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Iron and Palladium Catalyzed C-H Functionalization

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Erklärung

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Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig, ohne unerlaubte Hilfe erarbeitet.

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WEI HAN

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...dedicated to my parents

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Wei Han, Armin R. Ofial, *Chem. Commun*. **2009**, 6023–6025.

Iron-Catalyzed Oxidative Mono- and Bis-phosphonation of *N,N*-Dialkylanilines
Wei Han, Peter Mayer, Armin R. Ofial, *Adv. Synth. Catal*. **2010**, *352*, 1667-1676.

***trans*-1-Phenylpyrrolidine-2,5-dicarbonitrile**
Wei Han, Armin R. Ofial, Peter Mayer, *Acta Crystallogr.*, *Sect*. *E*: *Struct. Rep*. *Online* **2010**, *66*, o397.

Palladium-Catalyzed Dehydrogenative Cross Couplings of Benzazoles with Azoles
Wei Han, Peter Mayer, Armin R. Ofial, *Angew. Chem. Int. Ed.* **2010**, *50*, 2178-2182.

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Catalytic and Highly Selective Double C-H Bonds Cross-Coupling of Azoles
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List of Abbreviations:

Ac	acetyl
Ar	aryl
atm	atmosphere
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bpy	2,2'-bipyridine
BQ	1,4-benzoquinone
Bu	butyl
cf.	compare
calc.	calculated
d	doublet
dba	dibenzylideneacetone
CDC	cross-dehydrogenative coupling
CMD	concerted metallation deprotonation
cod	1,5-cyclooctadiene
DCE	1,2-dichloroethane
DMAc	*N,N*-dimethylacetamide
DMF	dimethylformamide
DMOP	2,6-dimethoxypyridine
DMSO	dimethyl sulfoxide
dppbz	1,2-bis(diphenylphosphino)benzene
E	electrophile
EI	electron impact
e.g.	exempli gratia
Eq.	equation
equiv	equivalent
ESI	electrospray-ionization
Et	ethyl
et al	et alii
FG	functional group

GC-MS	gas chromatography- mass spectrometry
h	hour(s)
HRMS	high resolution mass spectrospcopy
i.e.	id est
*i*Pr	isopropyl
IR	infra-red
J	coupling constant (NMR)
m	meta
Me	methyl
mp	melting point
Ms	methanesulfonyl
n	normal
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
Phen	1,10-phenanthroline
Piv	pivalate
q	quartet
R	organic substituent
r.t.	room temperature
s	singlet
SEM	2-(trimethylsilyl)ethoxymethyl
SET	single electron transfer
t	triplet
TBHP	*tert*-butylhydroperoxide
*t*Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethylpiperidinyloxy
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tol	toluene
Ts	4-toluenesulfonyl

Chapter 0

Summary

0.1 General

C–H functionalization is a class of reactions that could lead to a paradigm shift in organic synthesis, relying on the selective activation of ubiquitous C–H bonds in organic molecules instead of the standard approach of conducting transformations on pre-existing functional groups. This dissertation describes iron-catalyzed C(sp^3)–H functionalization of tertiary amines (including α-cyanation and α-phosphonation reactions) and palladium-catalyzed C(sp^2)–H functionalization of azoles (including direct Hiyama reactions, oxidative dehydrogenative couplings and trifluoromethylation reactions).

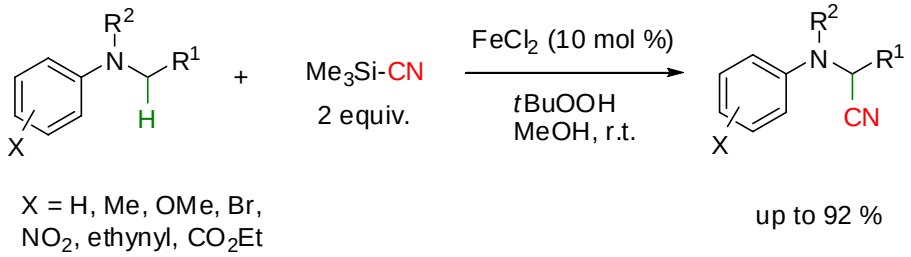
0.2 Fe Catalyzed C-H Bond Activation

Iron is ubiquitous in the geosphere with 4.7% wt abundance and in the biosphere where it is often found as part of catalytic systems. The low cost and ample supply of iron salts coupled with their environmentally benign nature and lack of toxicity make them ideal for industrial scale synthesis of fine chemicals. Commonly, Fe-catalyzed reactions require high temperature because iron often possesses low catalytic reactivity. So it is attractive to develop Fe catalytic systems for performing reactions at milder temperature, best at room temperature.

0.2.1 Iron Catalyzed Oxidative Cyanation of Tertiary Amines

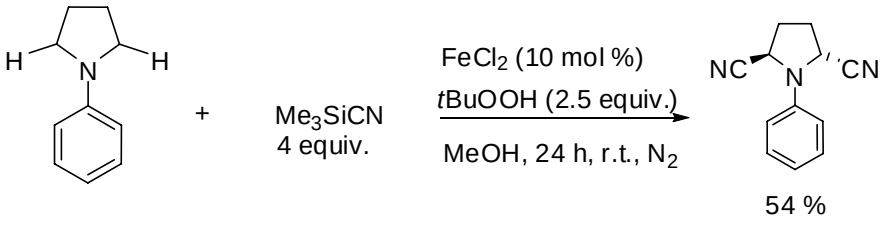
The α-aminonitriles are versatile synthetic intermediates and can be readily converted to biologically active compounds, such as α-amino acids, unsymmetrical 1,2-diamines, and quinoline skeletons. Metal-catalyzed oxidative α-cyanation of tertiary amines via direct

functionalization of C(sp^3)–H bonds provides access to these α-aminonitriles. So far, many toxic and/or noble metals, such as $RuCl_3$, V_2O_5, and $AuCl_3$, were used for this transformation. According to the requirements of green chemistry, a more environmentally benign and economical catalytic system is highly desirable. Here, we report the selective synthesis of α-aminonitriles under mild and acid-free conditions by activating C(sp^3)–H bonds of tertiary amines in the presence of inexpensive and non-toxic iron salts without designed ligands, as shown in Scheme 1.



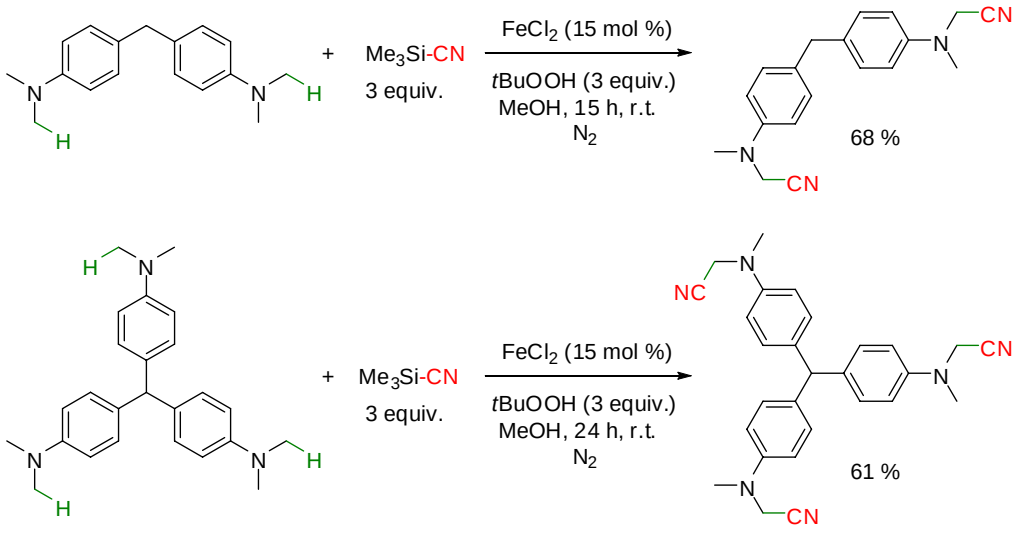
Scheme 1. Iron catalyzed oxidative cyanation of tertiary amines with Me_3SiCN.

The reaction conditions are tolerated by a wide variety of functional groups, such as methoxy, bromo, nitro, ethynyl and carboxylate. Additionally, 2-aryl-1,2,3,4-tetrahydro-isoquinolines (aryl = phenyl, *p*-anisyl) or *N*-phenyl-substituted cyclic amines were cyanated in high yield by the catalytic system. Interestingly, the 2,5-dicyanopyrrolidine moiety, which has been evaluated as a key part of inhibitors of dipeptidyl peptidase IV for the treatment of type 2 diabetes, was obtained from *N*-phenyl-pyrrolidine by using 4 equivalents of Me_3SiCN (Eq. 1).



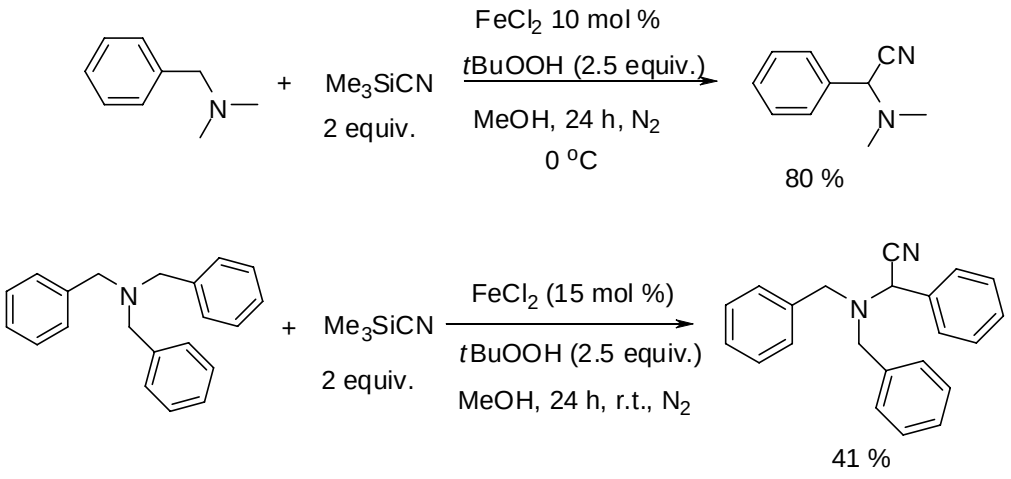
Eq. 1

Furthermore, bis(4-(dimethylamino)phenyl)methane and tris(4-(dimethylamino)-phenyl)methane were double cyanated and triple cyanated, respectively, whereas the readily oxidizable benzylic C-H bonds remained intact during the reactions (Scheme 2).



Scheme 2. Iron catalyzed double cyanation and triple cyanation reactions.

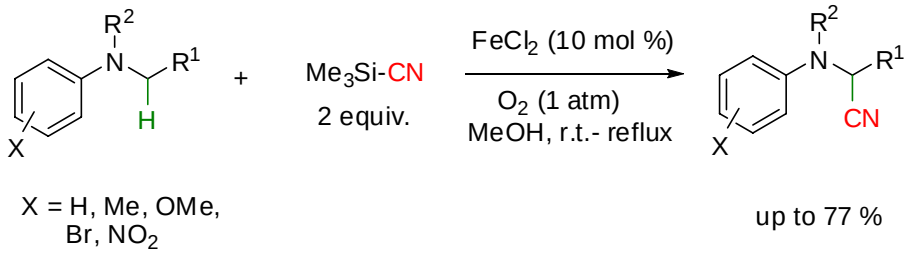
So far, metal-catalyzed α-cyanations of tertiary alkyl amines have not been described. Gratifyingly, *N,N*-dimethyl-benzylamine and tribenzylamine were selectively converted to the corresponding products in 80 % and 41 %, respectively, under similar conditions (Scheme 3).



Scheme 3. Iron catalyzed α-cyanations of *N,N*-dimethylbenzylamine and tribenzylamine.

Oxygen is an attractive, atom-economic, and environmentally benign oxidant due to the fact that it is cheap, widely available (20 vol % of air), and clean (only water as byproduct). We

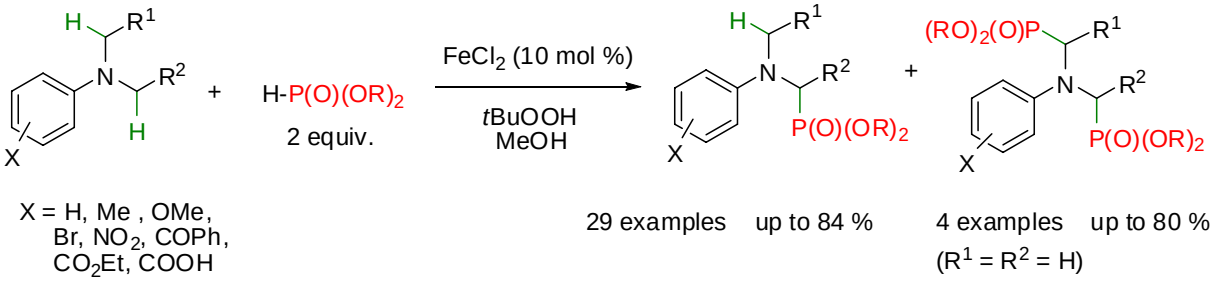
further developed the highly selective cyanation of various tertiary amines with molecular oxygen as the sole oxidant using $FeCl_2$ as catalyst in the presence of Me_3SiCN as cyanide source (Scheme 4).



Scheme 4. Iron catalyzed oxidative cyanation of tertiary amines with molecular oxygen as the sole oxidant.

0.2.2 Iron-Catalyzed Dehydrogenative Phosphonation of *N,N*-Dialkylanilines

α-Aminophosphonates and related α-aminophosphonic acids are important mimics for structurally analogous α-aminocarboxylic acids in which the planar carboxylic group is replaced by a sterically more demanding tetrahedral phosphonic acid moiety. Furthermore, α-aminophosphonates and the corresponding phosphonopeptides possess useful biological activity and have been studied, for example, as protease and human collagenase inhibitors, catalytic antibodies, neuroactive compounds, agrochemicals, antibacterial, antimicrobial, antifungal, anticancer, and antithrombotic agents. In this work, the selective synthesis of α-aminophosphonates under mild conditions was achieved by oxidizing tertiary amines in the presence of an inexpensive and non-toxic iron salt without designed ligands (Scheme 5). Moreover, the usefulness of the catalyst system described in this work is substantiated by the finding that direct α,α'-bisphosphonations of Ar-$N(CH_3)_2$ groups are feasible when both the oxidant and the phosphonation agent are employed in excess.

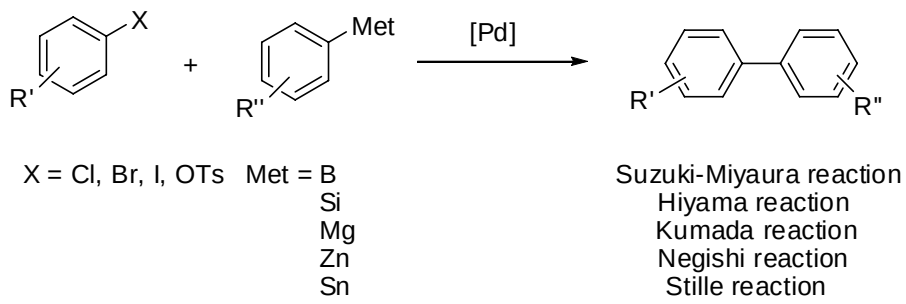


Scheme 5. Iron-catalyzed dehydrogenative phosphonation of tertiary aromatic amines.

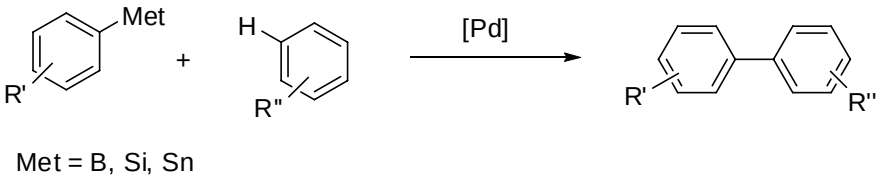
0.3 Palladium-Catalyzed Direct Arylations of Azoles with Aryl Silicon and Tin Reagents

Biaryl compounds play an important role in nature and many functional materials. Classical transition metal-catalyzed methods for the synthesis of biaryls, such as Kumada, Negishi, Stille, Suzuki, or Hiyama reactions, require functionalized arenes to enable the selective C–C bond formation between two arenes (Scheme 6). Such approaches require both coupling partners to be prefunctionalized prior to coupling, leading to long synthetic sequences for preparing the Ar-X and Ar'-Met starting materials from the corresponding arenes, during which waste is generated from reagents, solvents, and purifications. Furthermore, the introduced groups just yield undesirable inorganic salts after the cross couplings finish.

In comparison to the classic cross couplings, direct arylation reactions with organometallic reagents replace aryl halides/pseudohalides by simple arenes, leading to shorter synthetic schemes and an overall improved efficiency of chemical processes (Scheme 7). In recent years, the majority of the activities in the field of direct arylations concentrated on the use of organoboron reagents.



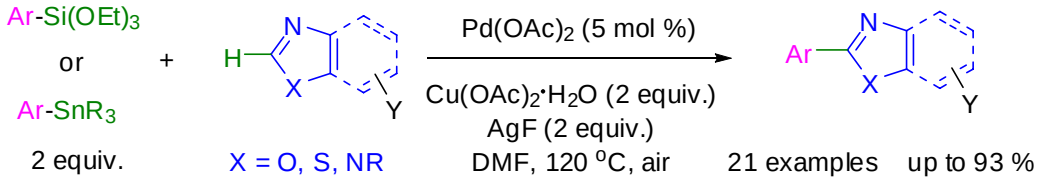
Scheme 6. Classical palladium-catalyzed methods for biaryls synthesis.



Scheme 7. Palladium-catalyzed direct arylation with organometallic reagents.

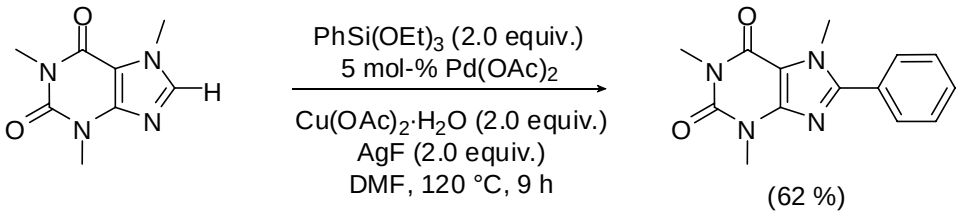
However, also the use of organosilicon compounds is of potential interest because of the low toxicity and safe handling of the organosilanes. Furthermore, the low electronegativity difference between carbon and silicon provides an advantageously high degree of compatibility with functional groups.

So far, only few intermolecular direct oxidative arylations of C(sp^2)–H bonds with organoelement compounds using group 14 elements have been investigated. We report on a convenient, efficient and "ligand-free" palladium-catalyzed direct arylation of C(sp^2)–H at C-2 of various azoles with trialkoxy(aryl)silanes and aryl tin compounds (Scheme 8).



Scheme 8. Palladium-catalyzed direct arylations of azoles with aryl silicon and tin reagents.

Caffeines with an aryl moiety at C-8 are of interest as potent and selective antagonists at human adenosine receptors. Indeed, the direct coupling between caffeine and triethoxy(phenyl)silane furnished 8-phenyl caffeine in 62 % yield (Eq. 2)

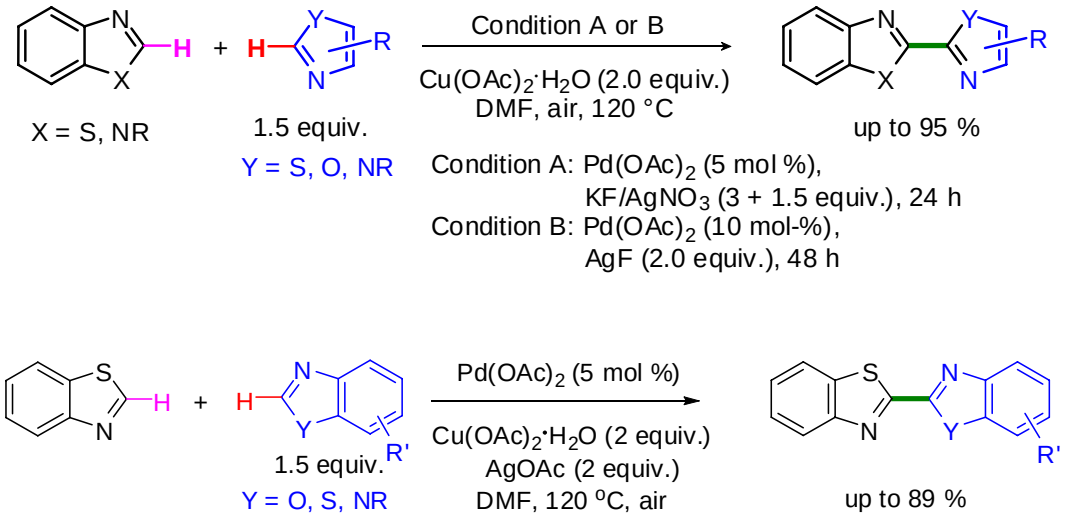


Eq. 2

0.4 Palladium-Catalyzed Dehydrogenative Cross Couplings of Azoles

The development of direct selective intermolecular heteroarylations of heteroarenes appears particularly beneficial because prefunctionalizations of heteroarenes are often difficult. From the viewpoint of atom economy, two-fold C–H bond activation is the ideal strategy for interconnecting two heteroarenes. Unfortunately, controlling the regioselectivity of the metal-catalyzed oxidative cross dehydrogenative reactions of two heteroaryl C-H bonds to form unsymmetrical biheteroaryl molecules remains a formidable challenge.

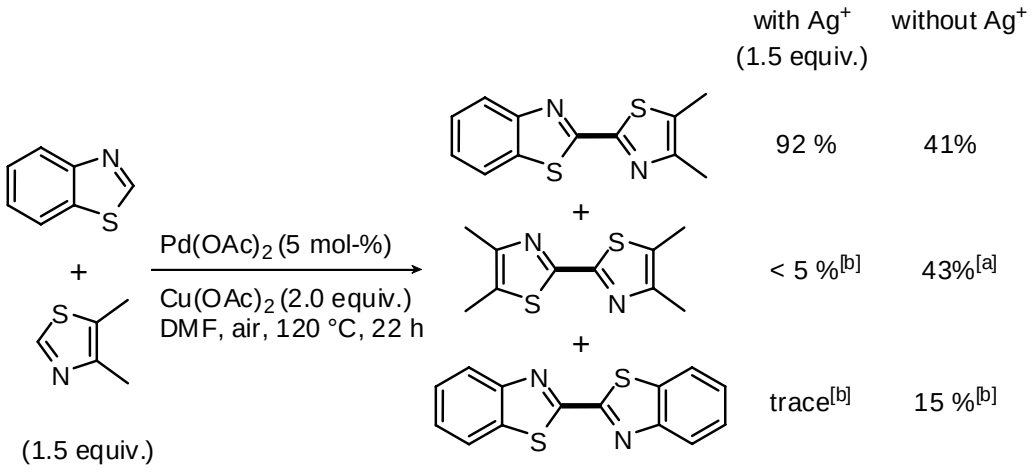
We report a method for the selective C–C coupling between the non-functionalized C-2 positions of azoles by a two-fold C–H bond activation which provides access to a class of widely unexplored unsymmetrical 2,2'-bisheteroaryls (Scheme 9). This is the first example of efficient C–H/C–H cross couplings between very similar partners.



Scheme 9. Palladium-catalyzed dehydrogenative cross couplings of azoles.

