 (12), 167 (100), 165 (11), 154 (13), 153 (12), 112 (16).
IR ATR ν (cm^{-1}): 3077, 2982, 2920, 2853, 1577, 1463, 1434, 1411, 1343, 1248, 1231, 1118, 1105, 1076, 1031, 991, 918, 780, 753.
HRMS (EI) for **$C_{11}H_{13}ClN_2$** (208.0767) $[M]^+$: 208.0759.

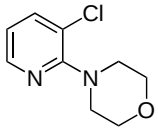
Synthesis of N-benzyl-3-chloro-N-methylpyridin-2-amine (19j) according to TP9:



According to **TP9**, the substituted pyridine **19j** was prepared from 1 mmol of **16e** (148 mg) with 2 mmol of **17g** (1 M from 242 mg of N-methyl-1-phenylmethanamine) at 50 °C for 3 h. Flash column chromatography (*i*-hexane/diethyl ether 9:1 + 0,5% NEt_3) furnished **19j** as colorless oil (193 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.91 (s, 3 H), 4.57 (s, 2 H), 6.79 (dd, *J*=7.7, 4.7 Hz, 1 H), 7.22 - 7.45 (m, 1 H), 7.59 (dd, *J*=7.7, 1.7 Hz, 1 H), 8.18 (dd, *J*=4.7, 1.4 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 38.3, 57.1, 116.9, 121.5, 127.0, 127.9 (2 C), 128.3 (2 C), 138.6, 138.9, 145.5, 158.7.
MS (70 eV, EI) m/z: 234 (16), 232 (53), 219 (33), 217 (100), 203 (37), 143 (26), 120 (65), 91 (89), 65 (26), 42 (53).
IR ATR ν (cm^{-1}): 3061, 3047, 3028, 2957, 2848, 2798, 1576, 1494, 1475, 1450, 1435, 1406, 1360, 1228, 1114, 1067, 1029, 946, 782, 731, 696.
HRMS (EI) for **$C_{13}H_{13}ClN_2$** (232.0767) $[M]^+$: 232.0758.

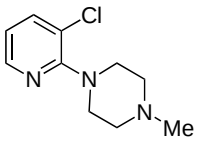
Synthesis of 4-(3-chloropyridin-2-yl)morpholine (19k) according to TP9:



According to **TP9**, the substituted pyridine **19k** was prepared from 1 mmol of **16e** (148 mg) with 2 mmol of **17b** (1 M from 174 mg of morpholine) at 50 °C for 4 h. Flash column chromatography (*i*-hexane/diethyl ether 4:1 + 0,5% NEt_3) furnished **19k** as white solid (171 mg, 86%).

m.p.: 99.0 - 100.8 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.35 (dd, *J*=4.7 Hz, 4 H), 3.86 (dd, *J*=4.4 Hz, 4 H), 6.86 (dd, *J*=7.7, 4.7 Hz, 1 H), 7.59 (dd, *J*=7.7, 1.7 Hz, 1 H), 8.19 (dd, *J*=4.7, 1.4 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 49.5 (2 C), 66.9 (2 C), 118.1, 122.6, 138.9, 145.8, 158.1.
MS (70 eV, EI) m/z: 200 (24), 199 (38), 198 (100), 197 (60), 169 (27), 168 (22), 167 (58), 154 (25), 153 (44), 152 (24), 153 (44), 142 (24), 141 (87), 140 (55), 115 (43), 43 (44).
IR ATR ν (cm^{-1}): 2960, 2854, 1577, 1440, 1430, 1422, 1370, 1247, 1226, 1109, 1071, 1031, 942, 924, 846, 798, 779, 760, 695.
HRMS (EI) for **$C_9H_{11}ClN_2O$** (198.0560) $[M]^+$: 198.0548.

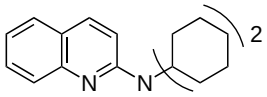
Synthesis of 1-(3-chloropyridin-2-yl)-4-methylpiperazine (19l) according to TP9:



According to **TP9**, the substituted pyridine **19l** was prepared from 1 mmol of **16e** (148 mg) with 2 mmol of **17h** (1 M from 200 mg of 1-methylpiperazine) at 50 °C for 5 h. Flash column chromatography (EtOAc/methanol 9:1) furnished **19l** as yellow oil (150 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 2.34 (s, 3 H), 2.53 - 2.60 (m, 4 H), 3.34 - 3.42 (m, 4 H), 6.80 (dd, *J*=7.7, 4.7 Hz, 1 H), 7.55 (dd, *J*=7.7, 1.7 Hz, 1 H), 8.16 (dd, *J*=4.7, 1.4 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 46.1, 48.9 (2 C), 55.0 (2 C), 117.7, 122.5, 138.7, 145.7, 158.3.
MS (70 eV, EI) m/z: 213 (6), 211 (16). 154 (22), 153 (14), 140 (100), 83 (15), 71 (11).
IR ATR ν (cm^{-1}): 2935, 2842, 2793, 1575, 1460, 1432, 1370, 1288, 1242, 1143, 1119, 1030, 1008, 944, 784, 759.
HRMS (EI) for $C_{10}H_{14}ClN_3$ (211.0876) $[M]^+$: 211.0878.

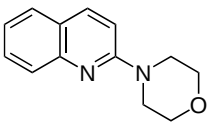
Synthesis of N,N-dicyclohexylquinolin-2-amine (19m) according to TP9:



According to **TP9**, the substituted quinoline **19m** was prepared from 1 mmol of **16f** (164 mg) with 2 mmol of **17i** (1 M from 363 mg of dicyclohexylamine) at 50 °C for 23 h. Flash column chromatography (*i*-hexane/ethyl acetate 15:1) furnished **19m** as light green oil (220 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.06 - 1.23 (m, 4 H), 1.26 - 1.41 (m, 5 H), 1.53 - 1.69 (m, 7 H), 1.78 (d, *J*=12.9 Hz, 5 H), 1.89 - 2.06 (m, 4 H), 3.71 - 3.83 (m, 2 H), 6.86 (d, *J*=9.3 Hz, 1 H), 7.05 (t, *J*=7.3 Hz, 1 H), 7.39 (t, *J*=7.6 Hz, 1 H), 7.45 (d, *J*=8.1 Hz, 1 H), 7.56 (d, *J*=8.3 Hz, 1 H), 7.67 (d, *J*=9.0 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 4.9 (2 C), 5.7 (4 C), 10.3 (4 C), 35.2 (2 C), 91.1, 100.2, 101.4, 105.4, 106.0, 107.9, 114.8, 127.10 135.7.
MS (70 eV, EI) m/z (%): 308 (18), 251 (20), 225 (100), 183 (18), 169 (43), 129 (14), 128 (19), 55 (11).
IR ATR ν (cm^{-1}): 3051, 2924, 2850, 1618, 1602, 1556, 1503, 1476, 1430, 1380, 1363, 1322, 1293, 1238, 1174, 1124, 1052, 1017, 893, 811, 750.
HRMS (EI) for $C_{21}H_{28}N_2$ (308,2252) $[M]^+$: 308.2247.

Synthesis of 4-(quinolin-2-yl)morpholine (19n) according to TP9:



According to **TP9**, the substituted quinoline **19n** was prepared from 1 mmol of **16f** (164 mg) with

2 mmol of **17b** (1 M from 174 mg of morpholine) at 50 °C for 8 h. Flash column chromatography (*i*-hexane/diethyl ether 1:1) furnished **19n** as white crystals (182 mg, 85%).

m.p.: 95.9 – 97.3 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.65 - 3.73 (m, 4 H), 3.80 - 3.87 (m, 4 H), 6.91 (d, *J*=9.1 Hz, 1 H), 7.21 - 7.29 (m, 1 H), 7.51 - 7.64 (m, 2 H), 7.75 (d, *J*=8.6 Hz, 1 H), 7.89 (d, *J*=9.1 Hz, 1 H).

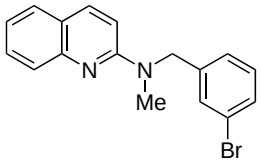
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 45.4 (2 C), 66.7 (2 C), 109.1, 122.5, 123.2, 126.6, 127.1, 129.5, 137.4, 147.6, 157.4.

MS (70 eV, EI) m/z: 214 (49), 213 (25), 183 (63), 169 (28), 157 (54), 156 (18), 129 (100), 128 (48), 101 (22), 92 (16).

IR ATR ν (cm^{-1}): 3044, 2971, 2858, 2829, 1614, 1602, 1506, 1477, 1430, 1393, 1332, 1318, 1264, 1234, 1218, 1112, 1054, 975, 966, 924, 865, 806, 780, 755, 685.

HRMS (EI) for **$C_{13}H_{14}N_2O$** (214.1106) $[M]^+$: 214.1099.

N-(3-bromobenzyl)-N-methylquinolin-2-amine (19o) according to TP9:



According to **TP9**, the substituted quinoline **19o** was prepared from 1 mmol of **16f** (164 mg) with 2 mmol of **17j** (1 M from 400 mg of 1-(3-bromophenyl)-*N*-methylmethanamine) at 50 °C for 6 h. Flash column chromatography (*i*-hexane/ethyl acetate 1:1) furnished **19o** as yellow oil (314 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.21 (s, 3 H), 4.95 (s, 2 H), 6.88 (d, *J*=9.1 Hz, 1 H), 7.16 - 7.25 (m, 3 H), 7.39 (d, *J*=8.0 Hz, 1 H), 7.46 (br. s, 1 H), 7.53 - 7.58 (m, 1 H), 7.62 (d, *J*=8.0 Hz, 1 H), 7.72 (d, *J*=8.5 Hz, 1 H), 7.89 (d, *J*=9.3 Hz, 1 H).

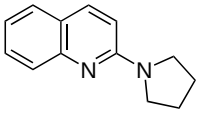
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 36.2, 52.6, 108.8, 121.9, 122.7, 122.8, 125.9, 126.5, 127.2, 129.5, 130.1 (2 C), 130.3, 137.6, 141.3, 148.0, 157.0.

MS (70 eV, EI) m/z (%): 328 (52), 327 (21), 326 (44), 314 (20), 313 (100), 311 (99), 157 (55), 129 (45), 128 (60).

IR ATR ν (cm^{-1}): 3054, 2948, 2922, 2854, 1616, 1604, 1558, 1508, 1492, 1426, 1388, 1339, 1111, 1069, 808, 777, 754.

HRMS (EI) for **$C_{17}H_{15}BrN_2$** (326.0419) $[M]^+$: 326.0416.

Synthesis of 2-(pyrrolidin-1-yl)quinoline (19p) according to TP9:



According to **TP9**, the substituted quinoline **19p** was prepared from 1 mmol of **16f** (164 mg) with

2 mmol of **17a** (1 M from 142 mg of pyrrolidine) at 50 °C for 10 h. Flash column chromatography (*i*-hexane/diethyl ether 1:1 + 1% NEt_3) furnished **19p** as yellow crystals (178 mg, 90%).

m.p.: 88.7 – 90.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.97 - 2.11 (m, 4 H), 3.53 - 3.71 (m, 4 H), 6.72 (d, *J*=9.1 Hz, 1 H), 7.12 - 7.22 (m, 1 H), 7.48 - 7.61 (m, 2 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.84 (d, *J*=8.8 Hz, 1 H).

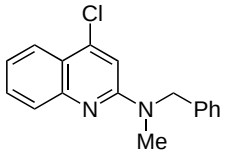
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 25.5 (2 C), 46.7 (2 C), 110.2, 121.2, 122.5, 126.1, 127.3, 129.3, 136.9, 148.6, 155.7.

MS (70 eV, EI) m/z (%): 198 (48), 170 (27), 169 (100), 143 (11), 129 (17), 128 (18).

IR ATR ν (cm^{-1}): 3053, 2966, 2923, 2862, 1605, 1506, 1478, 1468, 1456, 1428, 1401, 1343, 1309, 1165, 1143, 807, 779, 750.

HRMS (EI) for **$C_{13}H_{14}N_2$** (198.1157) $[M]^+$: 198.1152.

Synthesis of N-benzyl-4-chloro-*N*-methylquinolin-2-amine (19q) according to TP9:



According to **TP9**, the substituted isoquinoline **19q** was prepared from 1 mmol of **16g** (198 mg) with 2 mmol of **17g** (1 M from 242 mg of N-methyl-1-phenylmethanamine) at 50 °C for 5 h. Flash column chromatography (*i*-hexane/diethyl ether 8:2 + 0,5% NEt_3) furnished **19q** as yellow solid (153 mg, 54%).

m.p.: 73.8 – 75.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.20 (s, 3 H), 4.94 (s, 2 H), 7.02 (s, 1 H), 7.24 - 7.39 (m, 6 H), 7.56 - 7.63 (m, 1 H), 7.75 (d, *J*=8.3 Hz, 1 H), 8.02 (d, *J*=7.5 Hz, 6 H).

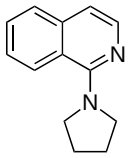
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 36.0, 53.1, 108.7, 120.8, 122.4, 123.8, 126.8, 127.1, 127.2 (2 C), 128.6 (2 C), 130.4, 138.1, 143.1, 148.8, 156.8.

MS (70 eV, EI) m/z: 284 (17), 283 (14), 282 (49), 269 (32), 268 (22), 267 (100), 193 (19), 191 (54), 162 (34), 128 (18), 162 (34), 128 (18), 120 (26), 91 (24).

IR ATR ν (cm^{-1}): 3057, 3022, 2905, 2864, 2791, 1595, 1583, 1544, 1505, 1495, 1418, 1409, 1390, 1384, 1354, 1189, 954, 824, 755, 725, 694, 682.

HRMS (EI) for **$C_{17}H_{15}ClN_2$** (282.0924) $[M]^+$: 282.0916.

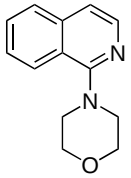
Synthesis of 1-(pyrrolidin-1-yl)isoquinoline (19r) according to TP9:



According to **TP9**, the substituted isoquinoline **19r** was prepared from 1 mmol of **16h** (164 mg) with 2 mmol of **17a** (1 M from 142 mg of pyrrolidine) at 50 °C for 2 h. Flash column chromatography (*i*-hexane/ethyl acetate 1:1 + 0,5% NEt_3) furnished **19r** as yellow oil (184 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 1.96 - 2.03 (m, 4 H), 3.80 - 3.86 (m, 4 H), 6.97 (d, *J*=5.8 Hz, 1 H), 7.38 (ddd, *J*=8.5, 6.8, 1.5 Hz, 1 H), 7.49 - 7.57 (m, 1 H), 7.66 (dd, *J*=8.0, 1.4 Hz, 1 H), 8.02 (d, *J*=5.5 Hz, 1 H), 8.20 (d, *J*=8.6 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 25.9 (2 C), 51.4 (2 C), 111.5, 120.0, 124.2, 126.1, 126.5, 129.0, 138.7, 140.8, 157.9.
MS (70 eV, EI) m/z (%): 198 (24), 170 (25), 169 (100).
IR ATR ν (cm^{-1}): 3047, 2965, 2865, 1547, 1504, 1451, 1413, 1360, 1338, 1288, 1140, 798, 742, 677.
HRMS (EI) for **$C_{13}H_{14}N_2$** (198.1157) $[M]^+$: 198.1159.

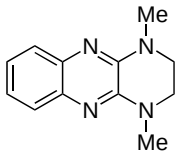
Synthesis of 4-(isoquinolin-1-yl)morpholine (19s) according to TP9:



According to **TP9**, the substituted isoquinoline **19s** was prepared from 1 mmol of **16h** (164 mg) with 2 mmol of **17b** (1 M from 174 mg of morpholine) at 50 °C for 2 h. Flash column chromatography (*i*-hexane/ethyl acetate 1:1 + 0,5% NEt_3) furnished **19s** as beige solid (191 mg, 89%).

m.p.: 74.0 - 75.8 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.43 (dd, *J*=5.0, 4.4 Hz, 4 H), 3.99 (dd, *J*=4.4, 4.4 Hz, 4 H), 7.27 - 7.30 (m, 1 H), 7.49 - 7.57 (m, 1 H), 7.59 - 7.68 (m, 1 H), 7.77 (d, *J*=8.6 Hz, 1 H), 8.11 (d, *J*=8.3 Hz, 1 H), 8.17 (d, *J*=5.8 Hz, 1 H).
^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 51.9 (2 C), 67.1 (2 C), 116.2, 121.6, 125.4, 126.2, 127.2, 129.8, 138.2, 140.5, 161.1.
MS (70 eV, EI) m/z (%): 214 (11), 213 (14), 169 (14), 157 (18), 156 (12), 129 (36), 128 (12), 70 (11), 61 (14), 45 (12), 44 (19), 43 (100).
IR ATR ν (cm^{-1}): 2983, 2974, 2965, 2833, 1556, 1398, 1361, 1263, 1115, 1107, 1070, 1031, 1014, 930, 857, 820, 756, 722, 682.
HRMS (EI) for **$C_{13}H_{14}N_2O$** (214.1106) $[M]^+$: 214.1126.

Synthesis of 1,4-dimethyl-1,2,3,4-tetrahydropyrazino[2,3-*b*]quinoxaline (19t) according to TP9:



According to **TP9**, the substituted quinoxaline **19t** was prepared from 1 mmol of **16i** (200 mg) with 2 mmol of **17k** (1 M from 176 mg of N^1,N^2-dimethylethane-1,2-diamine) at 50 °C for 3 h. Flash column chromatography (*i*-hexane/diethyl ether 2:1) furnished **19t** as beige solid (184 mg, 86%).

m.p.: 187.0 – 189.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm: 3.12 (s, 6 H), 3.41 (s, 4 H), 7.09 - 7.20 (m, 2 H), 7.46 (dd, *J*=5.9, 3.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm: 36.3 (2 C), 46.9 (2 C), 124.2 (2 C), 125.1 (2 C), 137.3 (2 C), 144.0 (2 C).