It is worth noting that under these reaction conditions, the active groups, such as allyl, vinyl, bromoaryl and even iodoaryl, remain intact. These groups are capable of undergoing further transformations to construct more complex molecules.

The success of these selective cross couplings is owed to Ag^{+} ions that suppress the formation of homocoupling products (Scheme 10).



[a] Isolated yield based on 4,5-dimethylthiazole.
[b] Estimated from GC-MS analysis.

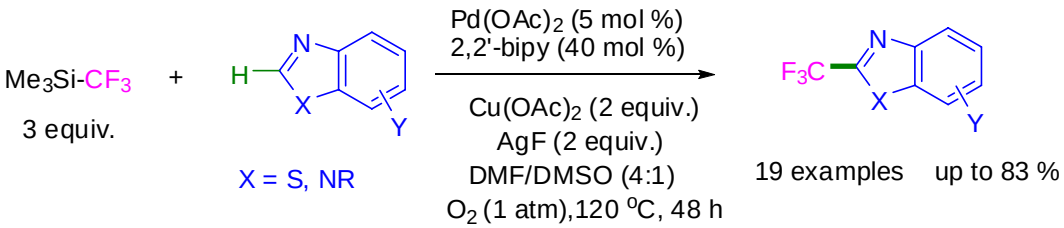
Scheme 10. Reaction of benzothiazole with 4,5-dimethylthiazole in the presence and the absence of Ag^+ ions.

0.5 Palladium-Catalyzed Direct Trifluoromethylation of Azoles via sp^2 C-H Activation

The substitution of CH_3 for CF_3 can remarkably alter the chemical and physical properties as well as the biological activity of the parent organic molecule leading to trifluoromethyl groups featured in numerous important pharmaceuticals. Notably, the two big selling antidepressants Prozac (fluoxetine) from Pfizer, and Luvox (fluvoxamine), made by Lilly, contain a trifluoromethylated phenyl group. Fluorine compounds are extremely rare in nature. Consequently, any fluorine-containing compound selected for fundamental studies or marketed as a pharmaceutical, agrochemical, or material has to be man-made. So, it has been a long-standing goal to invent new methods for preparing fluorinated molecules, in particular trifluoromethylarenes.

Traditional methods for introducing a trifluoromethyl group include the Swarts reaction and the treatment of benzoic acid derivatives with SF_4. The options usually require harsh conditions that limit the functional group tolerance. Alternatively, copper or palladium have been applied to mediate trifluoromethylation of prefunctionalized arenes, such as arylhalides or arylboronic acids. Meanwhile, it remains a big challenge to effectively achieve C-C bond formation from reductive elimination of CF_3 ligated metal complexes in catalysis.

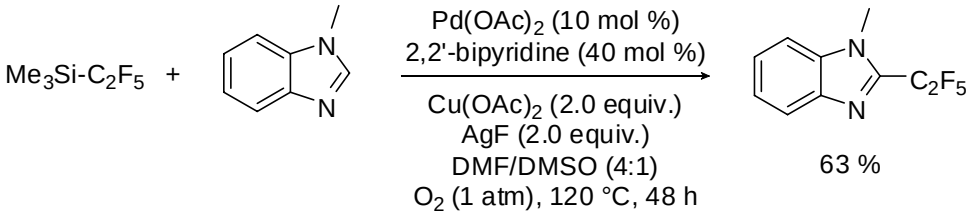
Hence, metal-catalyzed aryl C–H trifluoromethylation protocols remain rare. 2-(Trifluoromethyl)benzimidazoles are of wide interest due to their diverse biological activity acting as antiviral, antifungal, antibacterial, anticancer and antiparasitic drugs. We describe a novel palladium(II)-catalyzed direct aromatic trifluoromethylation via sp^2 C-H activation in the absence of a directing group (Scheme 11).



Scheme 11. Palladium-catalyzed direct trifluoromethylation of azoles via sp^2 C-H activation.

Active groups, such as allyl, fluoride, bromide or iodide were tolerated by the catalytic system. Especially noteworthy, the C-I bond on the aromatic ring remained intact, which could not be obtained by the previously reported copper- and palladium-mediated trifluoromethylations.

Gratifyingly, this protocol can be extended to pentafluoroethylation of 1-methyl-1H-benzimidazole with $Me_3SiCF_2CF_3$ to give the 1-methyl-2-(pentafluoroethyl)-1H-benzimidazole in 63 % yield (Eq. 3).



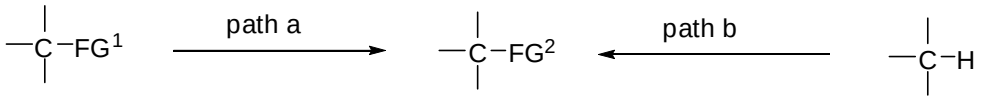
Eq. 3

Chapter 1

Introduction

1.1 General Overview

C-H functionalization represents an environmentally and economically attractive strategy to achieve efficient transformations.[1] Traditionally, the introduction of a functional group into a molecule needs a prefunctionalized starting material (Scheme 1, path a), that is to say, for the formation of a single chemical bond, one or more extra steps are required to preprepare the starting material from a raw material. Moreover, the introduced group FG^1 doesn't enter to the desired product. Consequently, much amount of waste is formed.



Scheme 1. Methods for introducing functional groups (FG) into organic molecules.

In contrast, C–H bonds are abundant in organic molecules; thus, viewing C–H bonds as "ubiquitous functionality" to attach various functional groups would be highly desirable (Scheme 1, path b).

However, the direct functionalizations of alkyl, alkenyl, and aryl C-H bonds are associated with two fundamental challenges in organic and organometallic chemistry. Firstly, selectivity is a large issue due to the numerous C–H bonds in nearly all organic molecules. For effective applications, one specific C-H bond must undergo activation, rather than multiple, diverse bonds in a molecule. Some strategies have been developed to achieve high selectivity such as directing group effect, intramolecular chelation effect, using one substrate in excess, electronic effect-regulated substrates, or steric effect-regulated substrates.[1]

The second challenge is the inert nature of C–H bonds. Their low reactivity can be attributed to the fact that they are strong and robust (bond dissociation energies in the range of 400-460 kJ/mol),[2] localized, and unpolarized bonds.[1b,3] This problem has been addressed by

using transition metals as reaction catalysts. Transition metals have been demonstrated as effective C–H bond activating agents via insertion into C–H bonds to form C–M bonds.[1] These C–M bonds are more reactive than the C–H counterparts and can subsequently be functionalized to afford the desired product. Among the metal catalysts, two metals have attracted considerable interest: one is iron, an ideal metal for catalysis.[4] The other is palladium, the most versatile metal catalyst in organic synthesis.[5]

In the following chapters, the use of iron as a catalyst for the functionalization of sp^3 C-H bonds adjacent to nitrogen is illustrated in "**1.2**". Futhermore, palladium as a catalyst for the activation of sp^2 C-H bonds will be introduced in "**1.3**" and "**1.4**".

1.2 Fe-Catalyzed Organic Reactions

1.2.1 Overview

Transition metal-catalyzed reactions are among the most powerful tools in organic synthesis. Extensive research effort has been invested in the development of palladium-, ruthenium-, rhodium-, iridium-, gold- and even nickel-catalyzed reactions. However, due to the high cost and toxic nature of most of these metal catalysts, there has been a recent surge in reports of organic transformations catalyzed by cheaper and more environmentally friendly metals such as copper and iron.[4]

In particular, iron-catalyzed reactions have several practical advantages over the analogous palladium- or nickel-mediated reactions. The low cost and ample supply of iron salts coupled with their environmentally benign nature and lack of toxicity make them ideal for industrial scale synthesis of fine chemicals. One of the most famous applications of iron in catalysis is Friedel-Crafts reaction.[6] Additionally, iron-catalyzed systems for C-H oxidation such as Gif[7] and Fenton chemistry[8] or nonheme mimic systems,[9] caused considerable interest. Until recently, however, iron was relatively underutilized in the field of catalysis if compared to other transition metals.[4,5c,10]

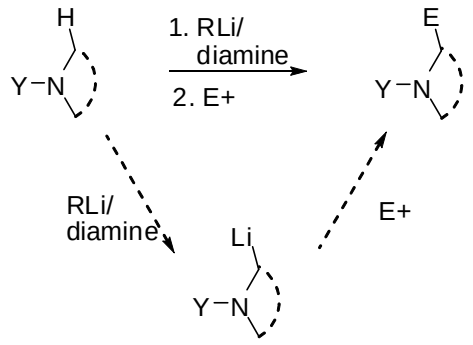
1.2.2 Functionalization of sp^3 C–H Bonds Adjacent to Nitrogen

Functionalization of nitrogen-containing compounds has attracted much interest in organic chemistry and the fine chemical industry in recent years, since functionalized nitrogen-containing compounds are versatile intermediates and have been widely used in the

construction of biologically active compounds and functional materials. Several methods exist for the synthesis of compounds that possess functional groups at the carbon atom adjacent to nitrogen. Nevertheless, most require long, impractical synthetic schemes. The most efficient introduction of a group at the α position of nitrogen-containing compounds would be performed by selective sp^3 C–H activation and subsequent carbon-carbon or carbon–heteroatom bond formation.[11]

Lithiation reactions

Historically, the oldest reported method for the sp^3 C–H functionalization of nitrogen-containing compounds is lithiation with alkyllithium/diamine complexes, forming a dipole-stabilized carbanion, followed by electrophilic substitution. The common dipole-stabilizing groups, including amide, phosphoramide, formamidine, oxazoline, nitroso, and carbamate functionalities, were effective for directed lithiations adjacent to nitrogen in tertiary amines. This general methodology is illustrated in Scheme 2 and has been reviewed.[12]



Y = NO, C(O)R, P(O)(NMe_2), -CH=N(*t*-Bu), Boc

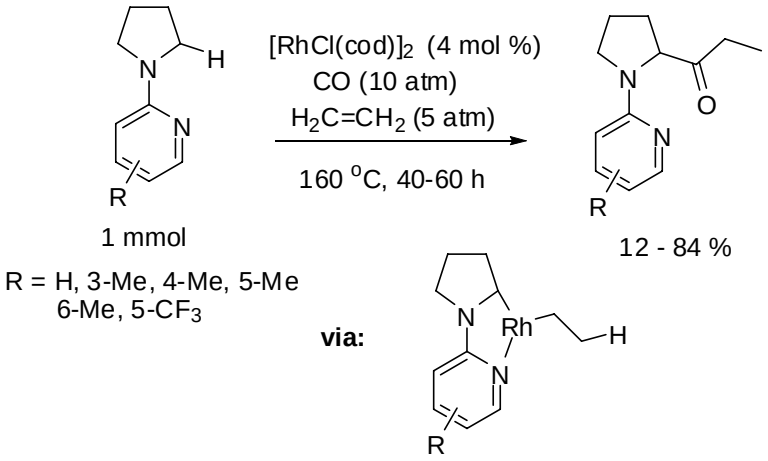
Scheme 2. α-Lithiation of nitrogen-containing compounds.

Noble metal catalysis

Despite the fact that this method showed high efficience and reactivity, lithium reagents are sensitive to air and moisture, leading to limitations for active groups already present in the substrate. In order to address these problems, the methodology of transition metal catalysis has been used to activate the sp^3 C–H bond adjacent to nitrogen atom.

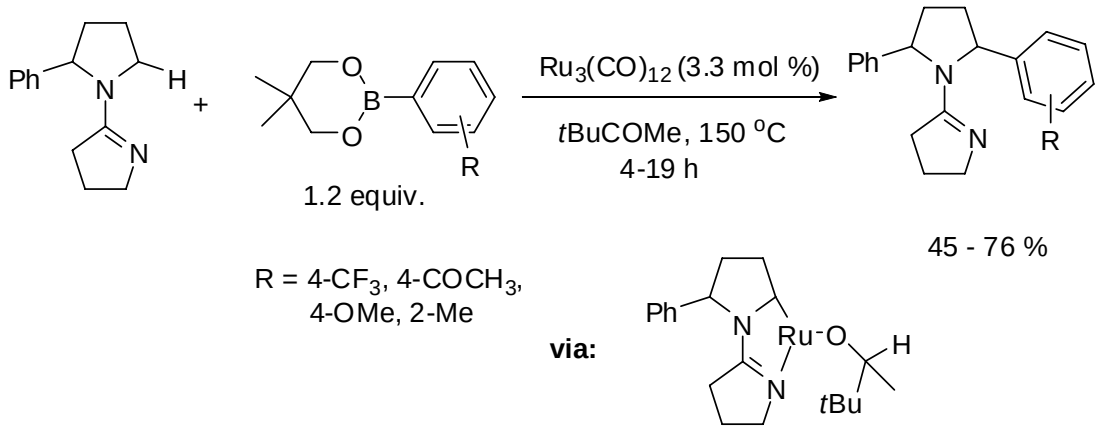
In 2000, Murai and co-workers described a pyridine-directed carbonylation at sp^3 C-H bonds adjacent to a nitrogen atom in alkylamines with the rhodium complex $[RhCl(cod)]_2$ as the catalyst (Scheme 3).[13] The reaction was slow (40–60 h) and required rather harsh

conditions (160 °C, 10 atm CO, 5 atm ethylene), affording the desired ketone in 12 to 84 % yield depending on the nature of the pyridine substituents. The reaction presumably involves a pyridine-directed C-H activation at the pyrrolidine ring, subsequent ethylene insertion into the hydride–rhodium bond, then CO insertion and reductive elimination.



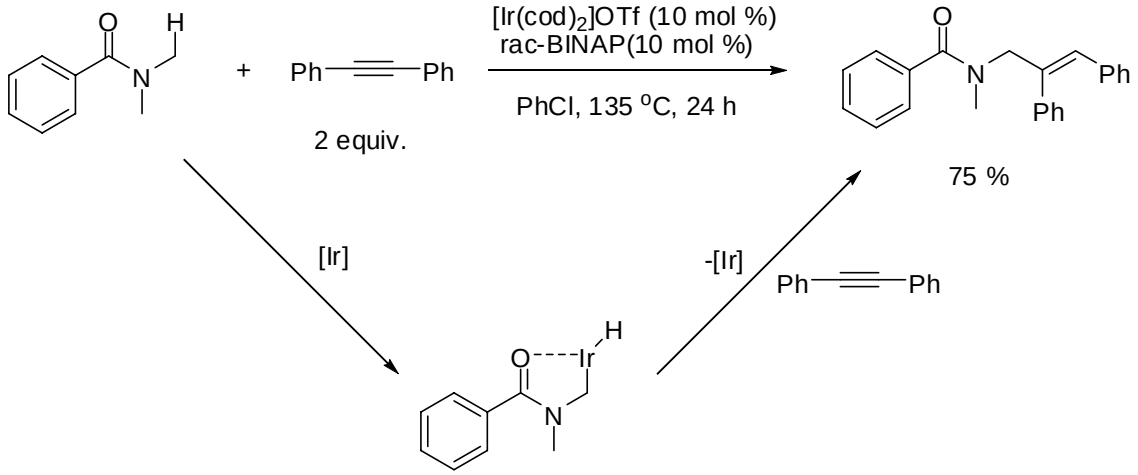
Scheme 3. Rh-catalyzed pyridine-directed carbonylation at sp^3C-H bonds in alkylamines by Murai.

Later, Sames' group disclosed a $Ru_3(CO)_{12}$-catalyzed sp^3C-H arylation of tertiary amines with arylboronates in the presence of an amidine protecting group (Scheme 4).[14] This catalytic method was compatible with a variety of arene donors containing both electron-donating and electron-withdrawing substituents. The mechanism was proposed to involve nitrogen-directed C-H activation to generate a ruthenium hydride intermediate that was trapped by ketone insertion, followed by transmetalation with the arylboronate and reductive elimination to afford the coupling product.



Scheme 4. $Ru_3(CO)_{12}$-catalyzed sp^3C-H arylation of tertiary amines with dihydropyrrole directing group by Sames.

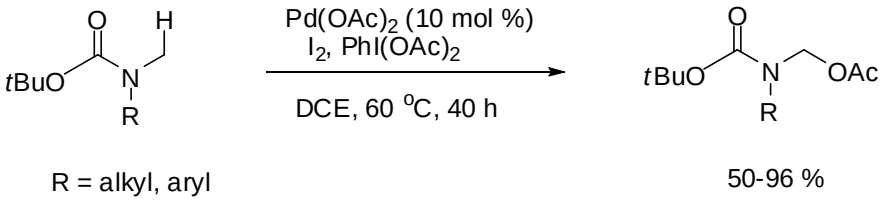
Shibata and co-workers developed a cationic iridium(I)–BINAP (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) complex-catalyzed alkenylation of arylamides α to the nitrogen with alkynes via carbonyl directed sp^3C-H bond activation. (Scheme 5).[15] This transformation was conducted at 135 °C and afforded moderate to good yields of allylamides with high regioselectivity. A deuterium-labeling experiment suggested that carbonyl-directed sp^3 C-H bond cleavage of amides is an initial step, which is followed by alkyne insertion to give the corresponding product.



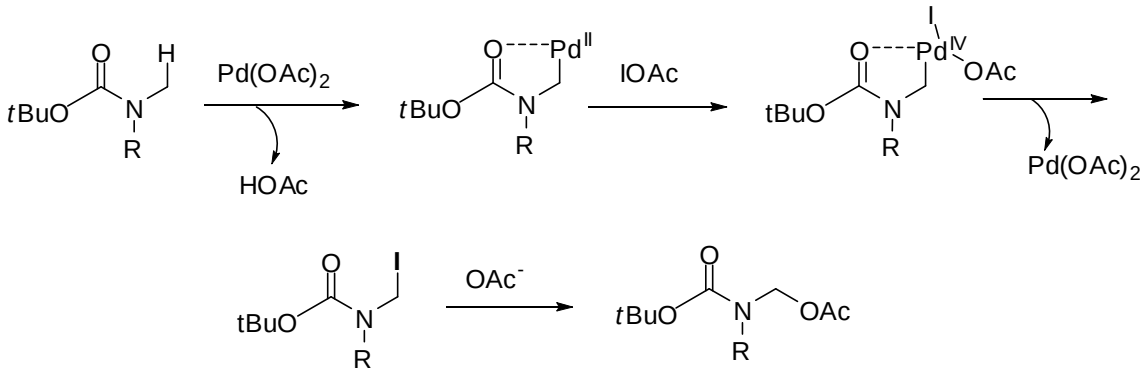
Scheme 5. Iridium(I)–BINAP-catalyzed carbonyl directed sp^3C-H bond activation/alkyne insertion by Shibata.

In 2006, Yu et al. reported Pd-catalyzed selective acetoxylations of *N*-methylamines directed by a Boc group with IOAc (or I_2 and $PhI(OAc)_2$) (Scheme 6).[16] This reaction proceeded under mild conditions and produced the acetoxylated products in good yields and

high selectivity. It was proposed that the transformation was initiated by σ-chelation-assisted sp^3 C-H insertion to form a Pd^{II} complex, followed by oxidative addition of IOAc to give a Pd^{IV} complex, which yields the iodinated product by reductive elimination. Subsequently, the iodinated product was attacked by acetate to afford the acetoxylated product.

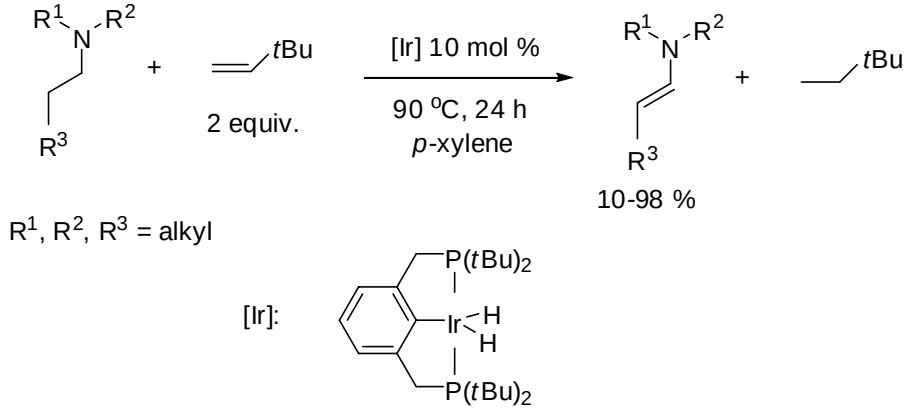


A possible mechanism:



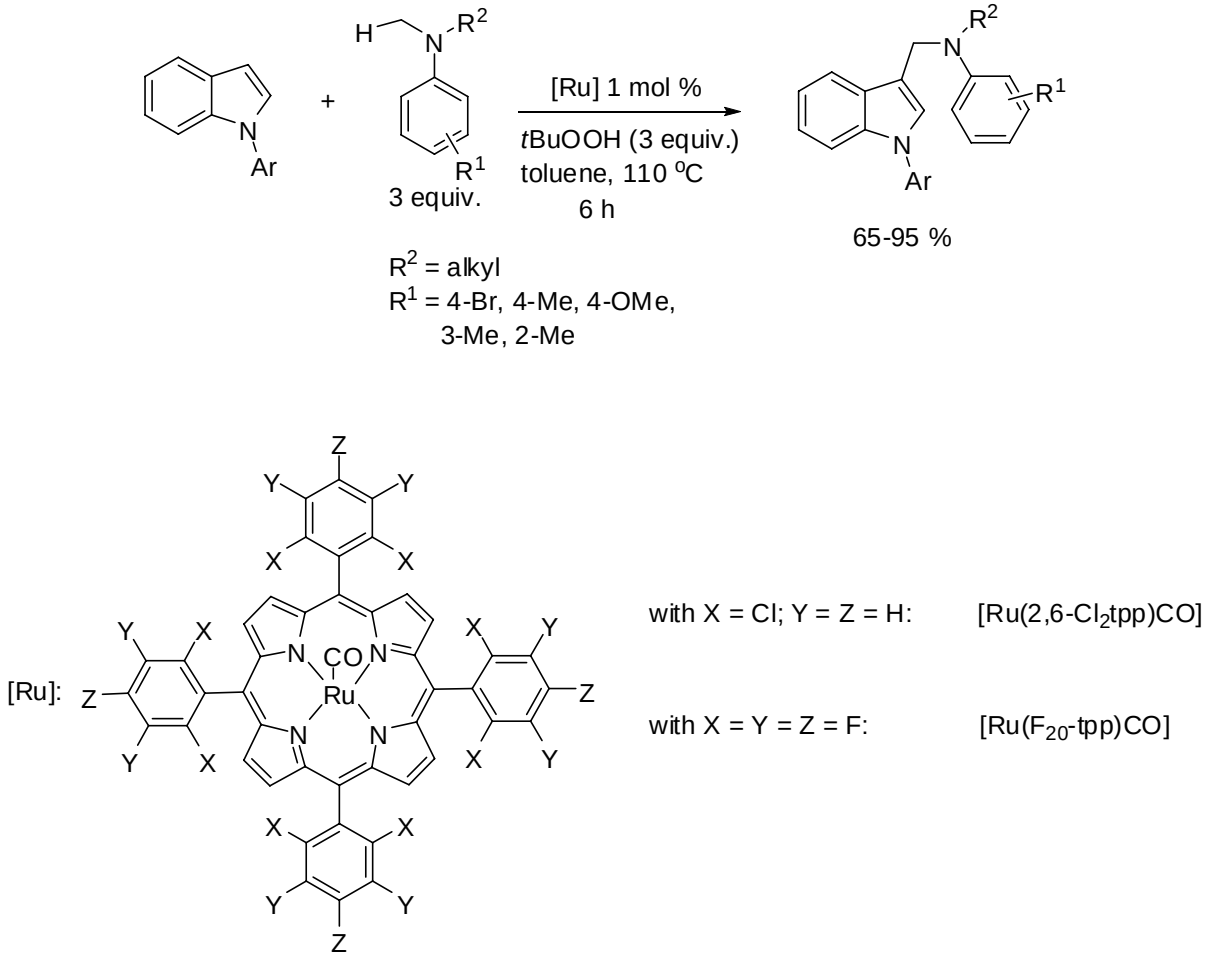
Scheme 6. Palladium(II)-catalyzed Boc-directed acetoxylation of sp^3C-H bonds by Yu.