MS (70 eV, EI) m/z: 215 (11), 214 (100), 213 (20), 199 (15), 186 (10), 185 (19), 128 (9), 102 (10), 42 (6).

IR ATR ν (cm^{-1}): 2921, 2885, 2856, 1568, 1528, 1465, 1458, 1418, 1393, 1356, 1342, 1287, 1261, 1201, 1116, 1082, 1025, 1014, 947, 846, 765, 749, 674.

HRMS (EI) for **$C_{12}H_{14}N_4$** (214.1218) $[M]^+$: 214.1216.

5. SYNTHESIS OF PYRIDO[3,2-F][1,7]NAPHTHYRIDINE AND RELATED HETEROCYCLES

5.1 STARTING MATERIAL SYNTHESIS

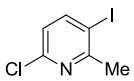
Starting materials **28a-b**, as well as **trichloroisocyanuric acid**, **potassium phthalimide** and **chloranil** are commercially available reagents and were used without further purification.

Synthesis of 3-iodo-2-methylpyridine (27a):

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with LiCl (128 mg, 1.5 equiv) and heated with a heat gun under high vacuum (5 min). After cooling to room temperature, magnesium turnings (122 mg, 2.5 equiv) were added, followed by THF (2 mL). The magnesium was activated using 1,2-dibromoethane (5 mol%) and TMSCl (5 mol%). Then, $ZnCl_2$-solution (2.2 mL, 1.1 equiv, 1 M in THF) was added followed by 3-bromo-2-methylpyridine (344 mg, 1 equiv). The reaction mixture was stirred at 25 °C until GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material (12 h). To the reaction mixture was added dropwise an iodine solution in THF (1.01 g, 2.0 equiv, 1 M in THF) at 0 °C and stirred for 1 h at 25 °C. The suspension was then quenched with a saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc (3x). The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to obtain the crude compound. Flash column chromatography (DCM) furnished **27a** as yellow solid (267 mg, 61%).

m.p.: 169.1 - 170.3 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 2.74 (s, 3 H), 6.82 (dd, *J*=7.78, 4.75 Hz, 1 H), 8.05 (d, *J*=7.88 Hz, 1 H), 8.44 (d, *J*=4.78 Hz, 1 H).
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 28.9, 96.3, 122.1, 146.2, 148.2, 160.0.
MS (70 eV, EI) m/z (%): 219 (5), 218 (100), 92 (49), 65 (29).
IR ATR ν (cm^{-1}): 2948, 2922, 2852, 1588, 1450, 1412, 1206, 1076, 1038, 1012, 792, 702.
HRMS (EI) for **C_6H_6IN** (218.9545) $[M]^+$: 218.9534.

Synthesis of 6-chloro-3-iodo-2-methylpyridine (27b):



A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with *n*-BuMgCl (7.15 mL, 0.5 equiv, 0.5 M in THF) in 10 mL THF and *n*-BuLi (8.2 mL, 1.0 equiv, 2.44 M) was added at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and added dropwise to a

solution of 6-chloro-3-bromo-2-methylpyridine (4.13 g, 1.0 equiv) in 8 mL THF at 0 °C. After 15 min, GC-analysis of hydrolyzed reaction aliquot showed full consumption of the starting material. An iodine solution in THF (10.1 g, 2 equiv) was added to the reaction mixture at 0 °C and stirred 30 min. The suspension was then quenched with a saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to obtain the crude compound. Flash column chromatography (DCM) furnished **27b** as yellow oil (4.49 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 2.70 (s, 3 H), 6.89 (d, *J*=8.21 Hz, 1 H), 7.95 (d, *J*=8.19 Hz, 1 H).
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 28.8, 93.8, 123.1, 148.7, 150.5, 161.3.
MS (70 eV, EI) m/z (%): 254 (28), 253 (100), 126 (48), 91 (24), 90 (29), 85 (28), 71 (37), 57 (73), 55 (29), 43 (45), 41(22).
IR ATR ν (cm^{-1}): 3096, 3048, 2998, 2952, 2920, 1556, 1538, 1432, 1412, 1380, 1206, 1146, 1012, 974, 876, 814, 724, 684.
HRMS (EI) for **C_6H_5ClIN** (252.9155) $[M]^+$: 252.9154.

5.2 GENERAL PROCEDURES

5.2.1 Typical procedure for the preparation of pyridyl-zinc reagents (**TP11**)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the neat pyridyl bromide (1 equiv) in THF (0.5 mL/mmol). *i*-PrMgCl·LiCl (1.1 equiv, 1.25 M in THF) was added dropwise to the starting material solution in THF at 0 °C and the reaction mixture was stirred at 0 °C until GC-analysis of iodinated reaction aliquot showed full consumption of the starting material. $ZnCl_2$ in THF (1.2 equiv, 1 M) was then added dropwise to the Grignard reagent at 0 °C and the solution was stirred 30 min for transmetallation. The synthesized organozinc reagents were then directly used in Negishi cross-couplings (see **TP12** and **TP13**).

5.2.2 Typical procedure for the $Pd(PPh_3)_4$-catalyzed Negishi cross-coupling (**TP12**)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the pyridyl iodide (0.9 equiv) and $Pd(PPh_3)_4$ (2 mol%). THF was added (1 mL/mmol) and the suspension was stirred 15 min at 25 °C. The desired freshly prepared zinc reagent in THF was added dropwise to the reaction mixture at 25 °C and the mixture was then stirred for the given time at 50 °C. The reaction mixture was quenched with sat. NaCl solution and extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

5.2.3 Typical procedure for the $Pd(OAc)_2$/SPhos-catalyzed Negishi cross-coupling (**TP13**)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with the pyridyl iodide (0.9 equiv), $Pd(OAc)_2$ (2 mol%) and SPhos (4 mol%). THF was added (1 mL/mmol) and the suspension was stirred 15 min at 25 °C. The desired freshly prepared zinc reagent in THF was added dropwise to the reaction mixture at 25 °C and the mixture was then stirred for the given time at 50 °C. The reaction mixture was quenched with sat. NaCl solution and extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

5.2.4 Typical procedure for the chlorination using trichloroisocyanuric acid (**TP14**)

A round-bottom flask was charged with the picolyl-derivative (1 equiv) and benzamide (0.03 equiv) in chloroform (3 mL/mmol) at 25 °C. Trichloroisocyanuric acid (0.54 equiv) was added portionwise to this solution at 25 °C. The reaction mixture was then stirred and heated to reflux until GC-MS analysis of a reaction aliquot showed full consumption of the starting material. After cooling down, water was added to the reaction mixture, the solution was neutralized with sat. $NaHCO_3$ and extracted with DCM (3x). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

5.2.5 Typical procedure for the chlorination *via* deprotonation by LDA and TMSCl trapping (**TP15**)

A dry, argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with a solution of lithium diisopropylamide (1.2 equiv, 0.5 M in THF) and was cooled to -78 °C. A solution of the desired picolyl-derivative (1 equiv) in THF (8 mL/mmol) was added dropwise to the cooled solution. This solution was stirred for 2 h at -78°C and TMSCl (1.3 equiv) was added to the rapidly stirred lithium reagent and let warm up to 25 °C overnight (12 h). Sat. aq. $NaHCO_3$ was added to the reaction mixture and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil containing the product and ca. 10% of the bis(trimethylsilylmethyl) compound was dried on the high vacuum line and used in the next step without further purification.
Hexachloroethane (2 equiv) and finely ground and dried CsF (2 equiv) were placed in a round-bottom flask equipped with a stirring bar, a septum and purged with argon. A solution of the freshly synthesized (trimethylsilyl)methyl-derivative (1 equiv) in dry MeCN (2 mL/mmol) was added to the flask and the mixture was stirred and heated to reflux for 3 h. Sat. NaCl was poured to the reaction mixture and extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to

give the analytically pure product.

5.2.6 Typical procedure for the Gabriel substitution of chloromethyl-derivatives (**TP16**)

A round-bottom-flask was equipped with the chloromethyl-derivative (1 equiv) in DMF (2 mL/mmol) and potassium phthalimide (1.2 equiv) was added at 25 °C. The reaction mixture was stirred and warmed up to 100 °C until TLC-monitoring showed full consumption of the starting material. Water was added to the solution and the aqueous phase was extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

5.2.7 Typical procedure for the Manske-Ing phthalimide deprotection (**TP17**)

A round-bottom-flask was equipped with the phthalimide-derivative (1 equiv) in abs. EtOH (15 mL/mmol). To the suspension was added hydrazine hydrate (3 equiv) at 25 °C and the reaction mixture was heated to reflux for 2 h. After cooling down to 25 °C, 2N HCl was added carefully (2 mL/mmol) and the suspension was brought to reflux for 5 min, until the precipitate dissolves. The solution was cooled down to 25 °C and sat. $NaHCO_3$ was added dropwise until neutralization. EtOH was evaporated *in vacuo* and the aqueous phase was extracted with DCM (3x). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue obtained was used without further purification.

5.2.8 Typical procedure for the aromatization with chloranil (**TP18**)

The crude dihydroazaphenanthrene (1 equiv) obtained by **TP17** was charged in a round-bottom flask and solubilized in DMF (3 mL/mmol) at 25 °C. Chloranil (1.2 equiv) was added portionwise and the reaction mixture was stirred 2 h at 25 °C until TLC-monitoring showed full consumption of the starting material. Water was added to the suspension and the aqueous phase was extracted with DCM (3x). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue obtained was purified by flash column chromatography to give the analytically pure product.

5.2.9 Typical procedure for the preparation of organolithium reagents (**TP19**)

Solutions of lithium reagents were freshly prepared and titrated against *i*-PrOH with 1,10-phenantroline as indicator: phenyllithium **34a** and (4-methoxyphenyl)lithium **34b** were prepared by addition of Li metal (2.0 equiv) to the iodides (1.0 equiv) in diethyl ether (0.5 M) at 0 °C and obtained as reddish ca. 0.5 M solutions after 30 min. (4-(trifluoromethyl)phenyl)lithium **34c** and (3-fluorophenyl)lithium **34d** were obtained as colored solutions (ca. 0.6-0.9 M) according to a literature procedure by adding *t*-BuLi solution (2.0 equiv) to the corresponding iodide (1.0 equiv) in

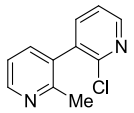
diethyl ether (1.0 M) at -78 °C and stirring for 30 min.[150] Heteroaryl *α*-lithiated reagents **34e-h** were prepared by adding *n*-BuLi solution (1.05 equiv) to the heteroaryl compound (1.0 equiv) in THF (1.0 M) at -78 °C and stirring for 30 min, followed by 1 h at -10 °C and 5 min at 25 °C. Titration indicated a 0.5-0.9 M concentration of these reagents. (1-ethoxyvinyl)lithium **34i** was prepared according to a literature procedure[151] and obtained as ca. 0.6 M solution in THF/hexanes.

5.2.10 Typical procedure for the addition of organolithiums and rearomatization (**TP20**)

Pyrido[3,2-*f*][1,7]naphthyridine (**23a**, 18 mg, 0.1 mmol, 1.0 equiv) was dissolved in 1 mL dry THF under an argon atmosphere. Brief heating was applied to ensure that all material was dissolved. The solution was then cooled to -60 °C in a dry ice/acetone bath. The organolithium solution was cooled to -60 °C prior to addition or -40 °C, if precipitation was observed at lower temperature. The precooled solution of organolithium compound (**34**, 0.15 mmol, 1.5 equiv) was then added dropwise via syringe to **23a** and the mixture was stirred for 30 min at -60 °C. The dry ice cooling was subsequently changed to an ice bath (0 °C) and stirring was continued for 5 min. In order to quench the reaction, 3 mL of sat. aq. NH_4Cl solution was added. The organic phase was separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were dried over $MgSO_4$ and solvents were removed *in vacuo*. The solid residues were dissolved in 2 mL DMF and chloranil (30 mg, 0.12 mmol, 1.2 equiv) was added at once. The mixture was stirred overnight at room temperature in an open flask. Water (10 mL) and ca. 200 mg LiCl were then added. The mixture was extracted with EtOAc (5x). After removal of the solvent *in vacuo*, the analytically pure product of type **33** was obtained after flash column chromatography (silica gel, EtOAc + 5% NEt_3).

5.3 COMPOUNDS SYNTHESIZED ACCORDING TO THE GENERAL PROCEDURES

Synthesis of 2-chloro-2'-methyl-3,3'-bipyridine (25a) according to (TP12):



According to **TP12**, the substituted bipyridine **25a** was synthesized from the Negishi cross-coupling of **26a** (1 mmol, preparation according to **TP11**) with **27a** (0.9 equiv) in the presence of 2 mol% $Pd(PPh_3)_4$ at 50 °C for 1 h. Flash column chromatography (*i*-hexane/ethyl acetate 8:2 + 2% NEt_3) furnished **25a** as yellow oil (171 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 2.33 (s, 3 H), 7.19 (dd, *J*=7.64, 4.90 Hz, 1 H), 7.31 (dd, *J*=7.50, 4.81 Hz, 1 H), 7.43 (dd, *J*=7.70, 1.79 Hz, 1 H), 7.56 (dd, *J*=7.49, 1.97 Hz, 1 H), 8.41 (dd, *J*=4.80, 1.98 Hz, 1 H), 8.53 (dd, *J*=4.89, 1.75 Hz, 1 H).

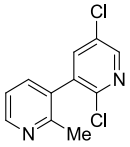
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 23.0, 121.0, 122.6, 132.5, 135.0, 137.2, 139.6, 149.3 (2C), 150.4, 156.3.

MS (70 eV, EI) m/z (%): 206 (29), 204 (100), 169 (79), 168 (57), 167 (12).

IR ATR ν (cm^{-1}): 3046, 2956, 2924, 2856, 1732, 1568, 1556, 1432, 1392, 1190, 1162, 1126, 1096, 1070, 1062, 1000, 802, 758, 752, 736, 722, 676.

HRMS (EI) for **$C_{11}H_9ClN_2$** (204.0454) $[M]^+$: 204.0446.

Synthesis of 2,5-dichloro-2'-methyl-3,3'-bipyridine (25b) according to (TP13):



According to **TP13**, the substituted bipyridine **25b** was synthesized from the Negishi cross-coupling of **26b** (1 mmol, preparation according to **TP11**) with **27a** (0.9 equiv) in the presence of 2 mol% $Pd(OAc)_2$ and 4 mol% SPhos at 50 °C for 5 h. Flash column chromatography (*i*-hexane/ethyl acetate 9:1 + 2% NEt_3) furnished **25b** as yellow oil (86 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 2.40 (s, 3 H), 7.24 (dd, *J*=7.70, 4.85 Hz, 1 H), 7.46 (dd, *J*=7.71, 1.78 Hz, 1 H), 7.60 (d, *J*=2.58 Hz, 1 H), 8.42 (d, *J*=2.58 Hz, 1 H), 8.60 (dd, *J*=4.90, 1.76 Hz, 1 H).

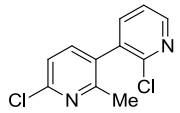
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 23.1, 121.1, 131.0, 131.4, 136.0, 137.2, 139.1, 148.0, 148.5, 149.8, 156.2.

MS (70 eV, EI) m/z (%): 240 (73), 238 (100), 203 (66), 168 (78), 57 (46).

IR ATR ν (cm^{-1}): 3050, 2924, 2854, 1566, 1440, 1430, 1402, 1388, 1278, 1214, 1124, 1088, 1016, 912, 822, 810, 744, 694, 678.

HRMS (EI) for **$C_{11}H_8Cl_2N_2$** (238.0065) $[M]^+$: 238.0065.

Synthesis of 2',6-dichloro-2-methyl-3,3'-bipyridine (25c) according to (TP12):



According to **TP12**, the substituted bipyridine **25c** was synthesized from the Negishi cross-coupling of **26a** (1 mmol, preparation according to **TP1**) with **27b** (0.9 equiv) in the presence of 2 mol% $Pd(PPh_3)_4$ at 50 °C for 2 h. Flash column chromatography (*i*-hexane/ethyl acetate 8:2 + 2% NEt_3) furnished **25c** as yellow solid (147 mg, 68%).

m.p.: 73.8 - 75.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 2.36 (s, 3 H), 7.26 – 7.29 (m, 1 H), 7.37 (dd, *J*=7.52, 4.80 Hz, 1 H), 7.44 (d, *J*=8.03 Hz, 1 H), 7.58 (dd, *J*=7.51, 1.97 Hz, 1 H), 8.49 (dd, *J*=4.83, 1.95 Hz, 1 H).

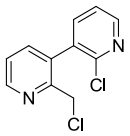
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 22.8, 121.6, 122.7, 131.3, 133.9, 139.7, 140.0, 149.8, 150.5, 150.7, 157.5.

MS (70 eV, EI) m/z (%): 240 (45), 238 (67), 167 (50), 71 (44), 57 (70), 43 (100).

IR ATR ν (cm^{-1}): 3066, 2924, 1556, 1398, 1384, 1150, 1126, 1090, 850, 810, 760, 752, 692.

HRMS (EI) for **$C_{11}H_8Cl_2N_2$** (238.0065) $[M]^+$: 238.0049.

Synthesis of 2-chloro-2'-(chloromethyl)-3,3'-bipyridine (29a) according to (TP14):



According to **TP14**, the substituted chloromethyl-bipyridine **29a** was synthesized from **25a** (1 mmol) with trichloroisocyanuric acid (0.53 equiv) in the presence of benzamide (0.03 equiv) at reflux for 4 h. Flash column chromatography (*i*-hexane/ethyl acetate 8:2 + 2% NEt_3) furnished **29a** as yellow oil (194 mg, 81%).

^{1}H NMR (800 MHz, $CDCl_3$) δ/ppm: 4.39 (d, *J*=11.34 Hz, 1 H), 4.59 (d, *J*=11.30 Hz, 1 H), 7.37 – 7.40 (m, 2 H), 7.58 (dd, *J*=7.74, 1.74 Hz, 1 H), 7.74 (dd, *J*=7.47, 1.94 Hz, 1 H), 8.50 (dd, *J*=4.85, 1.95 Hz, 1 H), 8.70 (dd, *J*=4.81, 1.73 Hz, 1 H).