In a seminal work, Goldman and co-workers described a pincer ligated Ir^{III} as a catalyst and *tert*-butylethylene (TBE) as a hydrogen acceptor for the transfer-dehydrogenation of alkyl groups of tertiary amines to give enamines in 10 % to 98 % yields at 90 °C without a directing group (Scheme 7).[17] Competition experiments showed that the reactivities of *N,N*-dialkylethylamines were dependent on the ancillary *N*-alkyl group as follows: $R^1 = R^2$ = isopropyl > ethyl > methyl in the ratio 140 : 7 : 1.



Scheme 7. Ir(III)-catalyzed dehydrogenation of tertiary amines by Goldman.

Alkylated indoles are widely present in bioactive natural products and medicinal molecules.[18] Very recently, Che's group developed ruthenium porphyrins (particularly [Ru(2,6-Cl_2tpp)CO]; tpp = tetraphenylporphinato)-catalyzed C-3 alkylation of indoles with tertiary amines via oxidation of a sp^3 C-H in high yields (Scheme 8).[19] The oxidative coupling reactions of various anilines and indoles bearing electron-poor or electron-rich substituents proceed well in the presence of *t*BuOOH as an oxidant, affording 3-{[(*N*-aryl-*N*-alkyl)amino]methyl}indoles from the alkylation of *N*-arylindoles and 3-[*p*-(dialkylamino)benzyl]indoles from the alkylation of *N*-alkyl or N-H indoles with high regioselectivity. The proposed mechanism involves an iminium ion intermediate which may be generated through oxidation of a sp^3 C-H bond of anilines with an oxoruthenium species, subsequently trapped by an *N*-arylindole to give the desired product.



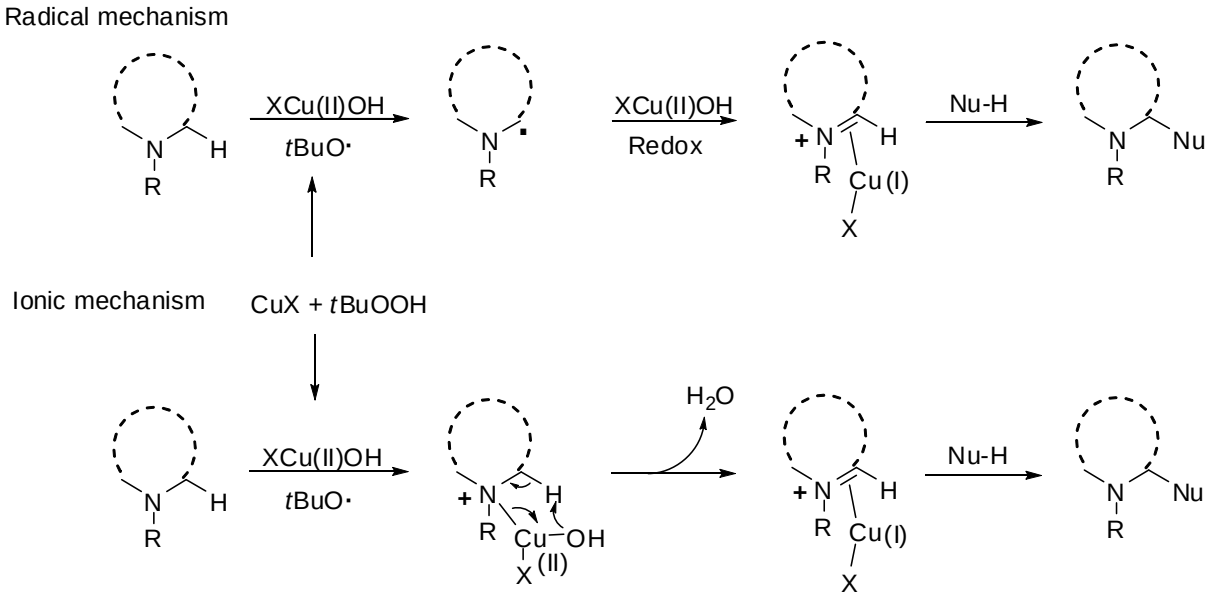
Scheme 8. Ru-catalyzed oxidative dehydrogenative indolation of tertiary amines by Che.

Inexpensive metal catalysis

Although the above mentioned methods are elegant, expensive metal catalysts, such as Ru, Rh, Pd and Ir, were generally used, limiting their wide application.

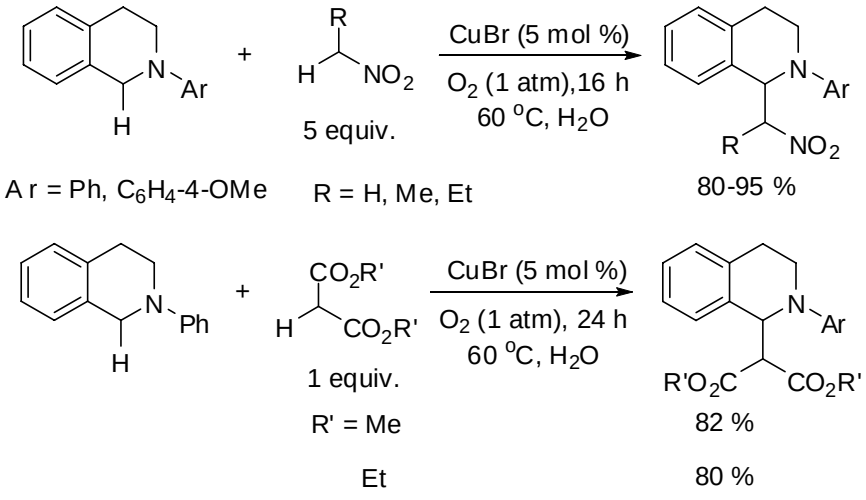
The breakthrough in inexpensive metals-catalyzed sp^3 C-H activation adjacent to nitrogen with high selectivity and efficiency has been made by Li's group.[20] The methodology, termed cross-dehydrogenative coupling (CDC), is to use Cu-*t*BuOOH to activate sp^3 C-H bonds α to nitrogen of amines to generate iminium ions, followed by nucleophiles' attack to afford the functionalized products. This general process has been proposed to follow either a radical or an ionic mechanism, as shown in Scheme 9. A vast array of nucleophilic partners including alkynes,[21] nitromethane,[22] malonates and malononitrile,[23] indoles,[24] naphthols[25] and indolizidines[26] reacted well with tertiary amines in the presence of a copper catalyst and *tert*-butyl hydroperoxide. The reaction temperature depended on the ease of activation of the pronucleophile (i.e. malonates and nitroalkanes, 25

°C; naphthols, 50 °C; alkynes, 100 °C). These data implied that the reaction of the iminium intermediate with a pronucleophile is the rate-determing step.



Scheme 9. Proposed mechanisms for CDC of tertiary amines.

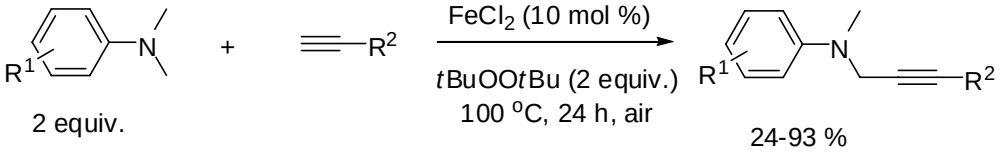
Considering that organic peroxides are potentially explosive, Li et al. replaced peroxides by molecular oxygen that offered a safer and more atom-economical process (Scheme 10).[27]



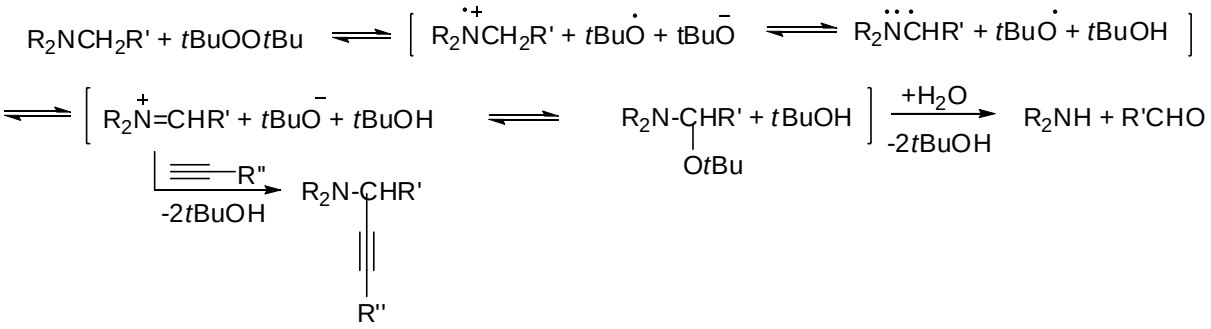
Scheme 10. CDC reactions of tertiary amines with oxygen as the oxidant by Li.

Iron is a cheap, nontoxic, and environmentally benign transition metal.[4] Despite its advantages, it is surprising that, until now, iron was relatively underrepresented as a catalyst for reactions that functionalize sp^3 C-H adjacent to the nitrogen atom in amines. Recently a

CDC using an iron(II) salt has been shown to catalyze the chemoselective oxidative C-C cross-coupling between tertiary amines and terminal alkynes to give propargyl amines in low to excellent yields with (*t*-BuO)$_2$ as oxidant and no solvent at 100 ^{o}C in air (Scheme 11).[28] The reaction was proposed to proceed via an iron catalyzed SET process to generate the iminium intermediate, which is subsequently trapped by an alkynyl carbanion to yield the corresponding product (Scheme 11).

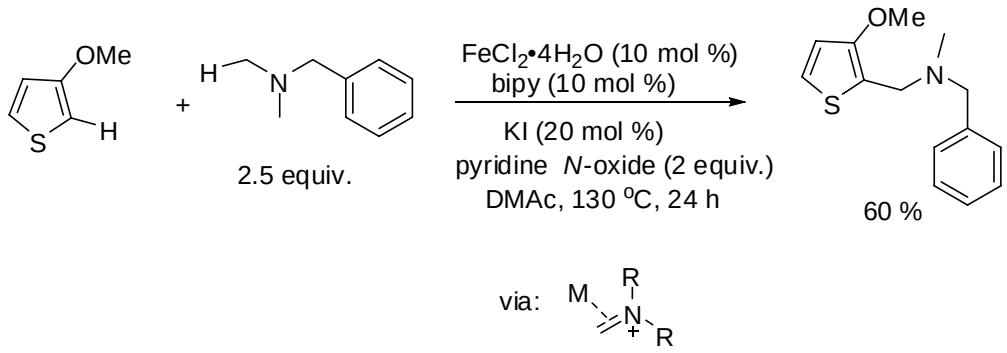


R^1 = 4-Br, 4-Me, 2-Me
R^2 = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-pyridyl, 3-pyridyl, *n*-hexyl, Et$_3$Si, CO$_2$Et, PhCOCH$_2$, ClCH$_2$(CH$_2$)$_2$



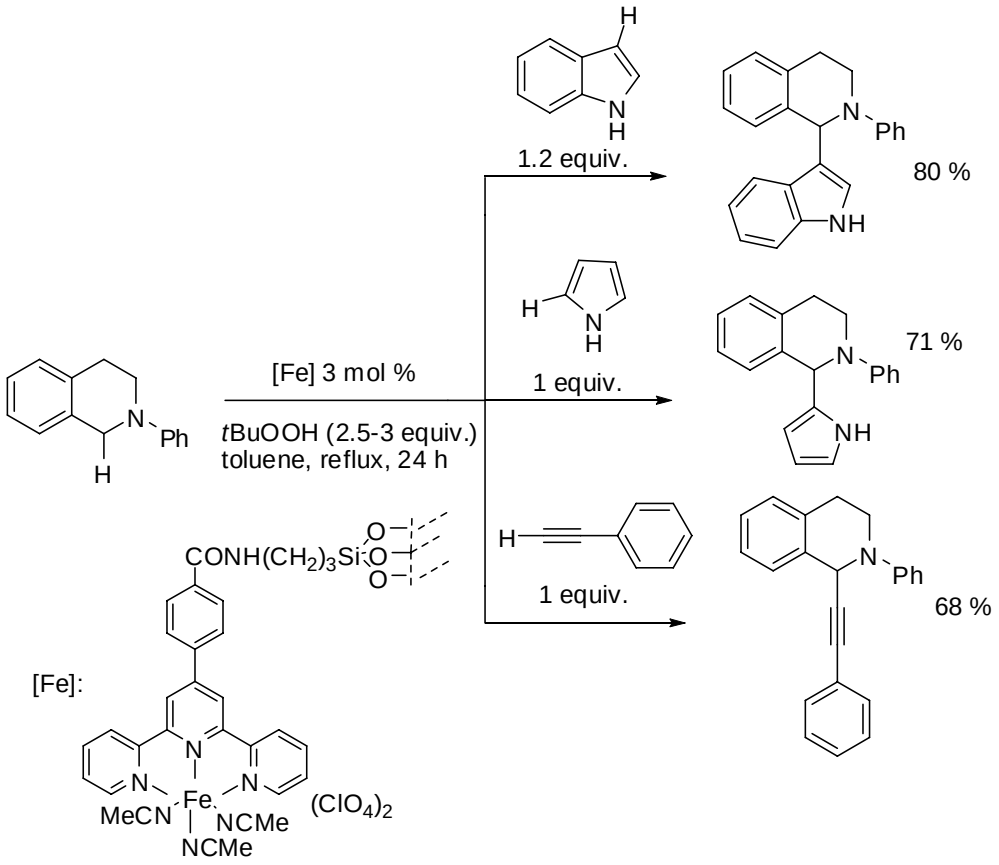
Scheme 11. FeCl$_2$-catalyzed oxidative alkynylation of tertiary amines by Vogel.

The groups of Itami and Wünsch had already described a FeCl$_2$·4H$_2$O/KI/bipy/pyridine N-oxide system for the oxidative cross-coupling of electron-rich heteroarenes and methylamines via sp^3 C-H activation at 130 ^{o}C (Scheme 12).[29] Mechanistically, the reaction was proposed to involve the formation of metal-bound iminium species, which are subsequently trapped by the nucleophilic heteroarenes to furnish the corresponding benzylic amines.



Scheme 12. $FeCl_2$-catalyzed oxidative coupling of heteroarenes and methylamines by Itami and Wünsch.

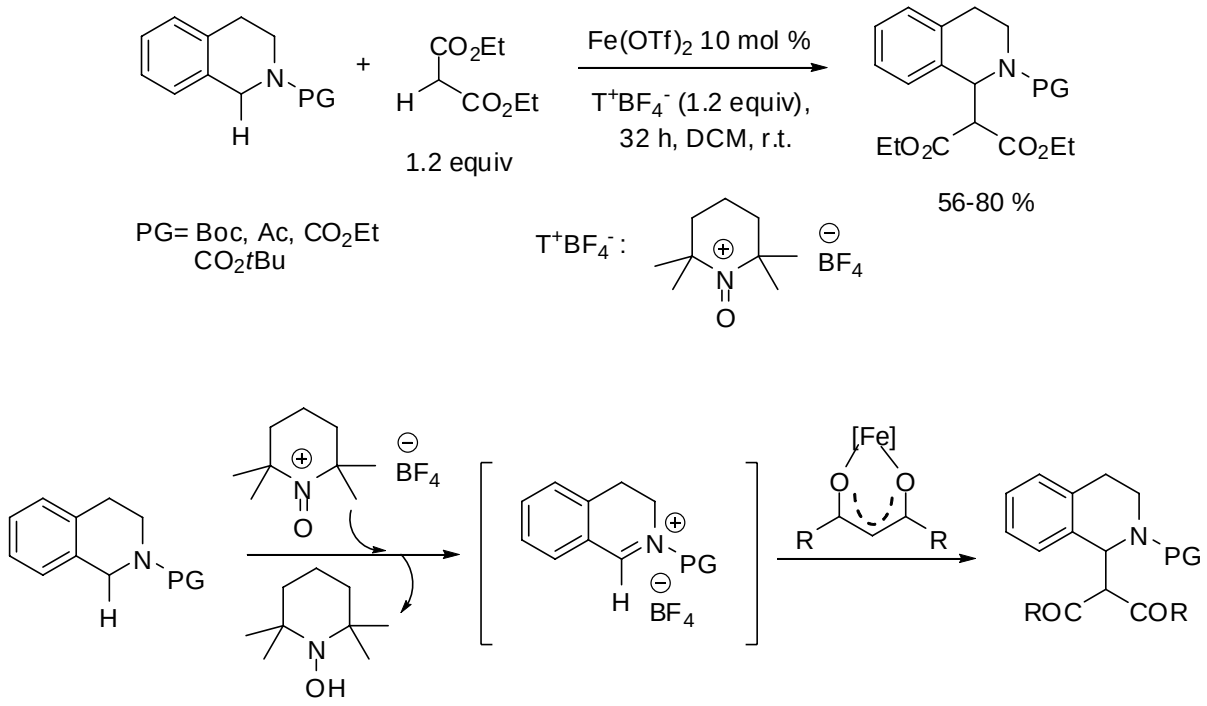
A well-defined catalyst $[Fe(terpy)_2](ClO_4)_2$ (terpy = 2,2',6',2''-terpyridine) supported on active silica was applied by Che's group in C–C cross-couplings of tertiary amines with carbon nucleophiles (Scheme 13).[30] A variety of carbon nucleophiles such as indoles, pyrroles and alkynes reacted well with tertiary amines using *t*BuOOH as the oxidant under reflux in toluene, giving the C–C bond coupling products in good to excellent yields. Although this protocol possesses the advantage that catalyst and product can easily be separated, the catalyst is complex and needs four steps to be prepared from commercially available starting materials.



Scheme 13. SBA-15-support iron terpyridine-catalyzed oxidative C-C coupling by Che.

Commonly, Fe-catalyzed reactions require high temperature because iron often possesses low catalytic reactivity. So it is attractive to develop Fe catalytic systems for performing reactions at milder temperatures, best at room temperature.

Very recently, an efficient method for the selective construction of C–C bonds by functionalization of benzylic sp^3 C–H bonds adjacent to a nitrogen atom at room temperature was developed by Mancheño and co-workers. The use of the oxoammonium TEMPO salt as the oxidant and $Fe(OTf)_2$ as the catalyst delivered the corresponding products in moderate to good yields (Scheme 14).[31] The proposed mechanism involved the generation of an iminium intermediate, which is then trapped by the pronucleophile that is activated by the iron catalyst.

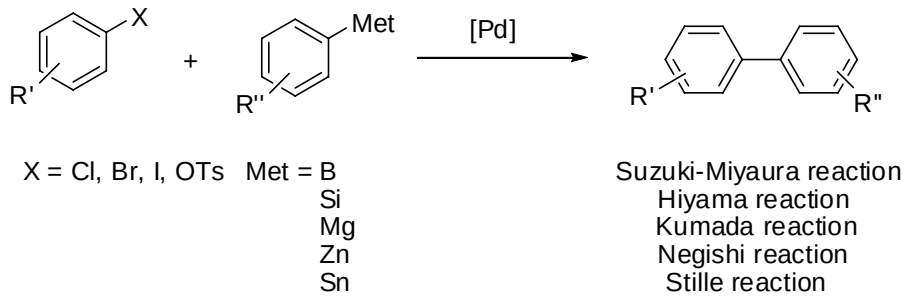


Scheme 14. Fe-catalyzed functionalization of sp^3 C-H bonds adjacent to nitrogen atom by Mancheño.

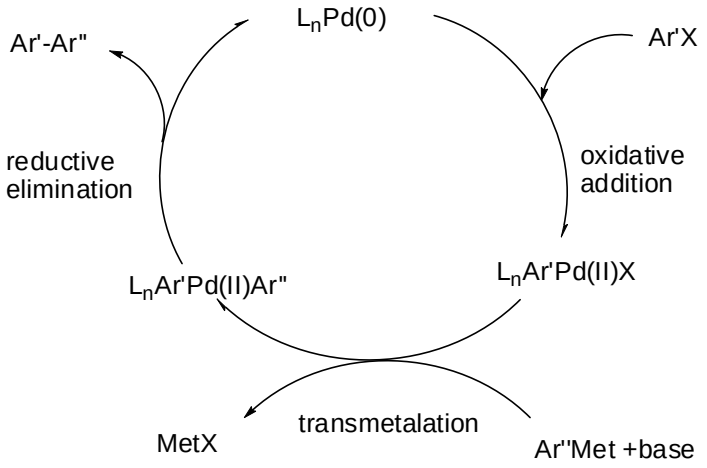
1.3 Pd-Catalyzed Direct Arylation of sp^2 C-H Bonds

1.3.1 Overview

Biaryls Ar–Ar' are structural motifs found in many biologically active compounds, pharmaceuticals, agrochemicals, and functional materials.[32] Regioselective C–C bond formation between carbocyclic and/or heterocyclic arenes has, therefore, been a longstanding goal in synthetic organic chemistry and stimulated the development of numerous catalytic methods for the construction of the C–C bond between Ar and Ar'. The most powerful tools are the palladium-catalyzed cross couplings, including Stille, Suzuki-Miyaura, Kumada, Hiyama, and Negishi couplings (Scheme 15).[5b,5c,5d,5e,33] These transformations are the reactions of aryl halides or, more recently, sulfonates Ar-X with tin, organoboron, Grignard, silicon, or organozinc reagents Ar'-Met, involving a Pd 0/II catalytic cycle (Scheme 16). Such approaches require both coupling partners to be prefunctionalized prior to coupling, leading to additional synthetic steps for preparing the Ar-X and Ar'-Met starting from the corresponding arenes, during which much waste is generated from reagents, solvents, and purifications. Furthermore, the introduced groups just yield undesirable inorganic salts after the cross couplings finish.



Scheme 15. Palladium-catalyzed traditional cross couplings for biaryl.

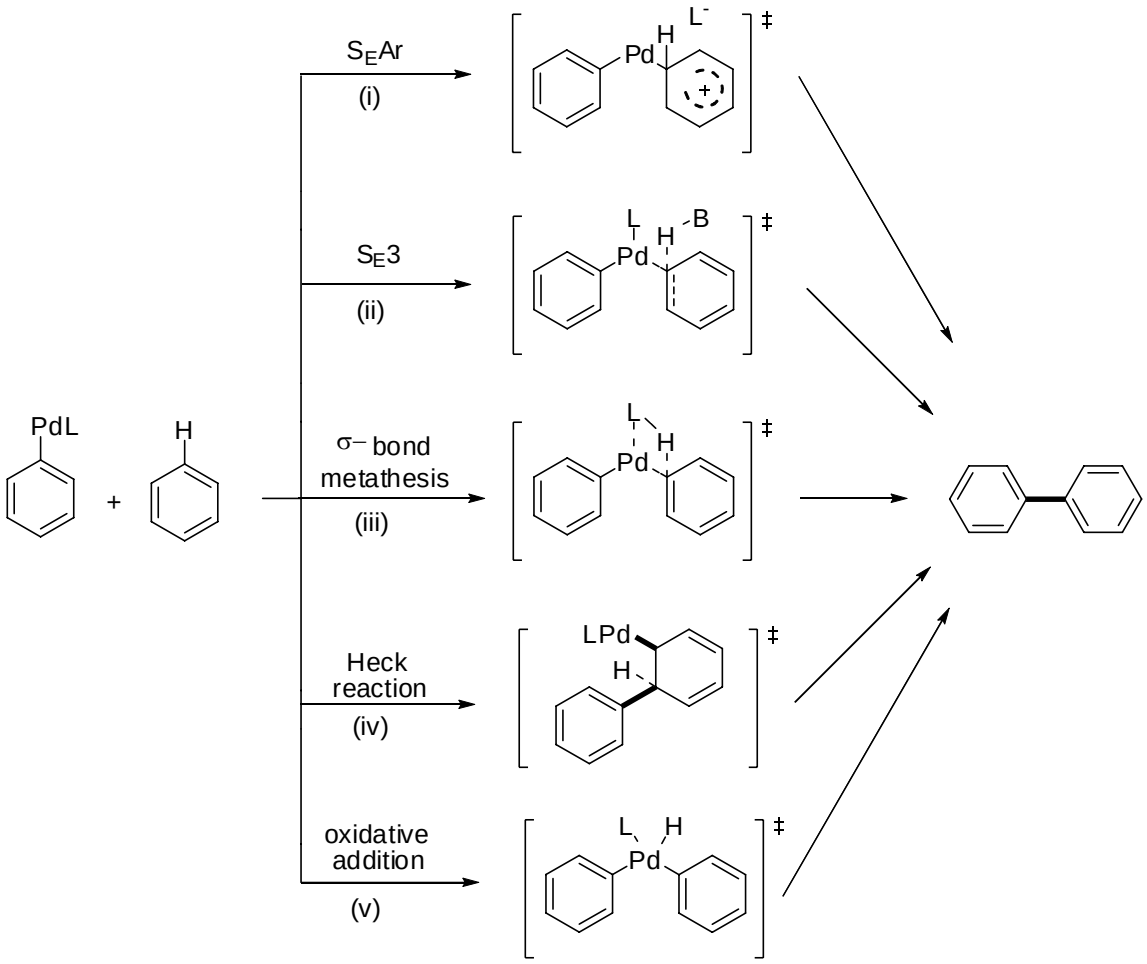


Scheme 16. Catalytic cycle of palladium-catalyzed traditional cross couplings for biaryl.

Therefore, transition metal-catalyzed C–H functionalization has attracted tremendous interest.[1d,1i] Direct arylations through activation of C–H bonds represent an environmentally and economically attractive strategy which avoids the extra steps for introducing functional groups at one of the potential coupling partners and hence provides a more direct approach to the synthetic targets.

Over the last few decades, significant advances have been achieved in the formation of aryl-aryl bond via transition-metal-catalyzed C-H activation.[1,34,35] Among the transition-metal catalysts, the palladium catalysts are most powerful and widely used in catalytic arylations of C-H bonds. As summarized in Scheme 17, a number of potential mechanisms have been proposed for the activation of the C-H bond[1k,35e,g,m] and identified namely (i) electrophilic aromatic substitution (S_EAr): electrophilic activation at electron deficient late transition metal centers, (ii) concerted S_E3 process, (iii) σ-bond metathesis: single step reaction by which two σ-bonds are broken and two new σ-bonds are formed in a concerted manner without change of the metal oxidation state, (iv) Heck-type carbometalation, and (v) oxidative addition: a

mechanism where an electron-rich metal reacts with the C-H bond to form a M-C and a M-H bond via a three membered transition state.



Scheme 17. Potential mechanisms for catalytic direct arylation reactions via C-H bond activation.

In 2006, Fagnou and co-workers studied arylations of sp^2 C-H with perfluorobenzenes in the presence of $Pd(OAc)_2$ and observed that the reactions were easier in the case of electron-poor arenes which is just opposite to a purely electrophilic activation process.[36] Nevertheless, a computational study located a transition state with a six-membered ring (Figure 1), showing that hydrogen bonding to acetate plays a critical role. Fagnou called this process a concerted metallation deprotonation (CMD) to describe that the hydrogen is abstracted by the coordinated base at the same time as the M-C bond is generated. The higher reactivities of electron-deficient arenes which were observed in competition experiments are therefore owing to the greater acidity of the proton being abstracted.

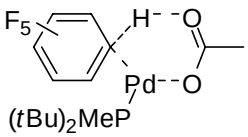
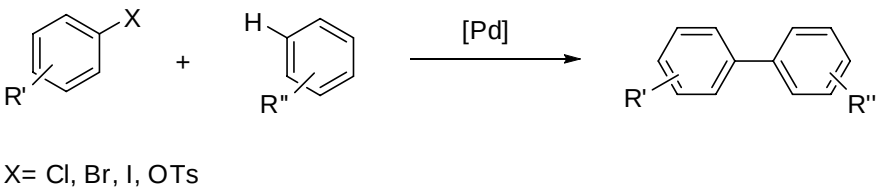


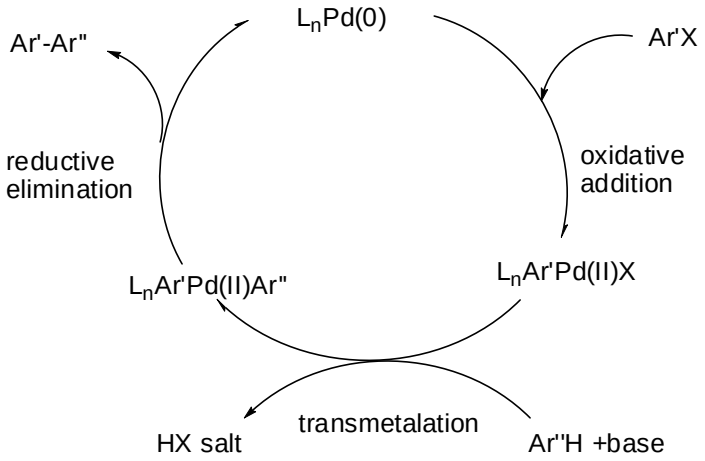
Figure 1. A transition state with a six-membered ring.

There are three main types of Pd-catalyzed aryl-aryl bond formations through cleavage of C-H bonds: (1) catalytic direct arylation with aryl halides/pseudohalides; (2) catalytic oxidative arylation with organometallic reagents; and (3) catalytic double C-H activation of two arenes.[1]

In the case of aryl halides/pseudohalides as coupling partners, the more-difficult-to-prepare organometallic coupling partner is substituted with a simple arene, which reduces the metal waste produced in the whole process (Scheme 18). In the past decades, the process has been well developed and examples of it increased exponentially.[1i,35a,35c,35e,35u] A wide range of aryl halides or pseudohalides, even including most difficult to activate ArOTs and more inexpensive and industrially attractive ArCl work well if sterically demanding and electron-rich phosphine ligands and N-heterocyclic carbene ligands are used. Mechanistically, these rections are thought to proceed via oxidative addition of aryl halides/pseudohalides to Pd(0) species, followed by the electrophilic attack of the generated Pd^{II} species to arene to yield $L_nPd(Ar)Ar'$ which undergoes reductive elimination to give the corresponding product and regenerates the $L_nPd(0)$ to complete the catalytic loop (Scheme 19).



Scheme 18. Palladium-catalyzed direct arylation with aryl halides/pseudohalides.



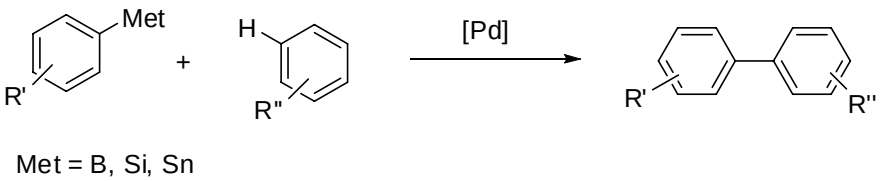
Scheme 19. Catalytic cycle of palladium-catalyzed direct arylation with aryl (pseudo)halides.

The other two types of C-H activation methodologies are introduced as follows by mainly discussing their important advances in recent years.

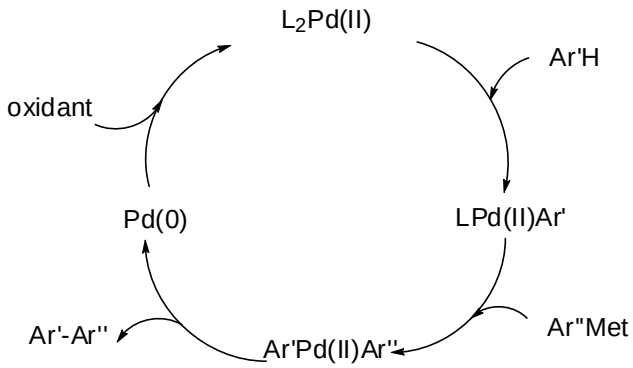
1.3.2 Pd-Catalyzed Direct Arylation of sp^2 C-H with Organometallic Reagents

In comparison to the classic cross couplings, the direct arylation reactions with organometallic reagents replace aryl halides/pseudohalides by simple arenes, leading to shorter synthetic schemes and an overall improved efficiency of chemical processes (Scheme 20).[35p]

Generally speaking, the transformations do not need ligands or bases, but oxidants are necessary to be present for good results. Usually, a Pd(II)-Pd(0)-Pd(II) catalytic cycle is proposed to be involved in the process (Scheme 21). Unfortunately, organometallic reagents easily form homocoupling side products in the presence of Pd(II) as the catalyst. So far, it remains a challenge to effectively suppress these homocouplings when organometallic reagents are used as the direct arylating reagents. Consequently, some highly reactive organometallic reagents, such as Grignard reagents, organozinc reagents, organoaluminium, and so on, hardly give good results in such C–H activation processes.

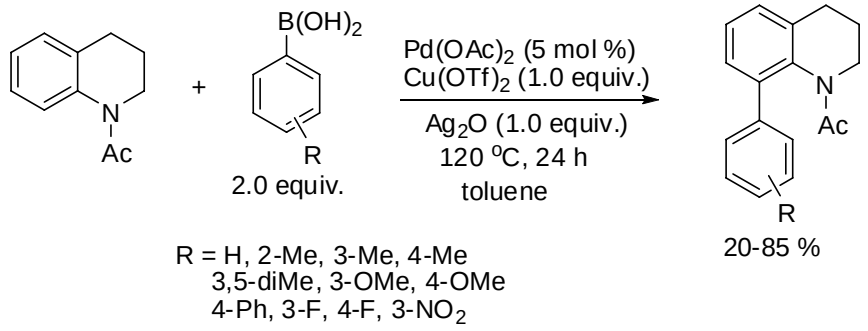


Scheme 20. Palladium-catalyzed direct arylation with organometallic reagents.

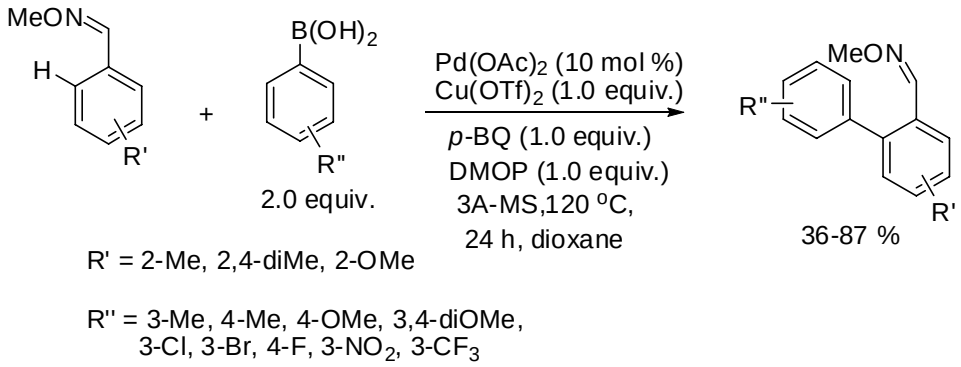


Scheme 21. Catalytic loop of palladium-catalyzed direct arylation with organometallic reagents.

Arylboron reagents have been widely used in the organic synthesis due to their availability, stability, nontoxicity. The most famous example is the Suzuki cross-coupling reaction which uses arylboronic acids or arylboronates as coupling partners for constructing aryl-aryl bonds. Provided that the aryl C-H activation can proceed well with arylboron reagents, this process will be significantly more appealing under the aspect of atom economy. Pioneering work of direct arylation with arylboronic acid as the arylating reagent in the presence of palladium catalyst was reported by the group of Shi (Scheme 22).[37] The reaction proceeded in high selectivity owing to chelation control of a directing acetamino group, giving rise to biaryls in moderate to high yields with stoichiometric $Cu(OTf)_2$ as the terminal oxidant. According to the proposed mechanism, this transformation started with electrophilic attack of a Pd(II) center at the aromatic ring under the help of the acetamino group, followed by transmetalation and reductive elimination to afford the desired product. Further, an intramolecular isotopic effect (k_H/k_D = 2.3) indicated that the cleavage of a C-H bond was involved in the rate-limiting step. As an extension of this methodology, the same group chose another type of directing group, the O-methyl oximyl group and results similar to those achieved with the acetamino group could be obtained (Scheme 23).[38]

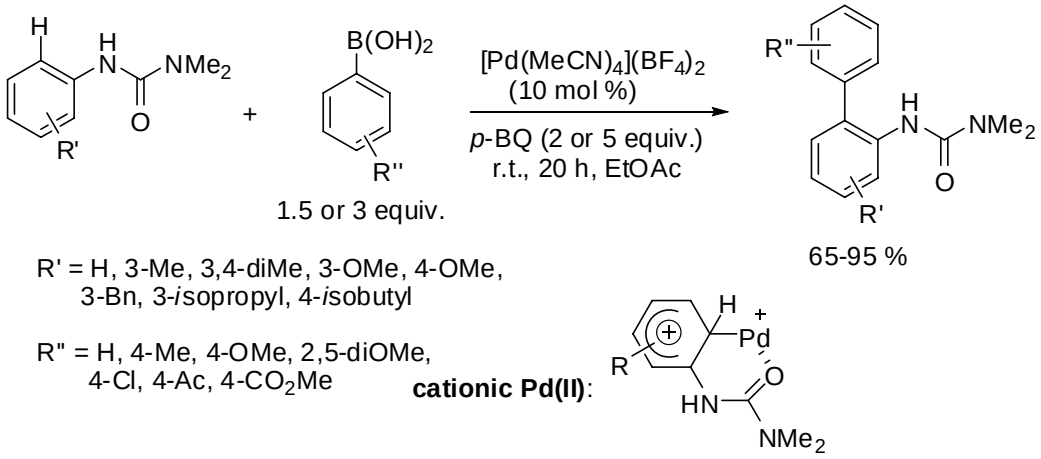


Scheme 22. Palladium(II)-catalyzed acetyl amino group directed arylation of sp^2 C-H bond by Shi.



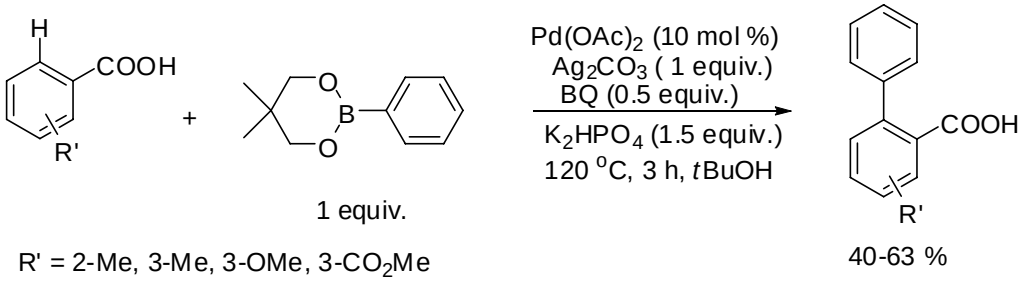
Scheme 23. Palladium(II)-catalyzed *O*-methyl oximyl group directed arylation of sp^2 C-H bond.

A seminal example of the chelation-assisted regioselective arylation of aryl ureas with arylboronic acids in high yields was described by Lipshutz et al. who employed a preformed cationic palladium(II) complex as the catalyst and BQ as the oxidant in EtOAc (Scheme 24).[39] Notably, the catalytic system enabled facile aromatic C-H activation and subsequent cross-couplings at room temperature. A key intermediate, **cationic Pd(II)**, is probably involved in the process of the reaction, which is generated from electrophilic C-H activation of aryl urea with $[Pd(MeCN)_4](BF_4)_2$, followed by transmetalation with the arylboronate and reductive elimination to form the desired product.

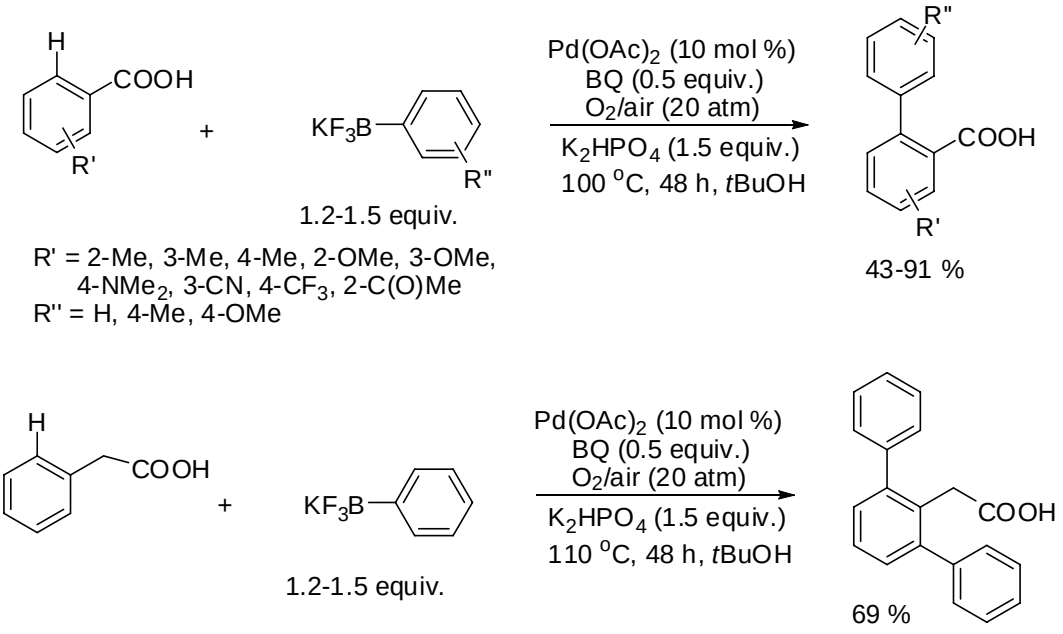


Scheme 24. Palladium(II)-catalyzed chelation-assisted arylation of aryl ureas with arylboronic acids.

An elegant extension to carboxyl-directed arylation of sp^2 C-H was reported by Yu et al., starting with more easily available potassium aromatic carboxylates, in situ generated from aromatic carboxylic acids and K_2HPO_4 (Scheme 25).[40] This process most likely proceeds via a Pd^{II}/Pd^0 catalysis. Shortly thereafter, the same group successfully extended the scope of substrates to aryltrifluoroborate salts as coupling partners with a new catalytic system for C−H activation/aryl-aryl coupling of benzoic and phenyl acetic acids (Scheme 26).[41] This protocol was the first example of the ortho-C-H coupling of phenyl acetic acids containing α-hydrogens and electron-poor arenes.



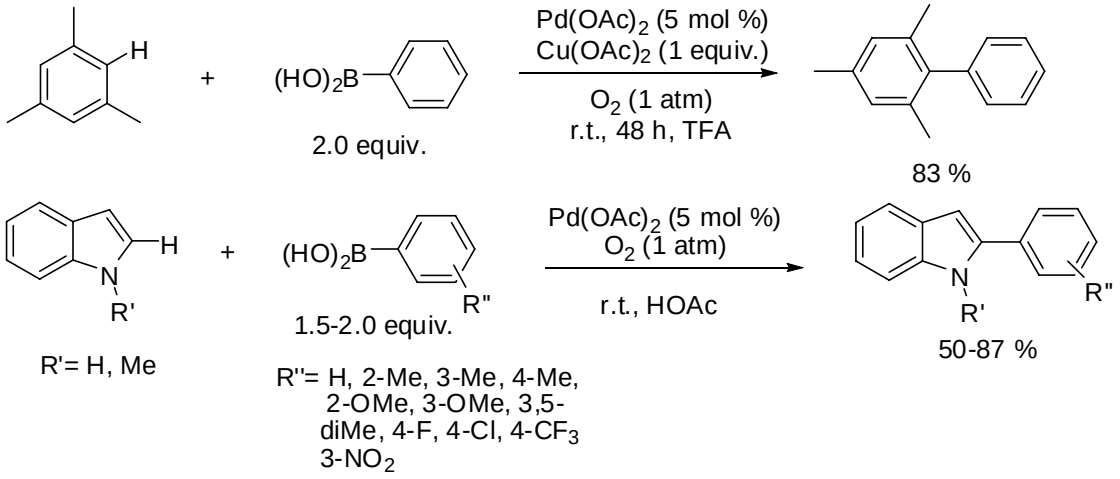
Scheme 25. Palladium(II)-catalyzed carboxyl directed arylation of sp^2 C-H by arylboronates.



Scheme 26. Palladium(II)-catalyzed carboxyl directed arylation of benzoic and phenyl acetic acids by aryltrifluoroborates.

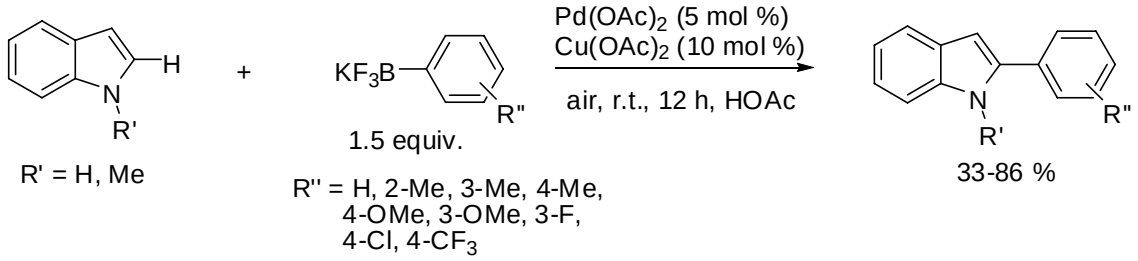
Although the cross-coupling between C–H bonds and organoboronic acids and their derivatives has advanced Suzuki–Miyaura coupling, directing groups are used to aid coordination, leading to severe limits for the scope of substrates, and reducing the potential for broad synthetic applications. Thus, expanding the scope to include simple or easily accessible substrates, was a major hurdle to general applicability.

As a first example of oxidative Pd-catalyzed direct arylation with arylboronic acids in the absence of directing group, Shi et al. described arylations of electron-rich heteroarenes and simple arenes with molecular oxygen as the oxidant at room temperature (Scheme 27).[42] The reactivities of electron-rich heteroarenes were higher than those of electron-poor heteroarenes, suggesting a process of electrophilic activation of the heteroaromatic C-H bonds.



Scheme 27. Palladium(II)-catalyzed direct arylation of (hetero)arenes.