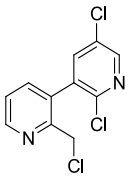
^{13}C NMR (201 MHz, $CDCl_3$) δ/ppm: 45.1, 122.6, 123.4, 133.0, 133.2, 138.5, 140.2, 150.0, 150.2, 150.2, 154.2.

MS (70 eV, EI) m/z (%): 240 (56), 238 (82), 203 (50), 168 (59), 167 (100), 140 (20), 43 (53).

IR ATR ν (cm^{-1}): 3052, 2253, 1558, 1437, 1427, 1393, 1265, 1130, 1116, 1092, 999, 903, 802, 723. 3050, 2924, 2854, 1566, 1440, 1430, 1402, 1388, 1214, 1124, 1088, 1016, 912, 822, 810, 790, 744, 694, 678.

HRMS (EI) for **$C_{11}H_8Cl_2N_2$** (238.0065) $[M]^+$: 238.0058.

Synthesis of 2,5-dichloro-2'-(chloromethyl)-3,3'-bipyridine (29b) according to (TP14):



According to **TP14**, the substituted chloromethyl-bipyridine **29b** was synthesized from **25b** (1 mmol) with trichloroisocyanuric acid (0.53 equiv) in the presence of benzamide (0.03 equiv) at reflux for 12 h. Flash column chromatography (*i*-hexane/ethyl acetate 9:1 + 2% NEt_3) furnished **29b** as yellow oil (213 mg, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 4.36 (d, *J*=11.31 Hz, 1 H), 4.55 (d, *J*=11.29 Hz, 1 H), 7.35 (dd, *J*=7.75, 4.79 Hz, 1 H), 7.54 (dd, *J*=7.73, 1.72 Hz, 1 H), 7.71 (d, *J*=2.62 Hz, 1 H), 8.40 (d, *J*=2.64 Hz, 1 H), 8.66 (dd, *J*=4.78, 1.73 Hz, 1 H).

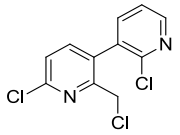
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 44.9, 123.4, 130.9, 131.7, 134.0, 138.3, 139.5, 148.0, 148.4, 150.4, 153.9.

MS (70 eV, EI) m/z (%): 276 (23), 274 (62), 272 (63), 237 (38), 203 (45), 202 (83), 201 (83), 97 (31), 71 (42), 57 (55), 43 (45), 43 (100).

IR ATR ν (cm^{-1}): 3050, 2924, 2854, 1566, 1440, 1430, 1402, 1388, 1214, 1124, 1088, 1016, 912, 822, 810, 790, 744, 694, 678.

HRMS (EI) for **$C_{11}H_7Cl_3N_2$** (271.9675) $[M]^+$: 271.9671.

Synthesis of 2',6-dichloro-2-(chloromethyl)-3,3'-bipyridine (29c) according to (TP15):



According to **TP15**, the substituted (trimethylsilyl)methyl-derivative **30** was synthesized from **25c** (1 mmol) after deprotonation with LDA (1.2 equiv), followed by trapping with TMSCl (1.3 equiv). The desired chloromethyl-bipyridine **29c** was then obtained from the reaction of **30** with CsF (2 equiv) and C_2Cl_6 (2 equiv) at reflux for 3 h. Flash column chromatography (DCM) furnished **29c** as beige powder (168 mg, 62% over these two steps).

m.p.: 79.6 - 81.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 4.29 (d, *J*=11.22 Hz, 1 H), 4.48 (d, *J*=11.20 Hz, 1 H), 7.36 – 7.40 (m, 2 H), 7.54 (d, *J*=8.10 Hz, 1 H), 7.72 (dd, *J*=7.52, 1.92 Hz, 1 H), 8.47 (dd, *J*=4.79, 1.94 Hz, 1 H).

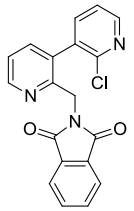
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 44.2, 122.6, 124.3, 131.8, 131.9, 140.1, 141.2, 150.0, 150.2, 151.3, 154.7.

MS (70 eV, EI) m/z (%): 276 (29), 274 (52), 272 (60), 237 (36), 202 (47), 201 (100), 85 (21), 71 (35), 66 (43), 57 (50), 44 (84).

IR ATR ν (cm^{-1}): 3050, 2924, 1570, 1552, 1432, 1396, 1380, 1126, 1116, 1082, 812, 750, 710, 696.

HRMS (EI) for **$C_{11}H_7Cl_3N_2$** (271.9675) $[M]^+$: 271.9664.

Synthesis of 2-((2'-chloro-[3,3'-bipyridin]-2-yl)methyl)isoindoline-1,3-dione (31a) according to (TP16):



According to **TP16**, the substituted phthalimide derivative **31a** was synthesized from **29a** (1 mmol) with potassium phthalimide (1.2 equiv) at 100 °C for 2 h. Flash column chromatography (*i*-hexane/ethyl acetate 7:3 + 2% NEt_3) furnished **31a** as white solid (283 mg, 81%).

m.p.: 166.9 - 168.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 4.59 (d, *J*=15.87 Hz, 1 H), 5.02 (d, *J*=15.89 Hz, 1 H), 7.27 – 7.30 (m, 1 H), 7.41 (dd, *J*=7.53, 4.79 Hz, 1 H), 7.52 (dd, *J*=7.70, 1.70 Hz, 1 H), 7.71 (dd, *J*=5.49, 3.05 Hz, 2 H), 7.82 – 7.86 (m, 3 H), 8.50 (dd, *J*=4.78, 1.95 Hz, 1 H), 8.55 (dd, *J*=4.79, 1.70 Hz, 1 H).

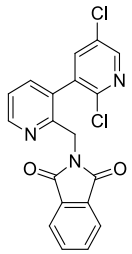
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 40.9, 122.4, 122.8, 123.5 (2C), 131.9, 132.4 (2C), 133.7, 134.1 (2C), 137.7, 140.1, 149.9 (2C), 150.8, 152.6, 168.3 (2C).

MS (70 eV, EI) m/z (%): 351 (10), 349 (28), 315 (20), 314 (100), 304 (11), 167 (36), 160 (17), 104 (12), 77 (11), 76 (12).

IR ATR ν (cm^{-1}): 3050, 2924, 2854, 1718, 1674, 1430, 1418, 1390, 1354, 1320, 1192, 1126, 1112,

1086, 1068, 1060, 998, 952, 942, 810, 798, 750, 736, 724, 710, 694, 684.
HRMS (EI) for $C_{19}H_{12}ClN_3O_2$ (349.0618) $[M]^+$: 349.0613.

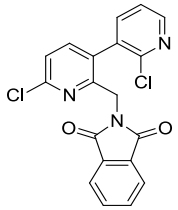
Synthesis of 2-((2',5'-dichloro-[3,3'-bipyridin]-2-yl)methyl)isoindoline-1,3-dione (31b) according to (TP16):



According to **TP16**, the substituted phthalimide derivative **31b** was synthesized from **29b** (1 mmol) with potassium phthalimide (1.2 equiv) at 100 °C for 2 h. Flash column chromatography (*i*-hexane/ethyl acetate 7:3 + 2% NEt_3) furnished **31b** as white solid (265 mg, 69%).

m.p.: 151.2 - 153.7 °C.
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 4.54 (d, *J*=15.85 Hz, 1 H), 4.94 (d, *J*=15.84 Hz, 1 H), 7.19 – 7.24 (m, 1 H), 7.44 (dd, *J*=7.71, 1.71 Hz, 1 H), 7.63 – 7.66 (m, 2 H), 7.75 – 7.79 (m, 3 H), 8.37 (d, *J*=2.58 Hz, 1 H), 8.50 (dd, *J*=4.83, 1.72 Hz, 1 H).
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 41.0, 122.5 (2C), 123.5, 130.6, 131.2, 132.3 (2C), 134.1 (2C), 134.6, 137.6, 139.5, 148.4, 148.6, 150.2, 152.6, 168.1 (2C).
MS (70 eV, EI) m/z (%): 385 (11), 383 (17), 385 (11), 383 (17), 350 (33), 349 (21), 348 (100), 203 (12), 201 (39), 160 (28), 104 (18), 77 (15), 76 (18).
IR ATR ν (cm^{-1}): 3048, 1710, 1392, 1016, 734, 724, 714.
HRMS (EI) for $C_{19}H_{11}Cl_2N_3O_2$ (383.0228) $[M]^+$: 383.0212.