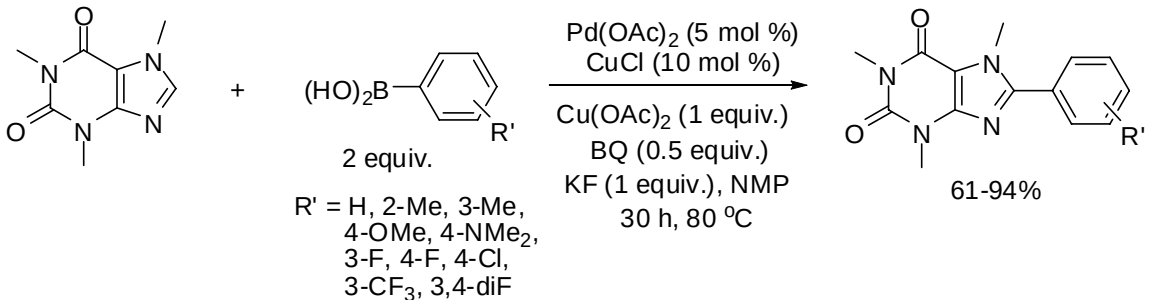
An extension of this work to use more stable aryltrifluoroborates as coupling partners was reported by Zhang and co-workers to achieve $Pd(OAc)_2$-catalyzed effectively regioselective arylated indoles with a catalytic amount of $Cu(OAc)_2$ in acetic acid at room temperature under air (Scheme 28).[43]

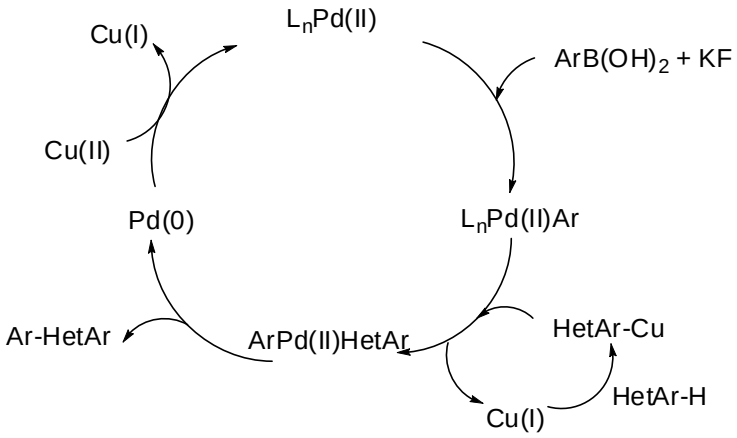


Scheme 28. Palladium(II)-catalyzed direct arylation of indoles with potassium aryltrifluoroborates.

Subsequently, You's group reported a palladium/copper [$Pd(OAc)_2$, 5 mol %/CuCl, 10 mol %] bimetallic catalytic system for direct arylations of azoles and xanthines with arylboronic acids which showed moderate to good yields and excellent regioselectivity at C2 position in the presence of one equivalent of $Cu(OAc)_2$ as the oxidant and 0.5 equivalent of BQ as the additive (Scheme 29).[44] The BQ was proven to suppress the undesired homocoupling of arylboronic acids. Given that the cross-coupling reactions proceeded more sluggishly in the absence of CuCl, the authors proposed that the transformation occurs through the formation of the azole-copper species [HetAr-Cu], subsequent transmetalation with the arylpalladium species [L_nPdAr] to form the key heterocoupling intermediate

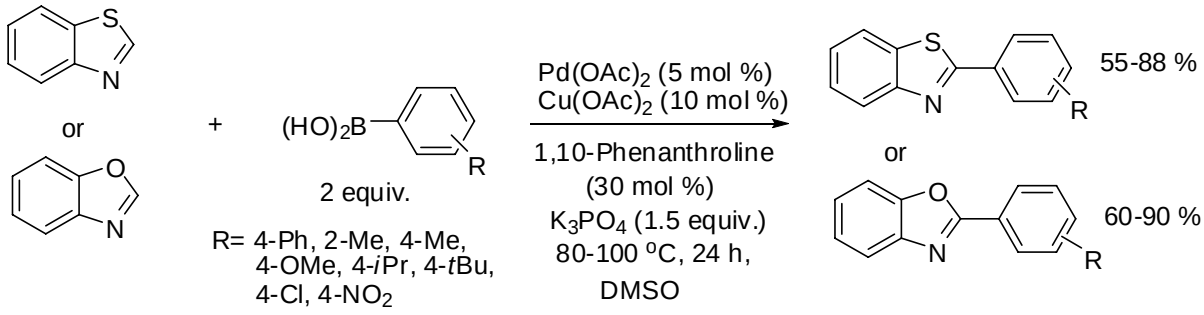
[HetArPdAr], followed by reductive elimination which delivers the corresponding product and releases Pd^0. Oxidation of the Pd^0 by $Cu(OAc)_2$ regenerates the initial Pd^{II} species and completes the catalytic cycle.





Scheme 29. Palladium(II)-catalyzed direct arylation of xanthines with arylboronic acids.

Very recently, Liu et al. performed the reactions of azoles and aryl boronic acids in DMSO at 100 °C under air using a combination of Pd/Cu (5:10 mol%) and phenanthroline (30 mol %) as the catalyst without extra oxidants, affording the desired products in 55-90 % with high regioselectivity (Scheme 30).[45]



Scheme 30. Palladium(II)-catalyzed direct arylation of azoles with arylboronic acids.

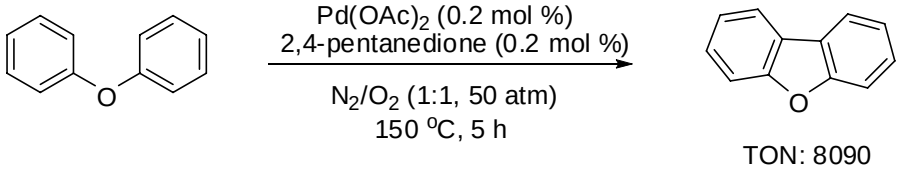
Besides organoboron reagents, silicon and tin reagents have also been used for palladium-catalyzed direct arylations of sp^2 C-H bonds. These reactions will be introduced in "**Chapter 4**".

1.3.3 Pd-Catalyzed Direct C-H/C-H Cross-Coupling of Arenes

Although the above-mentioned processes offer attractive strategies to approach green, clean and efficient transformations, they are not the most straightforward methodologies for synthesizing biaryls due to the fact that one of the coupling partners has to be preactivated to either aryl halide/pseudohalide or organometallic reagent. Ideally, the biaryl bond is constructed by double C-H bond functionalization of two simple arenes, neither of which needs to be prefunctionalized, only losing nontoxic hydrogen gas or water as by-product. Unfortunately, more than one aromatic C-H bond activated in one pot easily results in yielding side products such as dimers and regioisomers. The past decades have witnessed noticeable progress in the development of palladium-catalyzed two-fold C-H activation/aryl-aryl bond-forming processes.[1i, 35m]

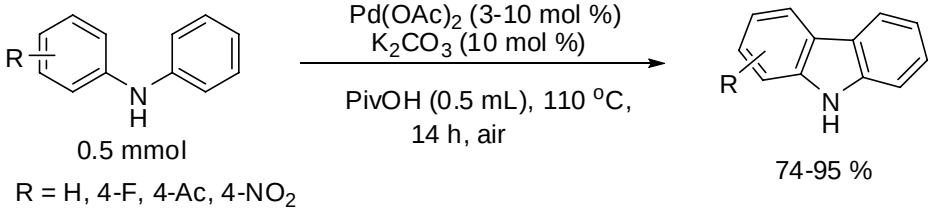
The aryl-aryl bond formation reaction through intramolecular two-fold C-H activation can achieve high selectivity due to the directing effect of the favorable formation of five- or six- membered rings.

As early as in 1974, Itatuni et al. reported intramolecular coupling reactions for the synthesis of dibenzofuran through two-fold C-H activation of diphenyl ether with $Pd(OAc)_2$ as the catalyst (Scheme 31).[46]



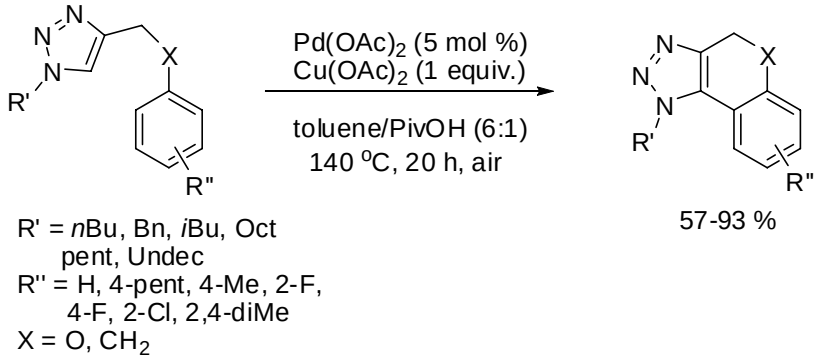
Scheme 31. Palladium(II)-catalyzed intramolecular oxidative aryl-aryl bond formation.

Recently, Fagnou and co-workers applied the intramolecular palladium(II)-catalyzed oxidative biaryl coupling for the synthesis of carbazoles from diarylamines as substrates under air (Scheme 32).[47]



Scheme 32. Palladium(II)-catalyzed intramolecular oxidative aryl-aryl bond formation for the synthesis of carbazoles.

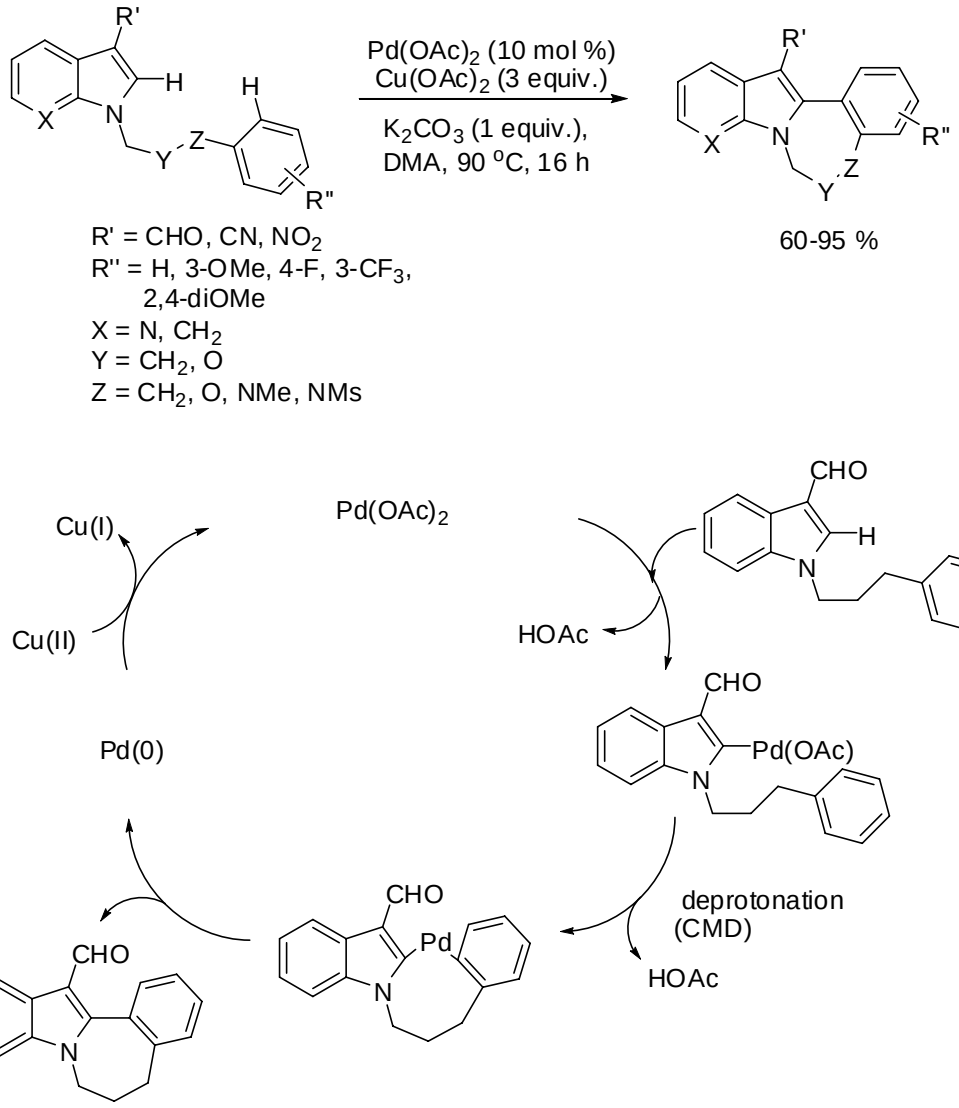
Ackermann et al. devised palladium-catalyzed dehydrogenative direct arylations of 1,2,3-triazoles in intramolecular processes, offering the efficient synthesis of six-membered rings (Scheme 33).[48]



Scheme 33. Palladium(II)-catalyzed intramolecular dehydrogenative direct arylation of 1,2,3-triazoles.

Remarkably, medium-ring-containing biaryls could also be constructed through intramolecular oxidative C-H couplings in high efficiency and selectivity with a combination of $Pd(OAc)_2/Cu(OAc)_2/K_2CO_3$ as the catalytic system (Scheme 34).[49] Based on deuterium

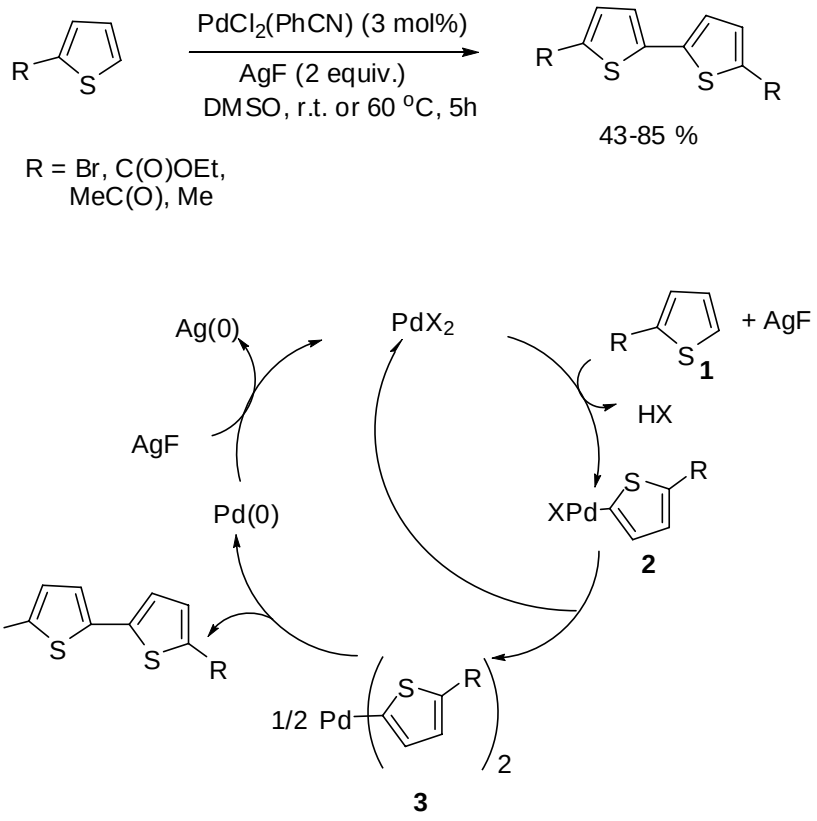
labeling experiments as well as intramolecular competition experiments, a preliminary reaction mechanism was proposed in which the reaction proceeds by electrophilic palladation of the indole at C2, followed by a concerted metalation-deprotonation (CMD) step to give the key intermediate [Ar'PdAr] that underwent reductive elimination to afford the desired product, and Pd(0). The Pd(0) species was then reoxidized by the oxidant $Cu(OAc)_2$ to regenerate the catalyst, as shown in the Scheme 34.



Scheme 34. Palladium(II)-catalyzed intramolecular dehydrogenative coupling for medium-ring synthesis.

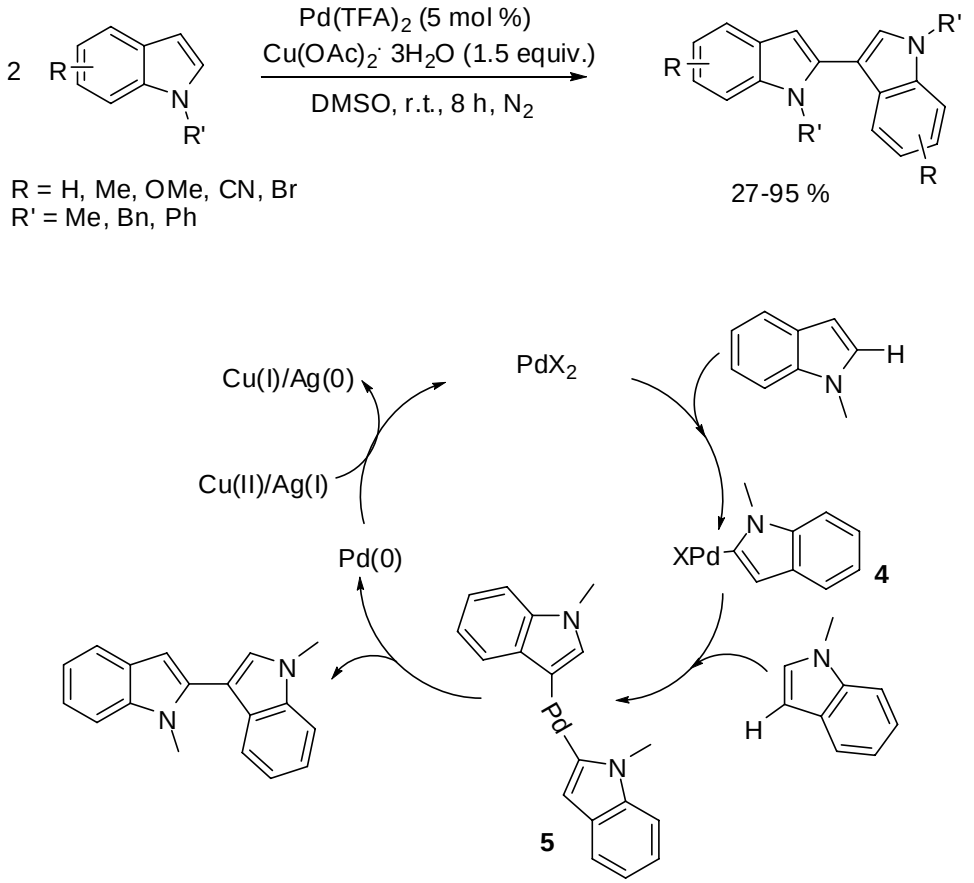
Palladium-catalyzed dehydrogenative homocoupling to give biaryls is one of the most important C-H activation methodologies. In this case, a representative example was reported by Mori and co-workers describing Pd-catalyzed homocoupling of 2-substituted thiophenes with AgF as an effective promoter under mild conditions (Scheme 35).[50] The process of the

reaction is proposed to start through electrophilic C-H substitution of $Pd^{II}X_2$ with **1** to give **2** which forms the bis-heteroarylpalladium species **3** by disproportionation. Subsequently **3** undergoes reductive elimination to yield the homocoupling product and Pd(0) which regenerates Pd(II) in the presence of AgF.



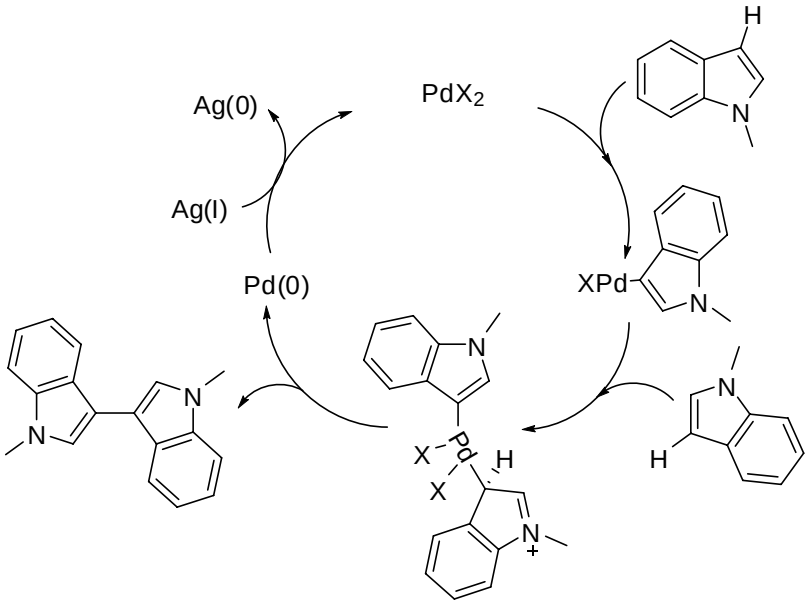
Scheme 35. Palladium(II)-catalyzed dehydrogenative homocoupling to biaryls.

Recently, the group of Zhang developed oxidative cross dimerization of N-protected indoles to give 2,3'-linked products in high yields using 1.5 equivalents of $Cu(OAc)_2 \cdot 3H_2O$ as the terminal oxidant at room temperature in DMSO (Scheme 36).[51] As to the mechanism, a palladium(II)/palladium(0) catalytic cycle was proposed as illustrated in Scheme 36. The transformation was initiated via electrophilic palladation of indole at C3 and the subsequent migration of the C3-PdX bond to the C2-position resulting in the formation of intermediate **4**, followed by the electrophilic palladation with the second indole to yield intermediate **5**, which underwent reductive elimination to afford 2,3'-biindolyl along with Pd(0) that could be oxidized to Pd(II) by Cu(II) or Ag(I) salts in the system to complete the cycle.



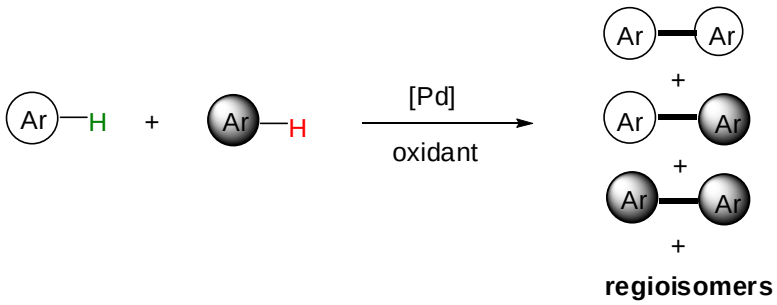
Scheme 36. Palladium(II)-catalyzed dehydrogenative 2,3'- homocoupling of indoles.

Later, Shi and co-workers reported an efficient catalytic system for the synthesis of 3,3'-biindolyls via oxidative homocoupling of N-protected and free indole derivatives in the presence of 1.5 equivalents of $AgNO_3$. A plausible pathway was proposed as shown in Scheme 37.[52] The reaction involves an important intermediate [ArPdX], which is formed by electrophilic substitution of indole. Then, the [ArPdX] attacks the other indole via electrophilic substitution to produce the key intermediate [ArPdAr'] which undergoes reductive elimination to deliver 3,3'-biindolyl.



Scheme 37. Palladium(II)-catalyzed dehydrogenative 3,3'homocoupling of indoles.

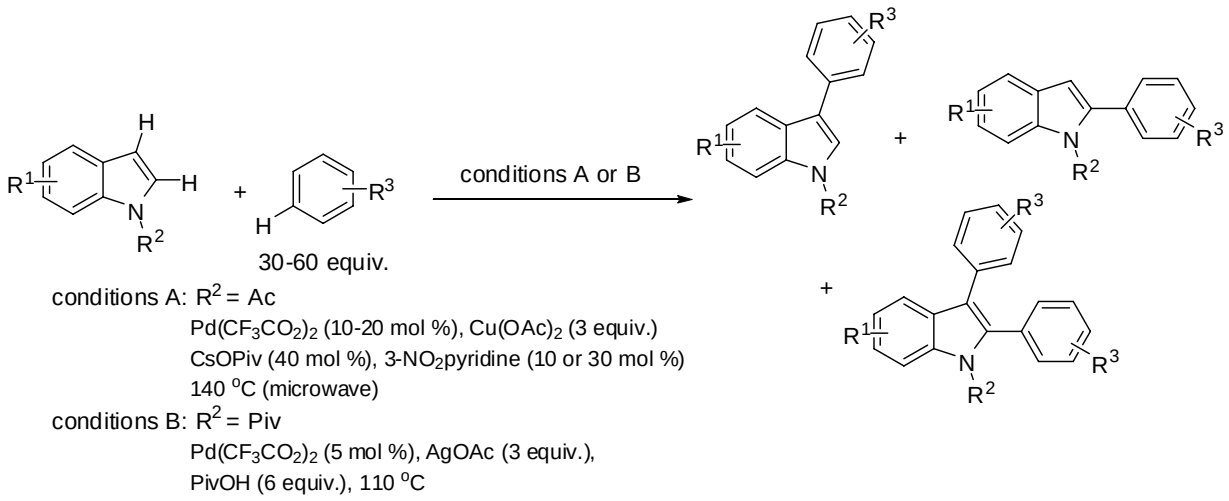
While achieving selectivity in either intramolecular oxidative arylation or intermolecular homocoupling is intrinsically less difficult, a bigger challenge is faced by intermolecular cross-dehydrogenative arylations between two different (hetero)arenes as shown in Scheme 38. So, suppressing or avoiding the homocoupling reactions represents a significant challenge for a successful cross-coupling reaction through two-fold C-H activation.



Scheme 38. Palladium(II)-catalyzed cross-dehydrogenative arylation via double C-H activation.

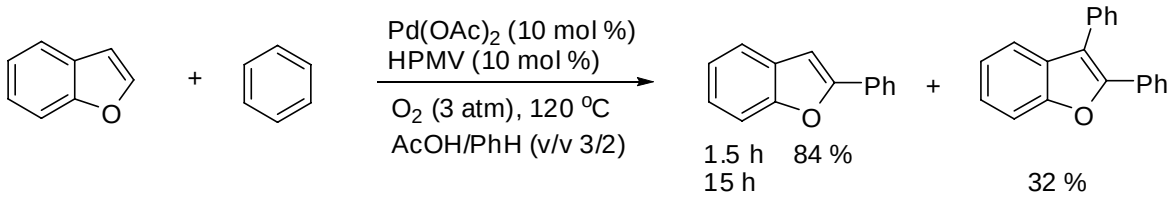
A seminal work in this respect was recently accomplished by Stuart and Fagnou, who devised the palladium-catalyzed direct arylation of *N*-protected indoles with large excess of arenes (Scheme 39).[53] Interestingly, the selectivity at C2-indole or C3-indole can be effectively controlled: 3-aryl *N*-acetyl indole as a major product was formed in moderate to

good yields via microwave heating at 140 °C in the presence of $Cu(OAc)_2$ (3 equiv.), while 2-aryl *N*-pivalyl indole as a major product was obtained in moderate to good yiels by thermal heating at 110 °C in the presence of AgOAc (3 equiv.). The authors proposed that C2 selectivity is increased because of carboxylate-induced cleavage of higher-order Pd clusters to generate monomeric Pd species when AgOAc is added. As for C3 selectivity, this may be caused by forming mixed Pd-Cu clusters upon the addition of $Cu(OAc)_2$.

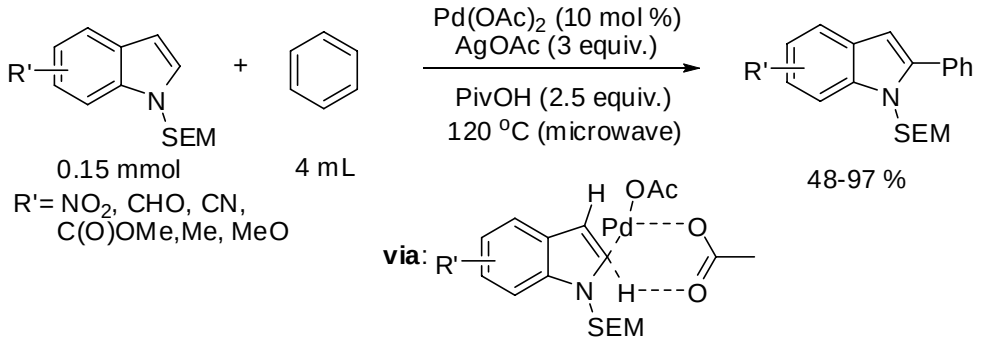


Scheme 39. Palladium(II)-catalyzed cross-dehydrogenative arylation of indoles with simple arenes.

Almost at the same time, a similar method for the oxidative arylation of benzofurans was reported by DeBoef and co-workers. Using $Pd(OAc)_2$ (10 mol %), $H_4PMo_{11}VO_{40}$ (HMPV) (10 mol %) and O_2 (3 atm), the coupling of benzofuran and benzene formed 84 % yield of 2-phenylbenzofuran (Scheme 40).[54] Unfortunately, the optimized conditions in Scheme 40 could not be applied for *N*-alkylindole substrates due to their decomposition. Further optimization showed that a slight excess of AgOAc relative to PivOH suppressed the decomposition. Based on complementary experimental and computational evidence, the reaction proceeds via a concerted metalation-deprotonation (CMD) mechanism. Furthermore, large KIE values (in the range of 3-5) were observed in competition reactions with equimolar amounts of benzene and benzene-d_6, indicating that cleavage of the solvent arene's C-H bond is rate-limiting (Scheme 41).[55]

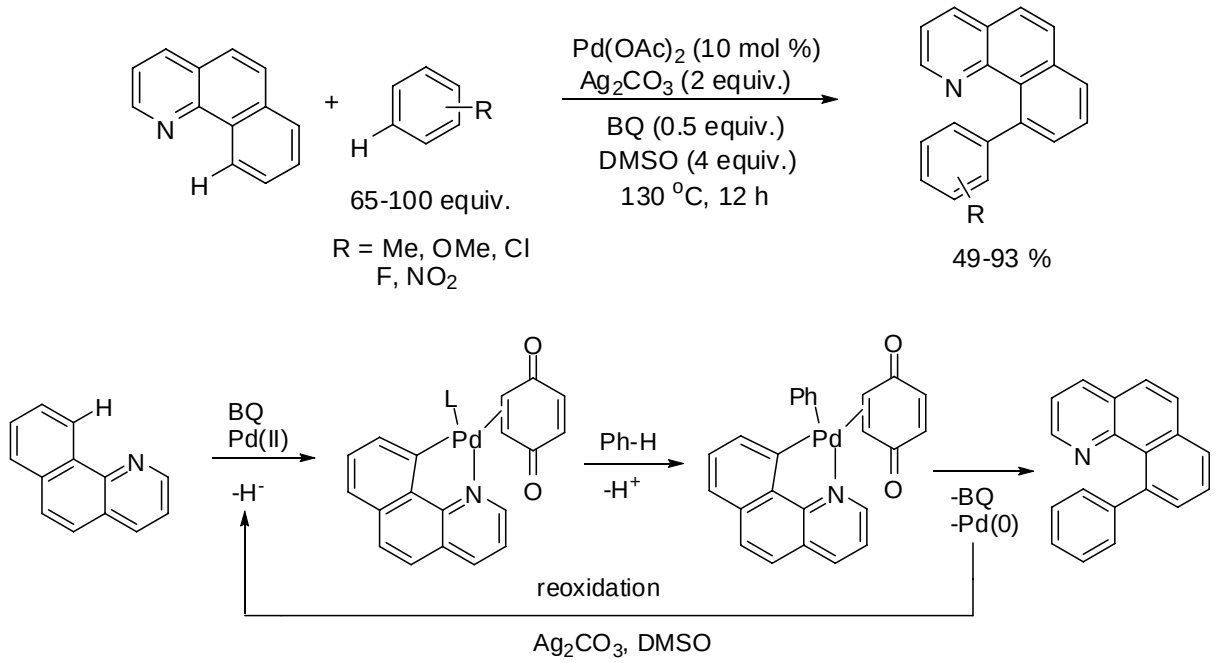


Scheme 40. Palladium(II)-catalyzed cross-dehydrogenative arylation of benzofuran with simple arene.

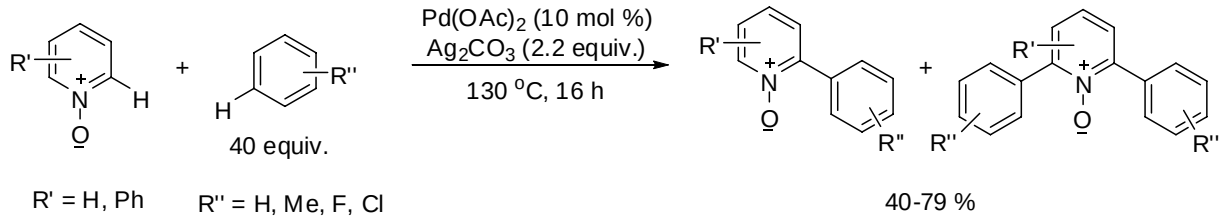


Scheme 41. Palladium(II)-catalyzed cross-dehydrogenative arylation of indoles with simple arene.

A strategy for ligand-directed C-H cross coupling of L~C-H (L: quinoline, pyridine, pyrimidine, and pyrazole) and Ar-H (as solvent) was reported recently (Scheme 42).[56] A variety of arenes including 1,2-, 1,3-, and 1,2,3-substituted aromatic substrates proceeded with high selectivity at the least sterically hindered site in the presence of benzoquinone as a promoter and Ag_2CO_3 as a stoichiometric oxidant, affording the biaryls in up to 93 % yield. The reaction was proposed to undergo by ligand-chelated C-H activation to form a cyclometalated intermediate, BQ-assisted C-H activation of the arene, C-C bond forming reductive elimination, and oxidation of the Pd^0 to Pd^{II} by Ag_2CO_3. Pyridine N-oxides have also been studied as coupling partners in the Pd-catalyzed oxidative arylation with arenes (40 equiv.) in the presence of Ag_2CO_3 as the oxidant, as shown in Scheme 43.[57]

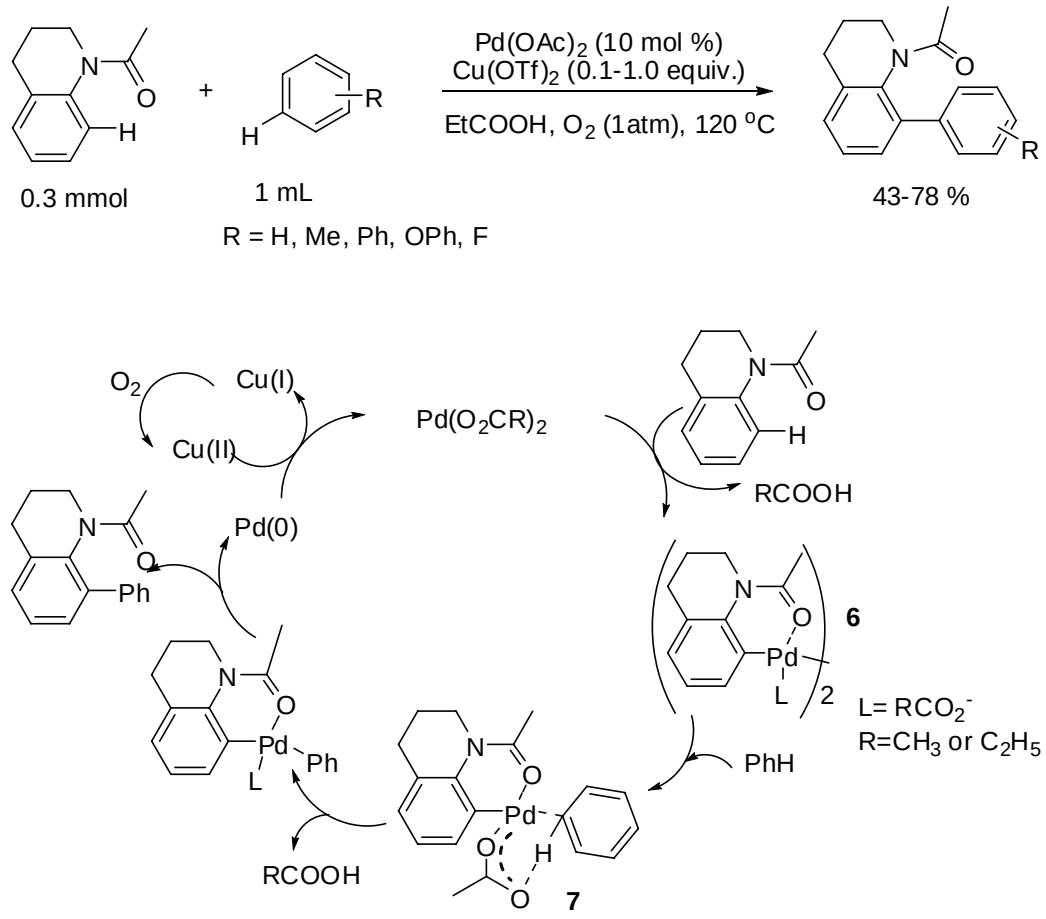


Scheme 42. Palladium(II)-catalyzed highly regioselective cross-coupling of aromatic C-H substrates.

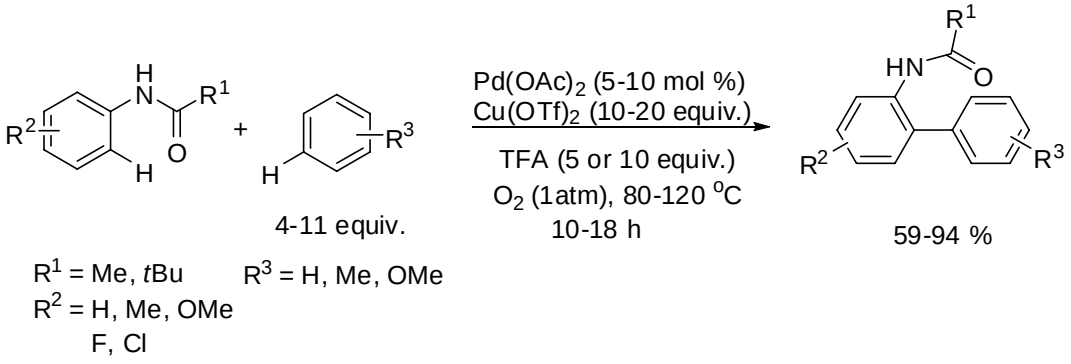


Scheme 43. Palladium(II)-catalyzed direct arylation with unactivated arenes.

Another class of substrates with acetamino directing groups could be utilized for dehydrogenative arylation involving two aromatic C-H bonds (Scheme 44).[58] The desired products were obtained with high regioselectivity in good yields using $Pd(OAc)_2$ (10 mol %) as the catalyst, $Cu(OTf)_2$ (10-100 mol %) and propionic acid as cosolvent under O_2. The proton-abstraction pathway which activates the C-H bond of a second arene to afford intermediate **7** via **6**, is described in the aforementioned catalytic cycle (Scheme 44). A similar reaction was reported by Buchwald and co-workers using TFA as the solvent under an atmosphere of molecular oxygen without any additional transition-metal oxidants (Scheme 45).[59] The transformation of electron-poor anilides proceeded only sluggishly, implying that a proton abstraction mechanism was of less importance.

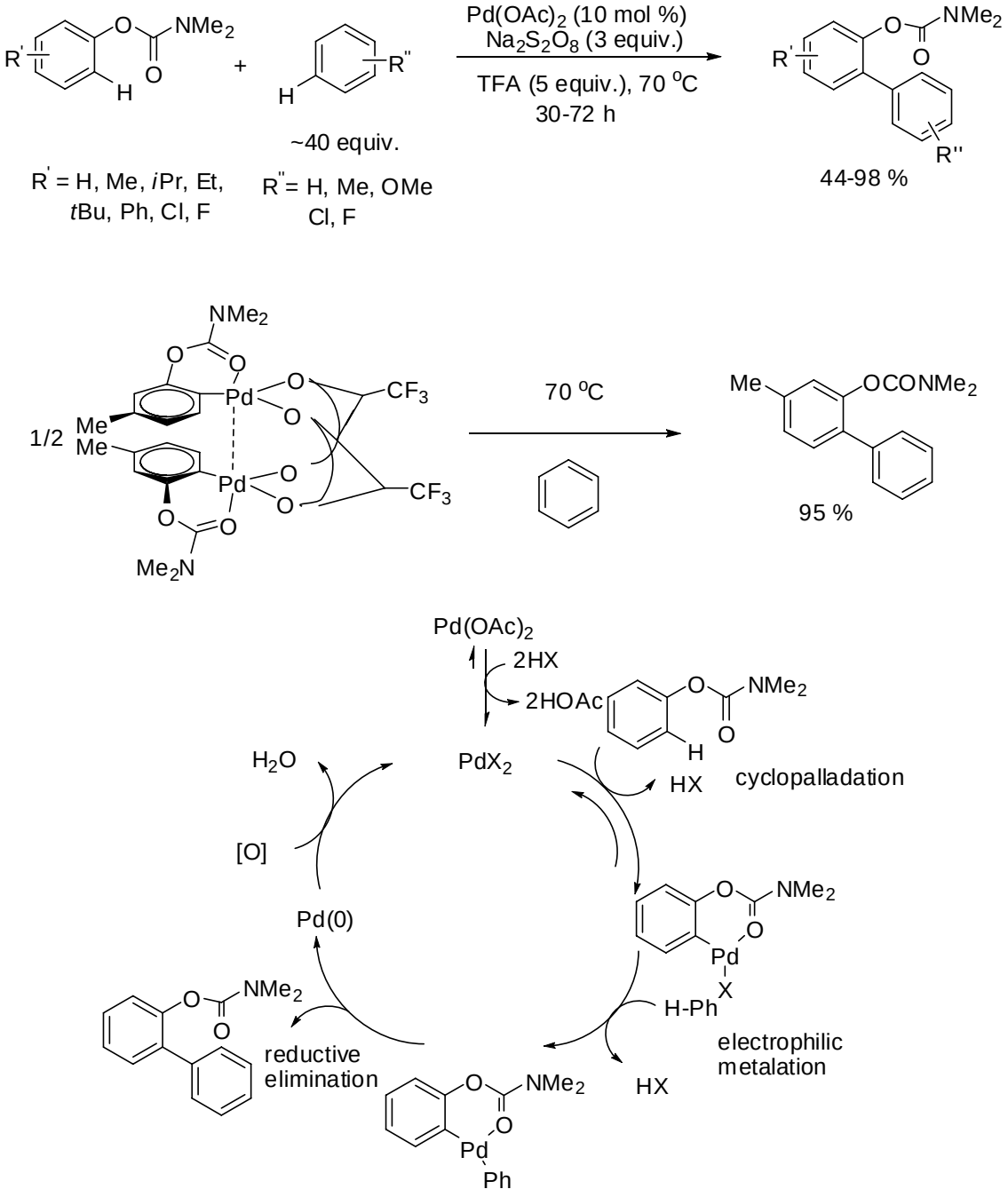


Scheme 44. Palladium(II)-catalyzed cross dehydrogenative arylation.



Scheme 45. Palladium(II)-catalyzed ortho arylation of anilides with simple arenes.

Very recently, the Dong group described $Pd^{II/0}$-catalyzed ortho-arylations of *O*-phenylcarbamates with simple arenes and sodium persulfate (Scheme 46).[60] In contrast to the aforementioned anilide arylations, *O*-phenylcarbamate arylation occurred with high efficiency using electron-deficient arenes (e.g., o-dichlorobenzene and *o*-difluorobenzene). On the basis of preliminary mechanistic studies, a distinct mechanistic proposal is shown in Scheme 46. The oxidative cross-coupling proceeds via a Pd(0/II) catalytic cycle involving (1) carbamate-directed C-H bond activation to afford a cyclopalladation intermediate, (2) C-H bond functionalization by electrophilic metalation, (3) C-C bond forming reductive elimination, and finally, (4) reoxidation of Pd(0) to an active Pd(II) catalyst by sodium persulfate. The preformed palladacycle intermediate could react smoothly with benzene in 95 % yield providing evidence for the first C-H bond activation by cyclopalladation. The significant differences in arene reactivity observed (i.e., *o*-dichlorobenzene, benzene, *o*-dimethoxybenzene) lead the authors to favor an S_EAr mechanism over both concerted metalation deprotonation and the σ-bond metathesis pathways.



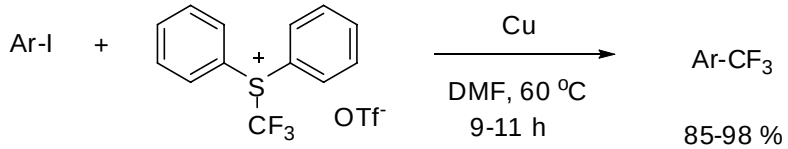
Scheme 46. Palladium(II)-catalyzed oxidative arylation of *O*-phenylcarbamates with simple arenes.

1.4 Transition-Metal-Catalyzed Arene Trifluoromethylation

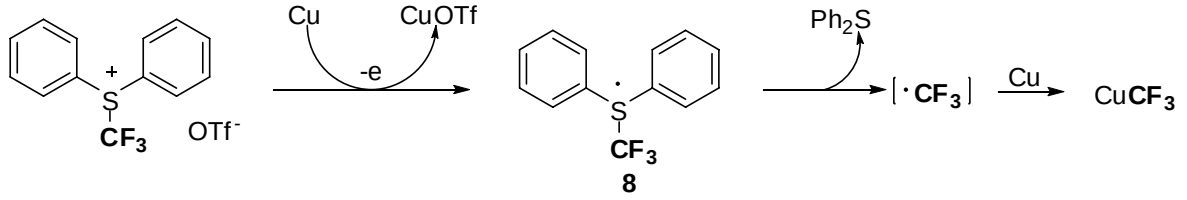
The substitution of CH_3 for CF_3 can remarkably alter the chemical and physical properties as well as the biological activity of the parent organic molecule leading to trifluoromethyl groups featured in numerous important pharmaceuticals.[61] Notably, the two big selling antidepressants Prozac (fluoxetine) from Pfizer, and Luvox (fluvoxamine), made by Lilly, contain a para-phenyl trifluoromethyl group.[62] Fluorine compounds are extremely rare in nature. Consequently, any fluorine-containing compound selected for fundamental studies or marketed as a pharmaceutical, agrochemical, or material has to be man-made. So, it is a long-standing goal to invent new methods for preparing fluorinated molecules, particular for trifluoromethylarenes.[61b,63]

Historically, benzotrifluorides are formed through treatment of benzotrichlorides with anhydrous hydrogen fluoride and/or antimony pentafluoride under harsh conditions (Swarts reaction).[64] Transition-metal mediated coupling reactions offer the potential for mild conditions. Pioneering investigations by Burton elucidated the instability and complexity of [Cu-CF_3].[65]

Commonly, [$CuCF_3$] species, generated in situ from stoichimetric copper or copper salts and trifluoromethylating reagents, are used to prepare trifluoromethylarenes under harsh conditions.[66] Recently, a well-defined carbene complex NHC-Cu-CF_3, which is thermally stable, was found to react well with aryl iodides and benzyl bromide at room temperature.[67] Very recently, Xiao and co-workers described a useful method for trifluoromethylation of iodo-substituted heteroaromatic compounds with (S)-(trifluoromethyl)diphenylsulfonium triflate $[Ph_2SCF_3]^+[OTf]^-$ (2 equiv.) in the presence of Cu (3 equiv.) (Scheme 47).[68] It is likely that $CuCF_3$ is the key intermediate involved in the transformation, which was proven by ^{19}F NMR (δ = -33.9 ppm) and ESI-MS (*m/z* 131.9). On the basis of these analyses, a mechanism was proposed, as shown in Scheme 48. Initially, the (S)-(trifluoromethyl)diphenylsulfonium triflate is reduced by copper through single electron transfer (SET). Intermediate **8** then decomposes rapidly to produce the CF_3 radical, which further yields $CuCF_3$.