Synthesis of 2-((2',6-dichloro-[3,3'-bipyridin]-2-yl)methyl)isoindoline-1,3-dione (31c) according to (TP16):



According to **TP16**, the substituted phthalimide derivative **31c** was synthesized from **29c** (1 mmol) with potassium phthalimide (1.2 equiv) at 100 °C for 4 h. Flash column chromatography (*i*-hexane/ethyl acetate 7:3 + 2% NEt_3) furnished **31c** as white solid (353 mg, 92%).

m.p.: 186.1 - 189.4 °C.
^{1}H NMR (800 MHz, $CDCl_3$) δ/ppm: 4.55 (d, *J*=16.08 Hz, 1 H), 4.96 (dd, *J*=16.09, 0.72 Hz, 1 H), 7.31 (d, *J*=8.00 Hz, 1 H), 7.39 (dd, *J*=7.50, 4.78 Hz, 1 H), 7.48 (d, *J*=7.99 Hz, 1 H), 7.72 (dd, *J*=5.49, 3.01 Hz, 2 H),

7.80 – 7.84 (m, 3 H), 8.48 (dd, *J*=4.78, 1.96 Hz, 1 H).

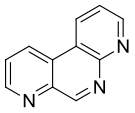
^{13}C NMR (201 MHz, $CDCl_3$) δ/ppm: 40.8, 123.0, 123.5, 123.7 (2C), 130.8, 132.4 (2C), 132.7, 134.3 (2C), 140.2, 140.6, 150.3, 150.8, 151.7, 153.7, 168.1 (2C).

MS (70 eV, EI) m/z (%): 385 (12), 383 (17), 385 (12), 383 (17), 350 (31), 349 (20), 348 (100), 201 (37), 160 (26), 104 (18), 77 (12), 76 (16).

IR ATR ν (cm^{-1}): 2959, 2922, 2850, 1768, 1713, 1555, 1419, 1389, 1109, 1082, 995, 947, 812, 728, 714, 698.

HRMS (EI) for **$C_{19}H_{11}Cl_2N_3O_2$** (383.0228) $[M]^+$: 383.0217.

Synthesis of pyrido[3,2-*f*][1,7]naphthyridine (23a) according to (TP17/18):



According to **TP17**, the substituted phthalimide derivative **31a** (1 mmol) reacted with $NH_2NH_2 \cdot H_2O$ (3 equiv) in EtOH at reflux for 2 h, leading to the dihydroazaphenanthrene **32a**. After acidic work-up and neutralization, the crude intermediate **32a** was aromatized with chloranil (1.2 equiv) at 25 °C for 2 h, as specified in **TP18**. Flash column chromatography (EtOAc + 2% NEt_3) furnished **23a** as beige powder (155 mg, 86% over these two steps).

m.p.: 230.1 - 232.3 °C.

^{1}H NMR (800 MHz, $CDCl_3$) δ/ppm: 7.70 (dd, *J*=8.08, 4.29 Hz, 1 H), 7.84 (dd, *J*=8.33, 4.25 Hz, 1 H), 8.89 – 8.93 (m, 2 H), 9.15 (dd, *J*=4.25, 1.56 Hz, 1 H), 9.18 (dd, *J*=4.26, 1.86 Hz, 1 H), 9.79 (s, 1 H).

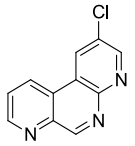
^{13}C NMR (201 MHz, $CDCl_3$) δ/ppm: 118.4, 123.1, 126.0, 128.4, 130.5, 132.0, 142.2, 152.1, 152.6, 153.9, 158.9.

MS (70 eV, EI) m/z (%): 182 (15), 181 (100), 180 (26), 97 (15), 85 (16), 83 (15), 71 (21), 57 (34), 43 (79).

IR ATR ν (cm^{-1}): 3054, 3006, 2922, 2852, 1744, 1602, 1572, 1440, 1370, 1350, 1316, 1160, 896, 786, 746, 710.

HRMS (EI) for **$C_{11}H_7N_3$** (181.0640) $[M]^+$: 181.0633.

Synthesis of 2-chloropyrido[3,2-*f*][1,7]naphthyridine (23b) according to (TP17/18):



According to **TP17**, the substituted phthalimide derivative **31b** (1 mmol) reacted with $NH_2NH_2 \cdot H_2O$ (3 equiv) in EtOH at reflux for 2 h, leading to the dihydroazaphenanthrene **32b**. After acidic work-up and neutralization, the crude intermediate **32b** was aromatized with chloranil (1.2 equiv) at 25 °C for 2 h, as specified in **TP18**. Flash column chromatography (EtOAc + 2% NEt_3) furnished **23b** as beige/light pink powder (161 mg, 75% over these two steps).

m.p.: decomposition starts at 276.3 °C.

^{1}H NMR (800 MHz, DMSO-d_6) δ/ppm: 8.05 (dd, *J*=8.34, 4.26 Hz, 1 H), 9.13 (d, *J*=2.52 Hz, 1 H), 9.21 (dd, *J*=4.26, 1.51 Hz, 1 H), 9.40 – 9.43 (m, 1 H), 9.54 (d, *J*=2.56 Hz, 1 H), 9.66 (d, *J*=0.80 Hz, 1 H).

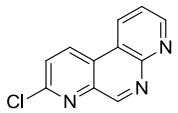
^{13}C NMR (201 MHz, DMSO-d_6) δ/ppm: 119.2, 126.6, 127.5, 129.8, 132.1, 132.3, 141.3, 150.6, 151.1, 152.7, 158.1.

MS (70 eV, EI) m/z (%): 217 (31), 216 (13), 215 (100), 180 (34), 153 (12).

IR ATR ν (cm^{-1}): 3064, 2946, 2924, 2854, 1600, 1568, 1464, 1450, 1366, 1330, 1234, 1120, 948, 900, 878, 826, 796, 742, 726.

HRMS (EI) for **$C_{11}H_6ClN_3$** (215.0250) $[M]^+$: 215.0243.

Synthesis of 8-chloropyrido[3,2-*f*][1,7]naphthyridine (23c) according to (TP17/18):



According to **TP17**, the substituted phthalimide derivative **31c** (1 mmol) reacted with $NH_2NH_2{\cdot}H_2O$ (3 equiv) in EtOH at reflux for 2 h, leading to the dihydroazaphenanthrene **32c**. After acidic work-up and neutralization, the crude intermediate **32c** was aromatized with chloranil (1.2 equiv) at 25 °C for 2 h, as specified in **TP18**. Flash column chromatography (EtOAc + 2% NEt_3) furnished **23c** as beige solid (191 mg, 89% over these two steps).

m.p.: decomposition starts at 226.8 °C.

^{1}H NMR (800 MHz, DMSO-d_6) δ/ppm: 7.87 (dd, *J*=8.11, 4.26 Hz, 1 H), 8.13 (d, *J*=8.64 Hz, 1 H), 9.15 (dd, *J*=4.28, 1.80 Hz, 1 H), 9.34 (dd, *J*=8.21, 1.82 Hz, 1 H), 9.39 – 9.43 (m, 1 H), 9.58 (d, *J*=0.76 Hz, 1 H).

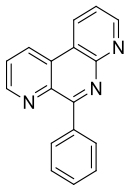
^{13}C NMR (201 MHz, DMSO-d_6) δ/ppm: 117.8, 123.6, 127.4, 127.6, 133.6, 135.8, 141.0, 151.9, 152.7, 152.9, 156.3.

MS (70 eV, EI) m/z (%): 217 (36), 215 (100), 180 (39), 153 (11), 84 (54), 66 (56), 46 (13).

IR ATR ν (cm^{-1}): 3483, 2249, 2124, 1997, 1622, 1438, 1222, 1053, 1024, 1005, 820, 757.

HRMS (EI) for **$C_{11}H_6ClN_3$** (215.0250) $[M]^+$: 215.0242.

Synthesis of 6-phenylpyrido[3,2-*f*][1,7]naphthyridine (33a) according to (TP19/20):



According to **TP20**, the substituted azaphenanthrene derivative **33a** was synthesized from **23a** (0.1 mmol) with the organolithium reagent **34a** (0.52 M in diethyl ether, 1.5 equiv, **TP19**) at -60 °C for 30 min in THF, followed by chloranil-mediated aromatization in DMF overnight. Flash column chromatography (EtOAc + 5% NEt_3) furnished **33a** as colorless solid (24 mg, 93%).

m.p.: 217 - 218 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.48 - 7.59 (m, 3 H), 7.64 (dd, *J*=8.2, 4.4 Hz, 1 H), 7.80 (dd, *J*=8.4, 4.3 Hz, 1 H), 8.30 (dd, *J*=7.7, 1.8 Hz, 2 H), 8.87 (dd, *J*=8.2, 1.8 Hz, 1 H), 8.94 (dd, *J*=8.4, 1.6 Hz, 1 H), 9.13 - 9.16 (m, 2 H).

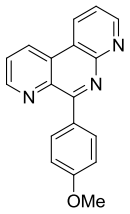
^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 118.1, 122.4, 125.2, 127.9 (2C), 129.2, 129.8, 130.6, 131.4, 131.8 (2C), 138.1, 141.1, 150.9, 152.6, 153.1, 164.0.

MS (70 eV, EI) m/z (%): 258 (25), 257 (100), 129 (10), 84 (12).

IR ATR ν (cm^{-1}): 3060, 2927, 2360, 2231, 1712, 1556, 1514, 1452, 1434, 1356, 1260, 905, 793, 710, 693, 686.