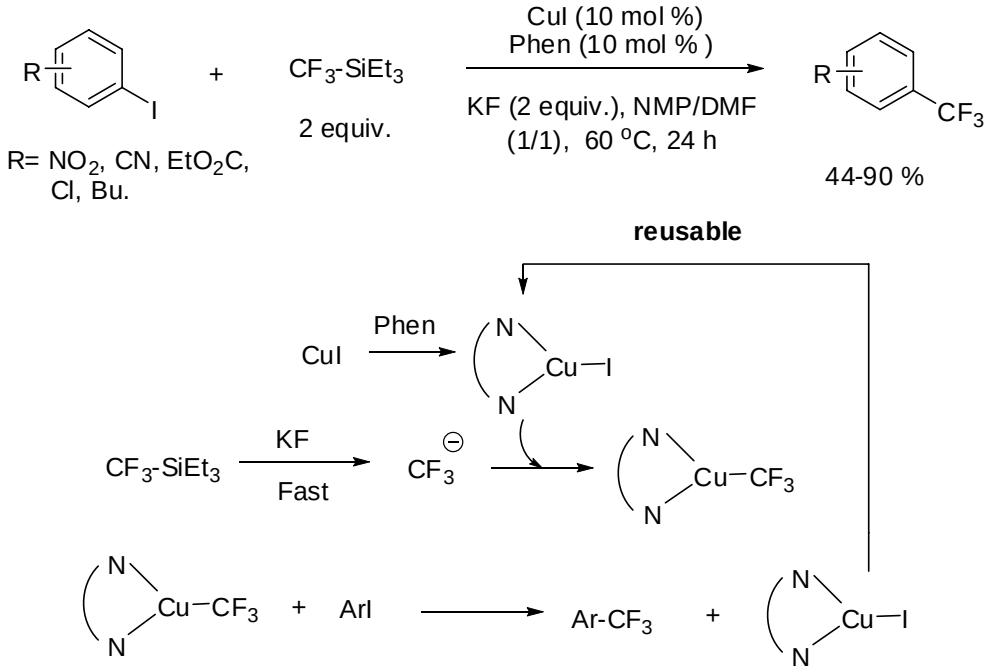


Scheme 47. Copper-mediated trifluoromethylation of heteroaromatic compounds by trifluoromethyl diphenyl sulfonium triflate.



Scheme 48. Proposed mechanism for formation of $CuCF_3$.

The first example of copper-catalyzed aromatic trifluoromethylation was reported by Amii et al. using CuI/1,10-phenanthroline complex as the catalyst (Scheme 49).[69] The key to the success of the transformation is the presence of the diamine ligand that can increase the electron density and stability of Cu-CF_3 by coordination, resulting in fast regeneration of the copper catalyst.

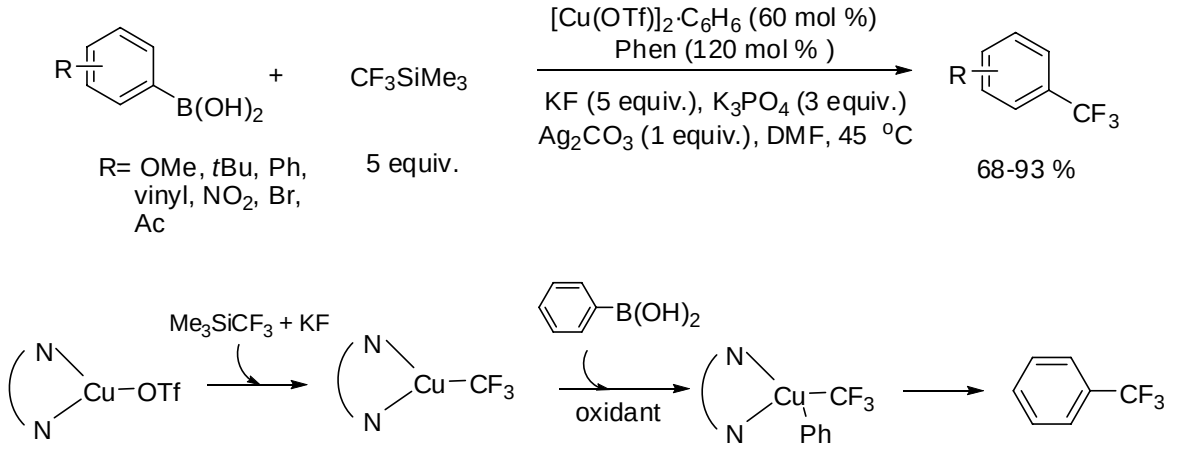


Scheme 49. Copper(I)-catalyzed trifluoromethylation of aryl iodides.

Considering the fact that CF_3-$SiEt_3$ is sensitive to air and moisture, Gooßen and coworkers introduced an air-stable CF_3 reagent, potassium (trifluoromethyl)trimethoxyborate, to react with aryl iodides employing a CuI/1,10-phenanthroline catalytic system (Scheme 50).[70] A variety of aryl iodides bearing electron-donating groups or electron-withdrawing groups could be smoothly converted in high selectivity and yields.

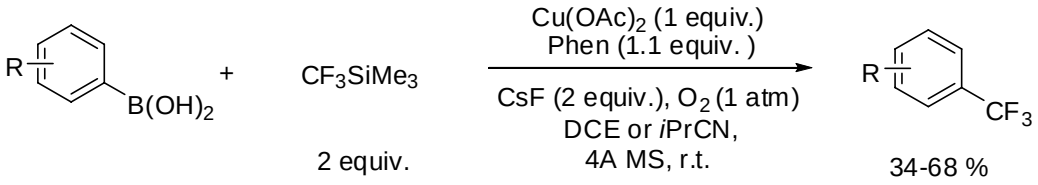
Scheme 50. Copper(I)-catalyzed trifluoromethylation with potassium (trifluoromethyl)-trimethoxyborate.

Arylboronic acids can carry a broad range of common functional groups, are easily available and air-stable, and widely applied in organic synthesis.[71] Pioneering work by Qing and co-workers described a stoichiometric copper-mediated oxidative trifluoromethylation of arylboronic acids at 45 °C (Scheme 51).[72] The transformation was initiated by $CuCF_3$ generated in situ from the combination of KF (5.0 equiv), Me_3SiCF_3 (5.0 equiv.), and $[Cu(OTf)]_2{\cdot}C_6H_6$ (0.6 equiv.) in the presence of 1,10-phenanthroline (1.2 equiv.) and followed by transmetalation with arylboronic acid in the presence of Ag_2CO_3 (1.0 equiv.) as the reoxidant.



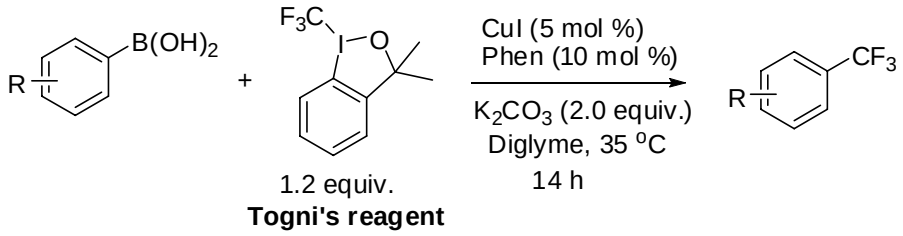
Scheme 51. Copper-mediated trifluoromethylation of arylboronic acids.

Simultaneously, Buchwald et al. reported a more benign and economic system for copper-mediated oxidative cross-coupling of aryl boronic acids and Me_3SiCF_3 just using O_2 (1 atm) as the oxidant at room temperature, affording trifluoromethylarenes in 34-68 % yields (Scheme 52).[73]



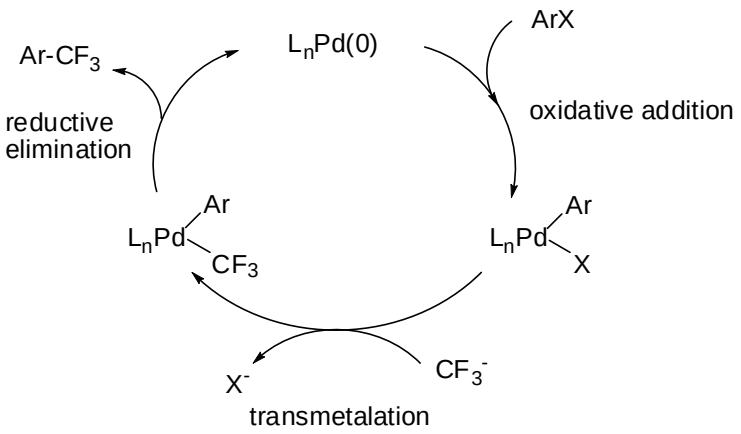
Scheme 52. Copper-catalyzed trifluoromethylation of arylboronic acids at room temperature.

Very recently, Shen and co-workers disclosed a CuI-catalyzed trifluoromethylation of arylboronic acids with Togni's reagent (Scheme 53).[74] This transformation can proceed well at 35 ^oC and give the corresponding products in 53-95 % yields.



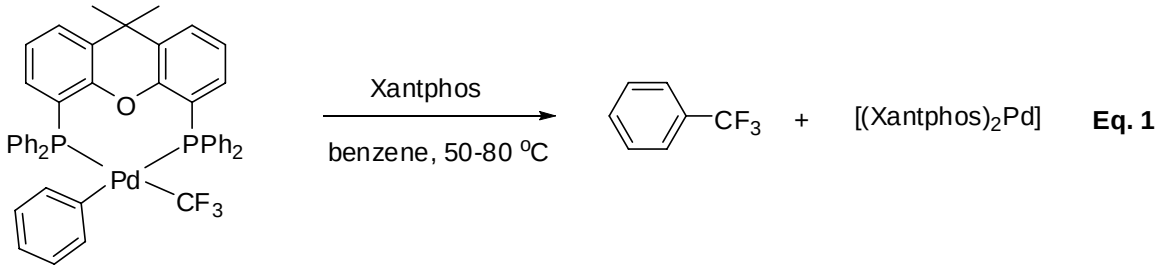
Scheme 53. CuI-catalyzed trifluoromethylation of arylboronic acids with Togni's reagent by Shen.

Palladium is a versatile metal in organic synthesis, particularly in cross-coupling reactions of carbon-carbon bond formation.[5] The Ar-CF_3 coupling reaction is one special type of C-C couplings, its catalytic cycle with palladium as the catalyst as shown in Scheme 54.[75]



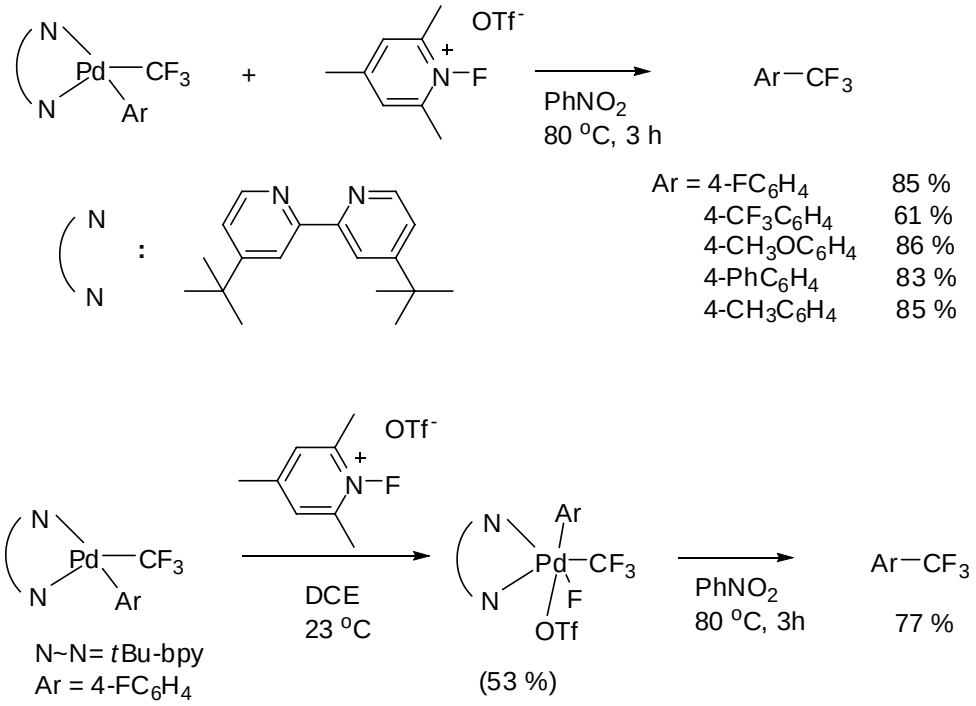
Scheme 54. Catalytic loop of Pd-mediated trifluoromethylation of arylhalides.

The challenging step of the catalytic cycle is the reductive elimination of $[L_nPd(Ar)CF_3]$ due to the inert nature and strength of Pd-CF_3 bond.[76] In sharp contrast to [(dppbz)Pd(CH_3)(*o*-Tol)] that can undergo C-C reductive elimination to afford xylene in 99 % yield at 40 ^oC, its trifluoromethyl analogue remains intact for days at 130 ^oC.[77] The breakthrough in the Ar-CF_3 reductive elimination from palladium complex was achieved by Grushin et al. The preprepared [(Xantphos)Pd(Ph)CF_3] easily underwent Ph-CF_3 reductive elimination at temperatures as low as 50-80 ^oC (Eq. 1).[78] The ligand Xantphos is critical for the CF_3-Ph bond formation.



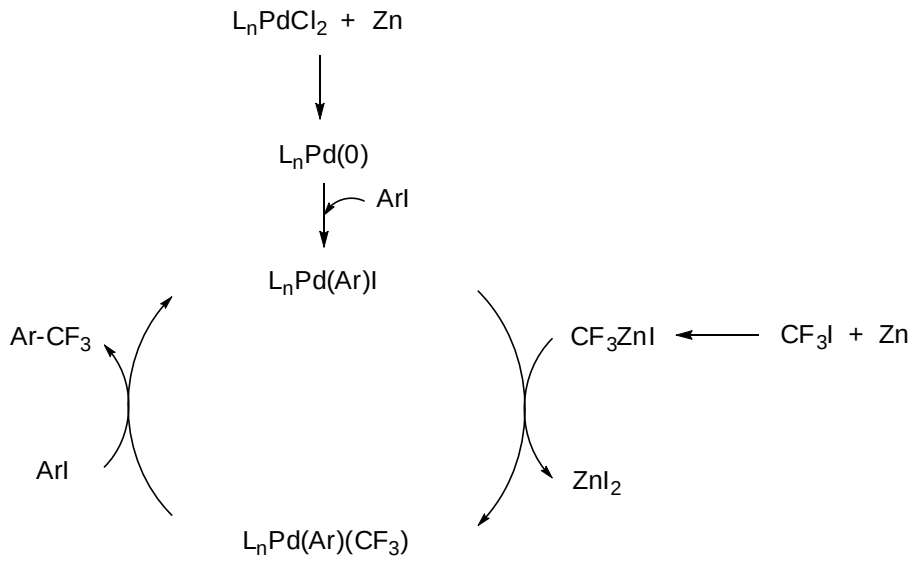
Eq. 1

A notable advance was achieved by Sanford and co-workers who described more general strategies for arene trifluoromethylation from a series of new $Pd^{IV}(Ar)(CF_3)$ species (Scheme 55).[79] These transformations proceed well with electron-donating and electron-withdrawing arene substituents at 80 ^oC. A stepwise experiment showed that the process involved $L_nPd^{II}(Ar)(CF_3)$ oxidized to $L_nPd^{IV}(Ar)(CF_3)(OTf)(F)$, followed by reductive elimination to produce trifluoromethylarenes.



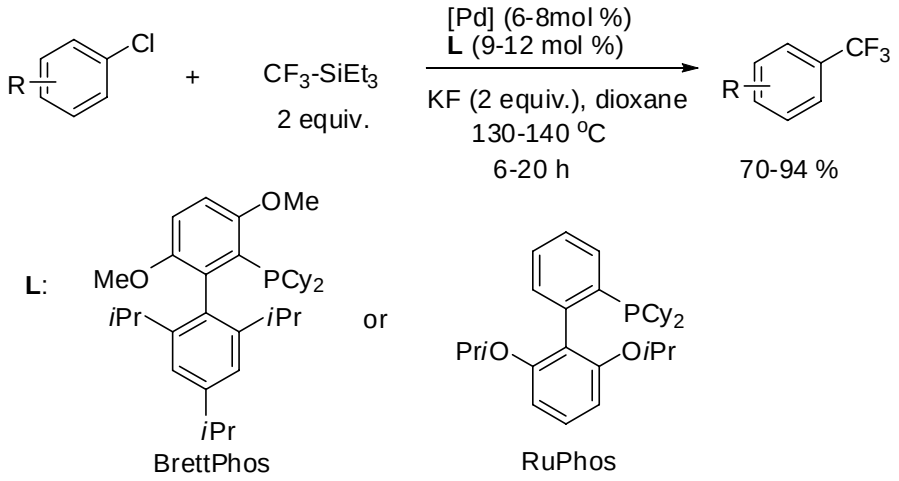
Scheme 55. Oxidatively induced reductive elimination of Pd complexes for Ar-CF_3.

A catalytic version of aromatic trifluoromethylation was reported by the Ishikawa group in 1982. The cross coupling of phenyl iodide and CF_3I (1.1 equiv.) proceeded smoothly to give the desired product in 82 % yield with ultrasonically dispersed zinc powder (2.0 equiv.) in the presence of $Pd(PPh_3)_2Cl_2$ (1 mol %) in THF (Scheme 56).[80] The zinc reduces Pd^{II} to Pd^0 and activates CF_3I to CF_3ZnI. The active Pd^0 species is oxidized to $L_nPd(Ar)I$ by ArI, followed by transmetalation of CF_3ZnI to form $L_nPd(Ar)CF_3$ that generate the corresponding product after reductive elimination, as depicted in Scheme 56.

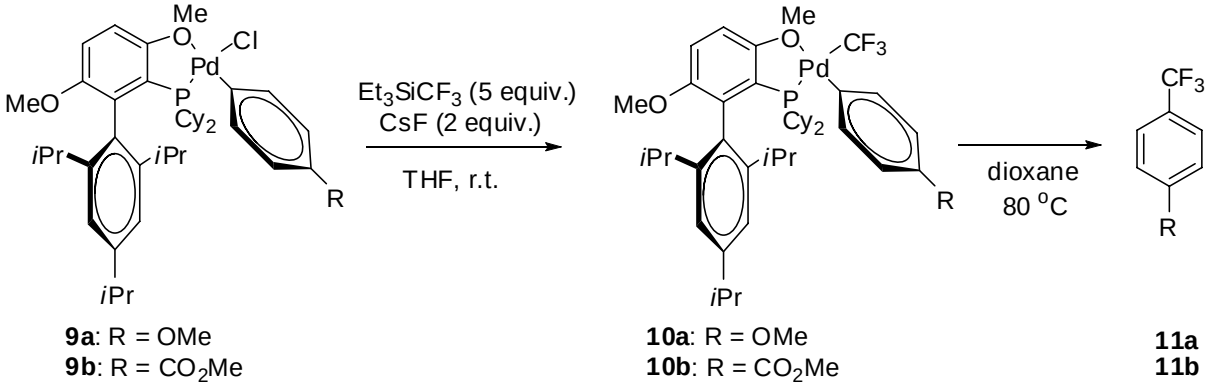


Scheme 56. Catalytic loop of Pd(0)-catalyzed aromatic trifluoromethylation.

Very recently, a landmark of Pd-catalyzed aromatic trifluoromethylation was described by Buchwald et al. (Scheme 57).[81] This methodology allowed for trifluoromethylation of aryl chlorides bearing electron-rich or electron-poor substitutes, including esters, acetals, amides, nitriles, ethers, dialkylamines, in good yields with $[(allyl)PdCl]_2$ or $[Pd(dba)_2]$ as the catalyst at 130 ^oC to 140 ^oC. Additionally, a variety of heteroaromatic substrates such as indoles, carbazoles, quinolines, and benzofuranes can also be efficiently transformed into the desired products. Mechanistically, a key intermediate $[LPd^{II}(Ar)CF_3]$ (L = BrettPhos) was isolated and characterized, which undergoes reductive elimination to afford benzotrifluorides in nearly quantitative yield upon heating in dioxane (Scheme 58). In addition, the complex **10b** reacted in the presence of aryl chloride to yield **9b** as well as **11b**. So, the reaction likely proceeds via a classical Pd(0)/Pd(II) catalytic cycle, including oxidative addition, transmetalation and reductive elimination.



Scheme 57. Pd(0)-catalyzed trifluoromethylation of aryl chlorides with Et_3SiCF_3.

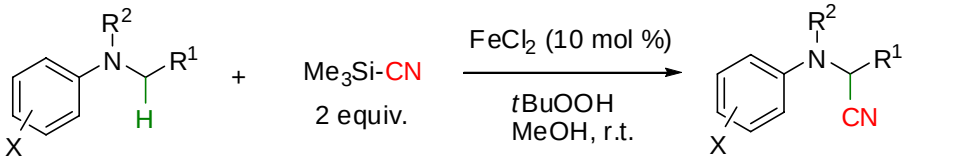


Scheme 58. Formation of and reductive elimination from $[LPd^{II}(Ar)CF_3]$ (L: BrettPhos) complexes.