HRMS (EI) for **$C_{17}H_{11}N_3$** (257.0953) $[M]^+$: 257.0950

Synthesis of 6-(4-methoxyphenyl)pyrido[3,2-*f*][1,7]naphthyridine (33b) according to (TP19/20):



According to **TP20**, the substituted azaphenanthrene derivative **33b** was synthesized from **23a** (0.1 mmol) with the organolithium reagent **34b** (0.50 M, 1.5 equiv, **TP19**) at -60 °C for 30 min in THF, followed by chloranil-mediated aromatization in DMF overnight. Flash column chromatography (EtOAc + 5% NEt_3) furnished **33b** as colorless solid (25 mg, 87%).

m.p.: 156 - 157 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 3.91 (s, 3 H), 7.07 - 7.10 (m, 2 H), 7.63 (dd, *J*=8.1, 4.4 Hz, 1 H), 7.81 (dd, *J*=8.4, 4.3 Hz, 1 H), 8.34 - 8.45 (m, 2 H), 8.86 (dd, *J*=8.2, 1.7 Hz, 1 H), 8.94 (dd, *J*=8.5, 1.5 Hz, 1 H), 9.10 - 9.21 (m, 2 H).

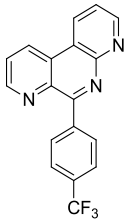
^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 55.5, 113.5, 117.9, 122.1, 125.1, 129.3, 130.6 (2C), 130.7, 131.3, 133.6 (2C), 141.2, 150.8, 152.5, 153.2, 161.3, 163.2.

MS (70 eV, EI) m/z (%): 288 (18), 287 (92), 273 (17), 272 (100), 256 (13), 244 (30), 243 (17), 122 (10).

IR ATR ν (cm^{-1}): 2956, 2927, 1605, 1574, 1552, 1449, 1436, 1354, 1299, 1213, 1175, 1030, 968, 833, 789, 712.

HRMS (EI) for **$C_{18}H_{13}N_3O$** (287.1059) $[M]^+$: 287.1054.

Synthesis of 6-(4-(trifluoromethyl)phenyl)pyrido[3,2-*f*][1,7]naphthyridine (33c) according to (TP19/20):



According to **TP20**, the substituted azaphenanthrene derivative **33c** was synthesized from **23a**

(0.1 mmol) with the organolithium reagent **34c** (0.65 M, 1.5 equiv, **TP19**) at -60 °C for 30 min in THF, followed by chloranil-mediated aromatization in DMF overnight. Flash column chromatography (EtOAc + 5% NEt_3) furnished **33c** as colorless solid (22 mg, 68%).

m.p.: 224 °C

^{1}H NMR (800 MHz, $CDCl_3$) δ/ppm: 7.72 (dd, *J*=8.1, 4.3 Hz, 1 H), 7.82 (d, *J*=8.0 Hz, 2 H), 7.87 (dd, *J*=8.3, 4.2 Hz, 1 H), 8.43 (d, *J*=8.0 Hz, 2 H), 8.94 (dd, *J*=8.2, 1.8 Hz, 1 H), 9.01 (dd, *J*=8.4, 1.6 Hz, 1 H), 9.17 (dd, *J*=4.2, 1.6 Hz, 1 H), 9.20 (dd, *J*=4.3, 1.8 Hz, 1 H).

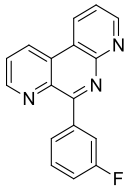
^{13}C NMR (200 MHz, $CDCl_3$) δ/ppm: 118.4, 123.0, 123.7, 124.9, 125.6, 129.4, 130.8, 131.4, 131.5, 132.1 (4C), 140.9, 141.4, 151.1, 152.9, 162.6.

MS (70 eV, EI) m/z (%): 326 (17), 325 (100), 325 (57).

IR ATR ν (cm^{-1}): 2924, 2854, 2360, 2340, 1737, 1714, 1597, 1565, 1453, 1442, 1322, 1259, 1207, 1155, 1119, 1066, 959, 784, 775, 712.

HRMS (EI) for **$C_{18}H_{10}N_3F_3$** (325.0827): $[M]^+$: 325.0821.

Synthesis of 6-(3-fluorophenyl)pyrido[3,2-*f*][1,7]naphthyridine (33d) according to (TP19/20):



According to **TP20**, the substituted azaphenanthrene derivative **33d** was synthesized from **23a** (0.1 mmol) with the organolithium reagent **34d** (0.91 M, 1.5 equiv, **TP19**) at -60 °C for 30 min in THF, followed by chloranil-mediated aromatization in DMF overnight. Flash column chromatography (EtOAc + 5% NEt_3) furnished **33d** as colorless solid (17 mg, 62%).

m.p.: 237 - 238 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.19 - 7.25 (m, 1 H), 7.48 - 7.56 (m, 1 H), 7.68 (dd, *J*=8.2, 4.4 Hz, 1 H), 7.84 (dd, *J*=8.4, 4.3 Hz, 1 H), 8.07 - 8.11 (m, 1 H), 8.12 - 8.16 (m, 1 H), 8.90 (dd, *J*=8.2, 1.8 Hz, 1 H), 8.97 (dd, *J*=8.5, 1.7 Hz, 1 H), 9.11-9.22 (m, 2 H).

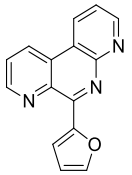
^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm: 116.6, 116.8, 118.3, 118.8, 119.0, 122.8, 125.4, 127.6, 129.3, 129.4, 130.7, 131.4, 151.0, 152.8, 161.3, 162.4, 163.7.

MS (70 eV, EI) m/z (%): 276 (14), 275 (100), 274 (75).

IR ATR ν (cm^{-1}): 2956, 2927, 2857, 1738, 1729, 1596, 1568, 1450, 1442, 1358, 1261, 1059, 791, 712.

HRMS (EI) for **$C_{17}H_{10}FN_3$** (275.0859): $[M]^+$: 275.0852.

Synthesis of 6-(furan-2-yl)pyrido[3,2-*f*][1,7]naphthyridine (33e) according to (TP19/20):



According to **TP20**, the substituted azaphenanthrene derivative **33e** was synthesized from **23a** (0.1 mmol) with the organolithium reagent **34e** (0.52 M, 1.5 equiv, **TP19**) at -60 °C for 30 min in THF, followed by chloranil-mediated aromatization in DMF overnight. Flash column chromatography (EtOAc + 5% NEt_3) furnished **33e** as colorless solid (20 mg, 80%).

m.p.: 228 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 6.68 (dd, *J*=3.4, 1.7 Hz, 1 H), 7.59 (dd, *J*=8.1, 4.3 Hz, 1 H), 7.76 - 7.84 (m, 2 H), 8.33 (dd, *J*=3.4, 0.7 Hz, 1 H), 8.79 (dd, *J*=8.1, 1.8 Hz, 1 H), 8.89 (dd, *J*=8.4, 1.6 Hz, 1 H), 9.12 (dd, *J*=4.3, 1.8 Hz, 1 H), 9.15 (dd, *J*=4.2, 1.6 Hz, 1 H).

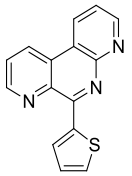
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 112.5, 117.6, 120.5, 122.1, 125.4, 128.9, 130.6, 131.1, 139.9, 145.7, 150.8, 150.8, 152.0, 152.7, 153.2.

MS (70 eV, EI) m/z (%): 248 (24), 247 (100), 246 (12), 220 (10), 219 (36), 218 (21), 191 (11), 44 (24), 43 (17).

IR ATR ν (cm^{-1}): 2956, 2943, 2858, 1737, 1729, 1671, 1601, 1569, 1519, 1450, 1442, 1359, 1261, 1058, 792, 712.

HRMS (EI) for **$C_{15}H_9N_3O$** (247.0746): $[M]^+$: 247.0745.

Synthesis of 6-(thiophen-2-yl)pyrido[3,2-*f*][1,7]naphthyridine (33f) according to (TP19/20):



According to **TP20**, the substituted azaphenanthrene derivative **33f** was synthesized from **23a** (0.1 mmol) with the organolithium reagent **34f** (0.64 M, 1.5 equiv, **TP19**) at -60 °C for 30 min in THF, followed by chloranil-mediated aromatization in DMF overnight. Flash column chromatography (EtOAc + 5% NEt_3) furnished **33f** as white solid (12 mg, 46%).

m.p.: 221 - 223 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.26 -7.28 (m, 1 H), 7.60 (dd, *J*=8.1, 4.3 Hz, 1 H), 7.68 (dd, *J*=5.0, 1.1 Hz, 1 H), 7.84 (dd, *J*=8.4, 4.2 Hz, 1 H), 8.82 (dd, *J*=8.1, 1.8 Hz, 1 H), 8.92 (dd, *J*=8.4, 1.6 Hz, 1 H), 8.96 - 9.00 (m, 1 H), 9.13 (dd, *J*=4.2, 1.6 Hz, 1 H), 9.20 (dd, *J*=4.2, 1.6 Hz, 1 H).

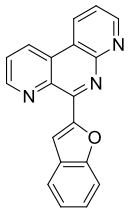
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 117.8, 121.9, 125.5, 127.7, 128.9, 130.7, 131.3, 133.1, 133.7, 140.0, 140.7, 150.3, 152.8, 153.2, 156.5.

MS (70 eV, EI) m/z (%):264 (18), 263 (100), 262 (61).

IR ATR ν (cm^{-1}): 2924, 2853, 1569, 1551, 1506, 1447, 1360, 1223, 1042, 848, 786, 714, 673.

HRMS (EI) for **$C_{15}H_9N_3S$** (263.0517): $[M]^+$: 263.0512.

Synthesis of 6-(benzofuran-2-yl)pyrido[3,2-*f*][1,7]naphthyridine (33g) according to (TP19/20):



According to **TP20**, the substituted azaphenanthrene derivative **33g** was synthesized from **23a** (0.1 mmol) with the organolithium reagent **34g** (0.64 M, 1.5 equiv, **TP19**) at -60 °C for 30 min in THF, followed by chloranil-mediated aromatization in DMF overnight. Flash column chromatography (EtOAc + 5% NEt_3) furnished **33g** as colorless solid (10 mg, 34%).

m.p.: 219 - 223 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.30 (ddd, *J*=7.8, 7.2, 0.9 Hz, 1 H), 7.43 (ddd, *J*=8.3, 7.2, 1.3 Hz, 1 H), 7.66 (dd, *J*=8.1, 4.3 Hz, 1 H), 7.74 (d, *J*=8.3 Hz, 1 H), 7.78 (d, *J*=7.7 Hz, 1 H), 7.88 (dd, *J*=8.4, 4.2 Hz, 1 H), 8.78 - 8.83 (m, 1 H), 8.86 (dd, *J*=8.2, 1.8 Hz, 1 H), 8.96 (dd, *J*=8.4, 1.6 Hz, 1 H), 9.19 (dd, *J*=4.3, 1.8 Hz, 1 H), 9.23 (dd, *J*=4.2, 1.7 Hz, 1 H).

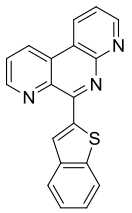
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 112.5, 116.7, 118.0, 122.6, 122.7, 123.2, 125.5, 126.8, 129.0, 129.2, 130.8, 131.2, 140.5, 150.9, 151.9, 152.3, 152.9, 155.7.

MS (70 eV, EI) m/z (%):298 (21), 297 (100), 296 (28), 269 (10), 268 (11).

IR ATR ν (cm^{-1}): 2923, 2853, 1595, 1561, 1513, 1462, 1449, 1364, 1343, 1261, 1166, 983, 789, 751, 694.

HRMS (EI) for **$C_{19}H_{11}N_3O$** (297.0902): $[M]^+$: 297.0898.

Synthesis of 6-(benzo[*b*]thiophen-2-yl)pyrido[3,2-*f*][1,7]naphthyridine (33h) according to (TP19/20):



According to **TP20**, the substituted azaphenanthrene derivative **33h** was synthesized from **23a** (0.1 mmol) with the organolithium reagent **34h** (0.78 M, 1.5 equiv, **TP19**) at -60 °C for 30 min in THF, followed by chloranil-mediated aromatization in DMF overnight. Flash column chromatography (EtOAc + 5% NEt_3) furnished **33h** as colorless solid (16 mg, 51%).

m.p.: 215 - 216 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 7.35 - 7.45 (m, 2 H), 7.60 (dd, *J*=8.0, 4.3 Hz, 1 H), 7.82 (dd, *J*=8.3, 4.2 Hz, 1 H), 7.95 (t, *J*=8.6 Hz, 2 H), 8.80 (dd, *J*=8.1, 1.7 Hz, 1 H), 8.89 (dd, *J*=8.3, 1.5 Hz, 1 H), 9.14 (dd,

J=4.1, 1.6 Hz, 1 H), 9.20 (dd, *J*=4.1, 1.4 Hz, 1 H), 9.32 (s, 1 H).

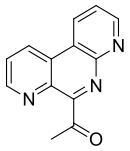
^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 118.1, 122.3, 122.4, 124.4, 125.4, 125.5, 126.0, 128.9, 130.7, 131.3 (2C), 140.2, 140.5, 141.5, 143.6, 150.4, 152.9 (2C), 156.4.

MS (70 eV, EI) m/z (%): 314 (26), 313 (100), 312 (53), 156 (15).

IR ATR ν (cm^{-1}): 3056, 2925, 2856, 1711, 1594, 1552, 1564, 1552, 1519, 1456, 1445, 1357, 1342, 1260, 1207, 1172, 1154, 954, 784, 775, 728, 712, 687.

HRMS (EI) for **$C_{19}H_{11}N_3S$** (313.0674): $[M]^+$: 313.0666.

Synthesis of 1-(pyrido[3,2-*f*][1,7]naphthyridin-6-yl)ethanone (33i) according to (TP19/20):



According to **TP20**, the substituted azaphenanthrene derivative **33i** was synthesized from **23a** (0.1 mmol) with the organolithium reagent **34i** (0.91 M, 1.5 equiv, **TP19**) at -60 °C for 30 min in THF, followed by chloranil-mediated aromatization in DMF overnight. After aqueous workup and extraction with EtOAc, all solvents were removed *in vacuo.* The crude was then re-dissolved in 2 mL of a mixture of methanol and 2 M *aq.* HCl (40:1, 0.05 N) and stirred at room temperature overnight. After aqueous workup, the crude was extracted with EtOAc and flash column chromatography (EtOAc + 5% NEt_3) furnished **33i** as colorless solid (20 mg, 90%).

m.p.: 147 °C.

^{1}H NMR (800 MHz, $CDCl_3$) δ/ppm: 2.94 (s, 3 H), 7.75 (dd, *J*=8.1, 4.3 Hz, 1 H), 7.85 (dd, *J*=8.4, 4.2 Hz, 1 H), 8.91 (dd, *J*=8.2, 1.7 Hz, 1 H), 8.94 (dd, *J*=8.4, 1.4 Hz, 1 H), 9.16 (dd, *J*=4.2, 1.5 Hz, 1 H), 9.20 (dd, *J*=4.1, 1.5 Hz, 1 H).

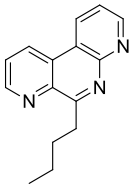
^{13}C NMR (200 MHz, $CDCl_3$) δ/ppm: 30.0, 119.2, 123.7, 126.1, 129.3, 130.6, 131.7, 139.3, 151.9, 152.2, 153.0, 162.2, 201.7.

MS (70 eV, EI) m/z (%): 224 (15), 223 (100), 195 (30), 181 (26), 180 (80), 154 (14), 153 (18), 126 (18), 43 (16).

IR ATR ν (cm^{-1}): 2928, 2360, 2338, 1714, 1601, 1567, 1455, 1442, 1378, 1346, 1264, 1210, 1152(w), 904, 789, 700.

HRMS (EI) for **$C_{13}H_9N_3O$** (223.0746): $[M]^+$: 223.0740.

Synthesis of 6-butylpyrido[3,2-*f*][1,7]naphthyridine (33j) according to (TP19/20):



According to **TP20**, the substituted azaphenanthrene derivative **33j** was synthesized from **23a** (0.1 mmol) with the organolithium reagent **34j** (2.43 M, 1.5 equiv, **TP19**) at -60 °C for 30 min in THF,

followed by chloranil-mediated aromatization in DMF overnight. Flash column chromatography (EtOAc + 5% NEt_3) furnished **33j** as colorless solid (18 mg, 76%).

m.p.: 131 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm: 1.01 (t, *J*=7.4 Hz, 3 H), 1.59 – 1.53 (m, 2 H), 2.00 - 2.07 (m, 2 H), 3.64 - 3.69 (m, 2 H), 7.60 (dd, *J*=8.1, 4.4 Hz, 1 H), 7.79 (dd, *J*=8.3, 4.3 Hz, 1 H), 8.83 (ddd, *J*=8.4, 1.6, 0.2 Hz, 1 H), 8.88 (ddd, *J*=8.3, 1.6, 0.3 Hz, 1 H), 9.10 (dd, *J*=4.4, 1.8 Hz, 1 H), 9.12 (dd, *J*=4.3, 1.6 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ/ppm: 14.3, 23.2, 30.9, 34.6, 117.7, 122.0, 125.4, 127.9, 130.5, 131.4, 141.4, 150.7, 152.1, 153.2, 169.7.

MS (70 eV, EI) m/z (%): 237 (45), 211 (15), 210 (23), 209 (20), 208 (100), 207 (42), 206 (17), 196 (53), 195 (20), 194 (25), 182 (27), 181 (26), 180 (25), 155 (12), 71 (13), 57 (21), 43 (13).

IR ATR ν (cm^{-1}): 2956, 2943, 2858, 1737, 1729, 1671, 1601, 1569, 1519, 1450(s), 1442, 1359, 1261, 1058, 792, 712.

HRMS (EI) for **$C_{15}H_{15}N_3$** (237.1266): $[M]^+$: 237.1274.

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