1.5 Objectives

Nitrogen-containing compounds are prevalent in a myriad of natural products, biologically active compounds and therapeutic drug molecules. Because of this, the functionalization of the nitrogen-containing compounds has attracted considerable interest. Among the many strategies accessible, sp^3 C–H activation and subsequent carbon-carbon or carbon-heteroatom bond formation is the most efficient process. As mentioned in Chapter 1.2, big progress has been made in this field, for example, by lithiation reactions (high reactivity but low compatibility of functional groups) or nobel metal catalysis (good tolerance of functional groups but expensiveness and toxicity of catalyst). Iron is an ideal catalyst because it is cheap, nontoxic and widely available. However, iron has rarely been utilized in the field, particularly under mild conditions. Herein, new methods to functionalize nitrogen-containing compounds via iron-catalyzed sp^3 C-H activation at room temperature have been developed:

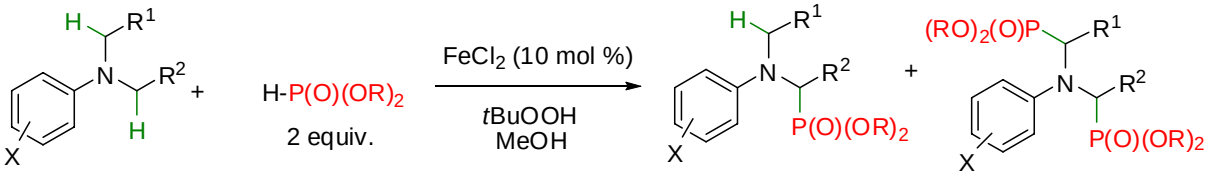
1. Benign iron salts activate sp^3 C-H bonds adjacent to nitrogen in tertiary amines selectively to allow for efficiently constructing α-aminonitriles at room temperature:



X = H, Me, OMe, Br, NO_2, ethynyl

24 examples up to 92 %

2. The successful extension of this catalytic system to proceed oxidative α-phosphonation of tertiary aromatic amines at room temperature:



X = H, Me, OMe, Br, NO_2, COPh, CO_2Et, COOH

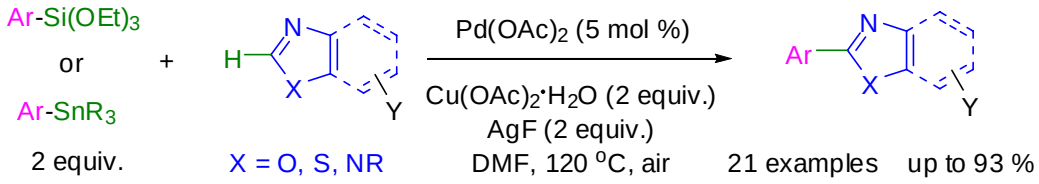
29 examples up to 84 %

4 examples up to 80 %

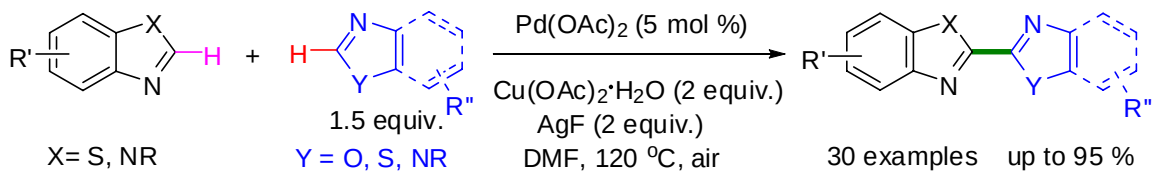
($R^1 = R^2 = H$)

In comparison to classical transition-metal-catalyzed couplings, C-H functionalization has the advantage of avoiding pre-activation of one or more of the substrates, thus producing

less waste. One of the most common C-H activation methodologies is to involve organometallic reagents. As mentioned in Chapter 1.3.2, the most popular organometallic reagents are organoboron compounds that have been widely used as arylating reagents in the process of palladium-catalyzed sp^2 C-H activation. Organosilicon reagents are attractive because of their low toxicity and safe handling. Meanwhile, they possess the lowest reactivity but better functional compatibility due to slight polarity of C-Si bonds. Consequently, there are quite few examples to demonstrate the direct arylation of sp^2 C-H with organosilanes. Herein, a convenient, efficient and "ligand-free" palladium-catalyzed direct arylation of sp^2 C-H at C-2 of various azoles with trialkoxy(aryl)silanes and aryl tin compounds has been reported.

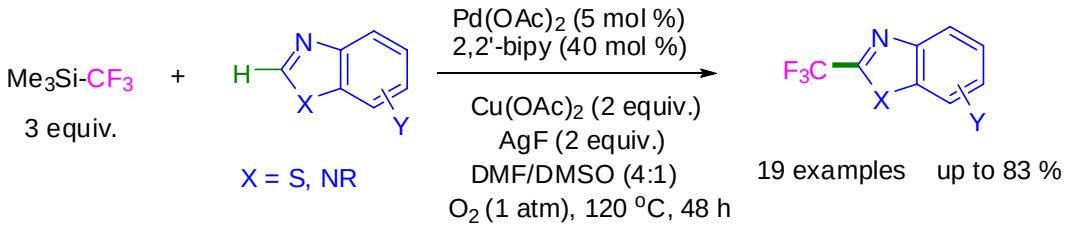


From the viewpoint of atom economy, two-fold C–H bond activation is the ideal strategy for constructing aryl-aryl bonds. As mentioned in Chapter 1.3.3, while achieving selectivity in either intramolecular oxidative arylation or intermolecular homocoupling is intrinsicly less difficult, a significant challenge remains by intermolecular cross-coupling arylation between two different (hetero)arenes. Although advance in this respect was accomplished by introducing directing group or using one coupling partner in large excess, the processes are limited or impractical in real synthesis. Herein, a method for the selective C–C coupling between the non-functionalized C-2 positions of azoles by double C–H bonds activation which provides access to a class of widely unexplored unsymmetrical 2,2'-bisheteroaryls has been described.



As exemplified in Chapter 1.4, the progress achieved in the field of aromatic trifluoromethylation catalysis is impressive. However, in nearly all the cases, the substrates have to be prefuctionalized to aryl halides or arylboronic acids from simple arenes prior to

use, that is to say, the process is not the most straigtforward way. Meanwhile, it remains a big challenge to effectively achieve C-C bond formation from reductive elimination of CF_3 ligated metal complex in catalysis. Herein, palladium(II)-catalyzed direct aromatic trifluoromethylation via sp^2 C-H activation in the absence of directing group has been described.



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Chapter 2

Iron Catalyzed Oxidative Cyanation of Tertiary Amines

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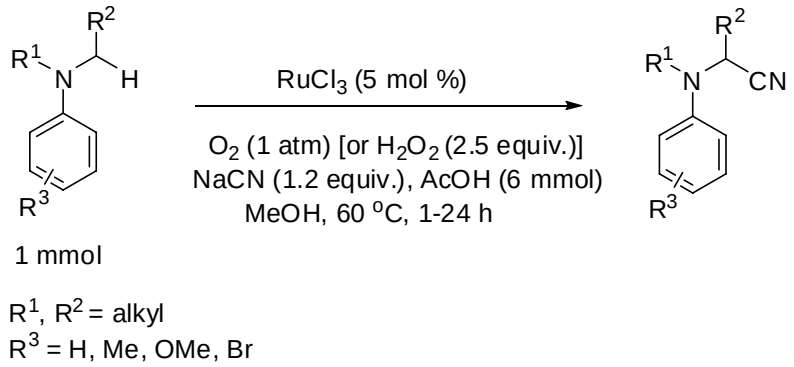
2.1 Introduction

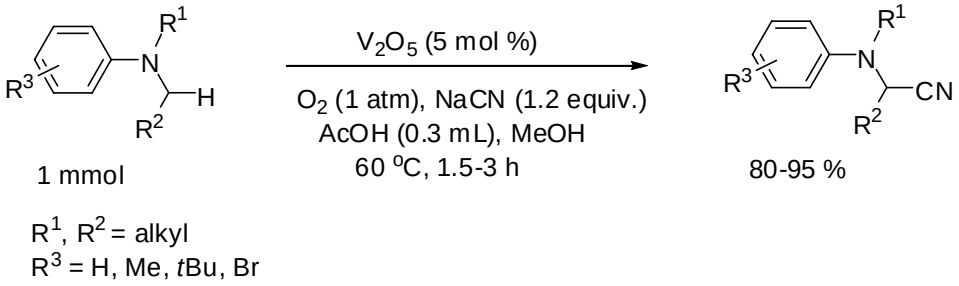
The formation of new carbon–carbon bonds is the most important transformation in organic chemistry.[1] Transition metal catalyzed activation of C(sp^3)–H bonds and subsequent C–C bond formation which avoids the use of prefunctionalized starting material is therefore a valuable and straightforward synthetic strategy.[2–4] In contrast to many toxic and/or rare metals previously used for this transformation, iron is ubiquitous in the geosphere with 4.7% wt abundance and in the biosphere where it is often found as part of catalytic systems. Consequently, in recent years iron catalysts have been used for a multitude of organic syntheses, including oxidations and cross couplings.[5] So far, C–C bond forming reactions via iron catalyzed functionalization of C(sp^3)–H bonds generally require elevated temperatures (60 to 100 ^oC),[6–9] and there are few literature reports on iron-based system sufficiently active to catalyze C(sp^3)–H cross couplings at room temperature.[10,15]

Metal-catalyzed oxidative α-cyanation of tertiary amines via direct functionalization of C(sp^3)–H bonds provides access to α-aminonitriles.[11,12] A seminal work by Murahashi et al. reported $RuCl_3$-catalyzed α-cyanations of sp^3 C–H bonds of tertiary amines with NaCN in good to excellent yields with high selectivity in the presence of molecular oxygen or hydrogen peroxide as oxidant under acid conditions, as shown in Scheme 1.[13]



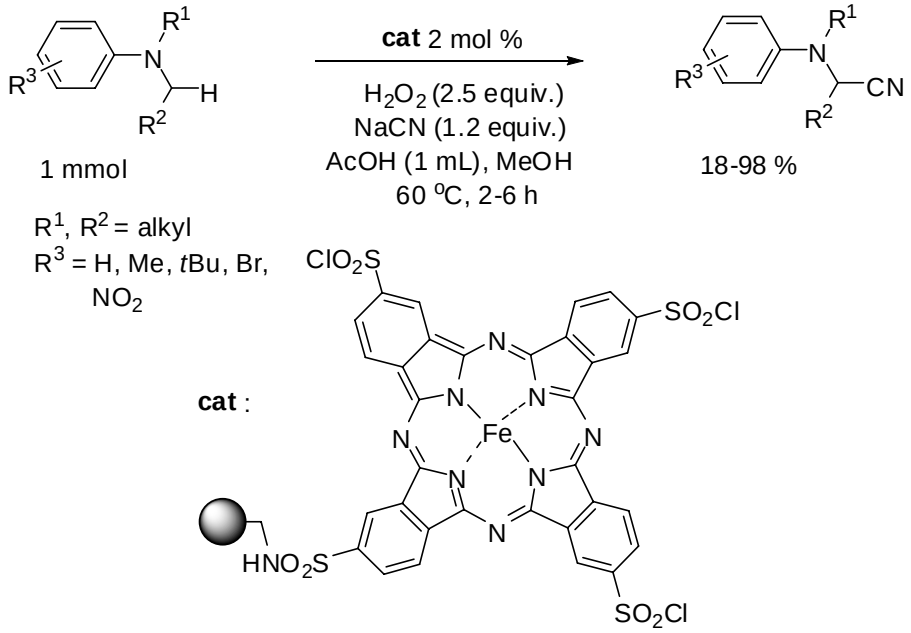
Scheme 1. $RuCl_3$-catalyzed oxidative cyanation of tertiary amines with molecular oxygen or hydrogen peroxide as oxidant (Murahashi group, 2003-2008).

However, the expensive nature, toxicity and moisture sensitivity of the $RuCl_3$ limits its wide utility. A subsequent report by Sain and co-workers described a more stable V_2O_5 catalyst for oxidative cyanation of various tertiary amines with sodium cyanide using molecular oxygen as oxidant and methanol-acetic acid (4 : 1) as reaction solvent at 60 °C (Scheme 2).[14] The catalytic efficiency of V_2O_5 for oxidative cyanation of tertiary amines appears to be comparable to that of $RuCl_3$.



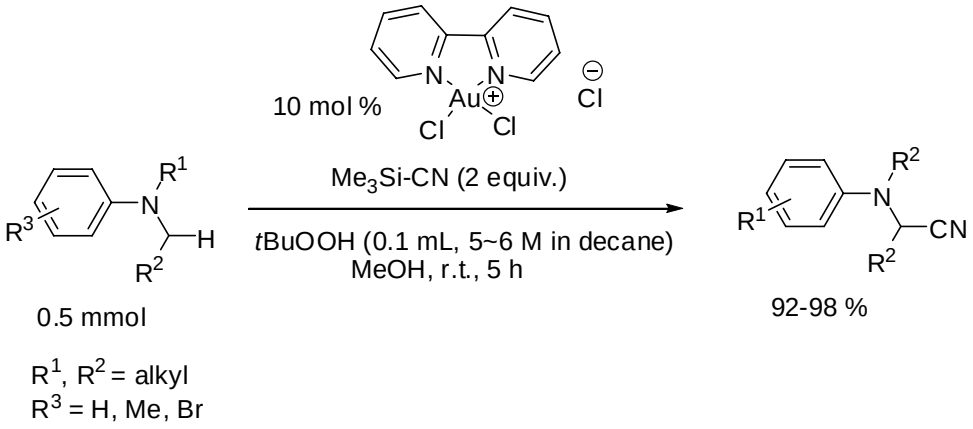
Scheme 2. V_2O_5-catalyzed cyanation of sp^3 C-H of *N,N*-dialkyl anilines (Sain group, 2009).

Considering that $RuCl_3$ and V_2O_5 are toxic catalysts, the Sain group disclosed an environmentally benign catalytic system for the efficient oxidative cyanation of tertiary amines with hydrogen peroxide as oxidant in the presence of NaCN by using polymer-supported iron phthalocyanines as catalysts in methanol-acetic acid (4 : 1) as reaction solvent at room temperature which afforded the corresponding α-aminonitriles in good to excellent yields with high selectivity (Scheme 3).[15]



Scheme 3. Oxidative cyanation of tertiary amines using supported Fe(II) phthalocyanine as catalyst (Sain group, 2009).

So far, all catalytic systems need the presence of acetic acid to achieve smooth reactions. Consequently, severely toxic HCN is formed during the course of the cyanation reactions. In order to avoid this problem, Zhu and co-workers developed an efficient method for α-cyanation of sp^3 C-H bonds in tertiary amines in good to excellent yields with Me_3SiCN using a gold catalyst and *tert*-butylhydroperoxide as the oxidant under acid-free conditions at room temperature (Scheme 4).[16]



Scheme 4. Au complex-catalyzed oxidative cyanation of tertiary amines (Zhu group, 2011).

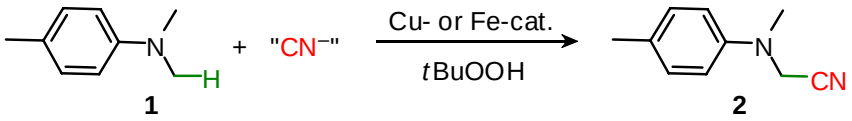
Herein we report the selective synthesis of α-aminonitriles under mild and acid-free conditions by oxidation of tertiary amines in the presence of inexpensive and non-toxic iron salts without designed ligands.

2.2 Results and Discussion

2.2.1 Optimizing the Catalytic System

Copper and iron salts in the presence of organic peroxides are capable of activating C(sp^3)–H bonds adjacent to nitrogen in amines.[3,5h,7,8] In a first series of experiments, we studied the

Table 1 Oxidative α-cyanation of *N,N*-dimethyl-*p*-toluidine (**1**) in MeOH[a]



1 **2**

Entry	Catalyst (mol %)	Cyanide source (equiv.)	*t*BuOOH (equiv.)	Time (h)	Solvent	Yield (%)
1	CuBr (5)	*n*-$Bu_4N^+CN^-$(1.2)	1.2	24	-	9
2	$CuBr_2$ (10)	*n*-$Bu_4N^+CN^-$ (1.2)	1.2	24	MeOH	15
3	CuBr (10)	*n*-$Bu_4N^+CN^-$ (1.5)	1.5	24	MeOH	21
4	CuBr (10)	Me_3SiCN (2.0)	2.5	10	MeOH	26
5	$FeCl_2$ (10)	*n*-$Bu_4N^+CN^-$ (1.5)	1.5	24	MeOH	10
6	$FeCl_2$ (10)	$K_3[Fe(CN)_6]$ (0.25)	1.5	24	MeOH	25
7	$FeCl_2$ (10)	Me_3SiCN (2.0)	1.5	24	MeOH	86
8	**$FeCl_2$ (10)**	**Me_3SiCN (2.0)**	**2.5**	**10**	**MeOH**	**92**
9	None	Me_3SiCN (2.0)	2.5	10	MeOH	19
10	FeF_2 (10)	Me_3SiCN (2.0)	2.5	10	MeOH	37
11	$FeSO_4$ (10)	Me_3SiCN (2.0)	2.5	10	MeOH	43
12	$Fe(gluconate)_2$ (10)	Me_3SiCN (2.0)	2.5	10	MeOH	51
13	$Fe(AcO)_2$ (10)	Me_3SiCN (2.0)	2.5	10	MeOH	63
14	$Fe(acac)_3$ (10)	Me_3SiCN (2.0)	2.5	10	MeOH	59
15	$FeCl_3$ (10)	Me_3SiCN (2.0)	2.5	10	MeOH	90
16	$FeCl_3 \cdot 6H_2O$ (10)	Me_3SiCN (2.0)	2.5	10	MeOH	82
17	$FeBr_3$ (10)	Me_3SiCN (2.0)	2.5	10	MeOH	88
18	$FeCl_2$ (10)	Me_3SiCN (2.0)	2.5	10	CH_3CN	52
19	$FeCl_2$ (10)	Me_3SiCN (2.0)	2.5	10	EtOH	53
20	$FeCl_2$ (10)	Me_3SiCN (2.0)	2.5	10	CF_3CH_2OH	71
21	$FeCl_2$ (10)	Me_3SiCN (2.0)	2.5	10	*i*PrOH	78
22	$FeCl_2$ (10)	Me_3SiCN (2.0)	2.5	10	*t*BuOH	47

[a] *Reaction conditions: N,N*-dimethyl-*p*-toluidine (1.0 mmol), MeOH (2.0 mL), room temperature, dry N_2 atmosphere. [b] Yield of isolated product after column chromatography on silica gel.

catalytic efficiency of various copper and iron salts for the oxidative cyanation of *N,N*-dimethyl-*p*-toluidine (**1**) with different cyanide sources using *tert*-butylhydroperoxide as the oxidant (Table 1).

Low yields of **2** were obtained by Cu(I) or Cu(II) bromide-catalyzed cyanation reactions with tetra-*n*-butylammonium cyanide or trimethylsilyl cyanide (Table 1, entries 1-4). Similarly, the $FeCl_2$-catalyzed reaction of **1** with tetra-*n*-butylammonium cyanide or potassium hexacyanoferrate(III) (Table 1, entries 5 and 6) gave only low yields.[17] The conversion to the α-cyano derivative **2** was significantly improved, however, when we employed 2 equivalents of Me_3SiCN (86 %). Reducing the excess of Me_3SiCN (1.5 equiv.) required extended reaction times (24 h, 85 % yield), and the use of equimolar amounts of Me_3SiCN affected the yield of **2** (24 h, 69 %). Optimum yields of **2** and shorter reaction times were obtained with 2.5 equivalents of *t*BuOOH (Table 1, entry 8). The presence of additional *n*-$Bu_4N^+CN^-$ (1.0 equiv.) under otherwise optimized reaction conditions (*cf.* entry 8 of Table 1) resulted in a slight retardation of the cyanation reaction (63 % isolated yield of **2** after 12 h) possibly because of a decrease in the concentration of the active catalyst. The α-cyanation was achieved with different iron(II) and iron(III) salts. Whereas catalysis by FeF_2 or $FeSO_4$ (Table 1, entries 10 and 11) increased the yields only moderately above the level that was reached without catalyst (Table 1, entry 9), catalysis by $Fe(gluconate)_2$ and $Fe(OAc)_2$ (Table 1, entries 12 and 13) produced already acceptable yields of the α-cyanoamine **2**. Iron(III) salts $FeCl_3$, $FeCl_3 \cdot 6H_2O$, or $FeBr_3$ (Table 1, entries 15–17) were comparable in activity (82–90 % yield) to $FeCl_2$.

The combination of $FeCl_2$ with di-*tert*-butylperoxide, which had been reported to induce C(sp^3)–H bond activation adjacent to nitrogen,[7,8] was found to be ineffective for the cross-coupling reaction with Me_3SiCN. Substitution of the standard solvent methanol by other alcohols or acetonitrile reduced the yields of **2** (Table 1, entries 18–22).

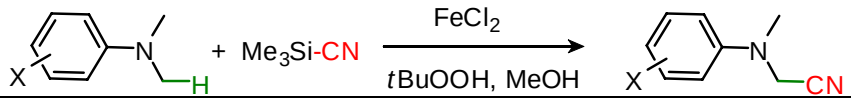
The addition of 5 or 100 mol% of the radical inhibitor 3,5-di-*tert*-butyl-4-hydroxytoluene to the $FeCl_2$ (10 mol%)/*t*BuOOH/Me_3SiCN mixture did not hinder the conversion of **1** into the corresponding α-cyanoamine **2** (87 % and 60 % isolated yields, respectively). This result is in agreement with previous reports on analogous $FeCl_3$-catalyzed oxidations of tertiary amines,[18] but differs from the observations of Sain and co-workers[13] on the V_2O_5-catalyzed formation of α-aminonitriles from tertiary amines and NaCN-AcOH under aerobic conditions.

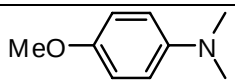
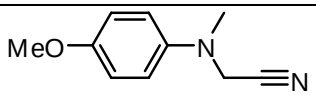
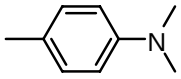
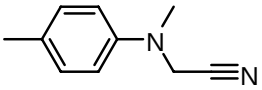
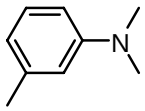
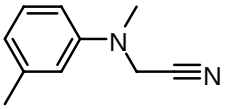
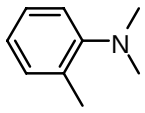
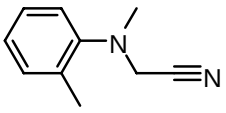
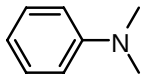
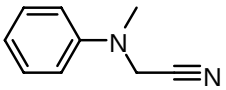
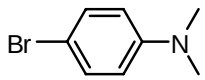
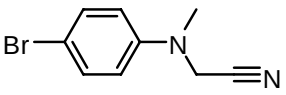
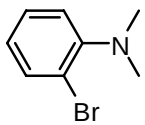
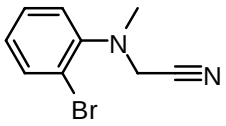
2.2.2 Scope and Limitations

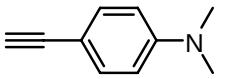
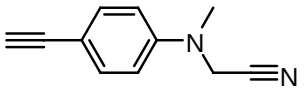
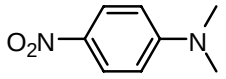
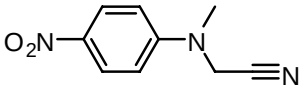
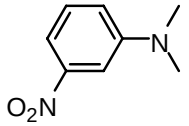
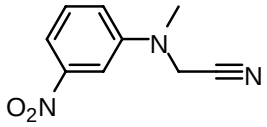
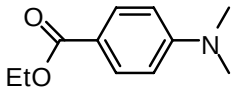
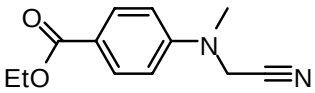
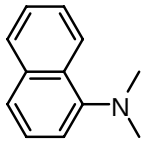
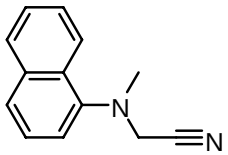
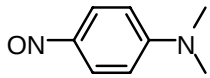
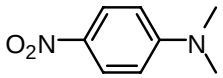
In order to explore the functional group tolerance of the oxidative cyanations by $FeCl_2$/Me_3SiCN/*t*BuOOH, a series of tertiary anilines were investigated as substrates in methanol at room temperature (Table 2).

Ring-substituted *N,N*-dimethylanilines in general reacted analogously and furnished the corresponding (*N*-aryl-*N*-methyl-amino)acetonitriles in high yield. The reaction times were found to be only loosely correlated with the electronic donor or acceptor properties of the substituents at the phenyl moiety. Additionally, *N,N*-dimethylnaphthalen-1-amine also delivered the expected product in 72 % yield (Table 2, entry 12).

Table 2 $FeCl_2$-catalyzed oxidative cyanations of X-substituted *N,N*-dimethylanilines[a]



Entry	substrate	Time (h)	Product	Yield[b] (%)
1		14		87
2		10		92
3		10		89
4		24		76
5		13		90
6		10		78
7[c]		24		85

8[c]		5		83
9[c]		24		45
10		15		80
11[d]		24		74
12		24		72
13		12		84

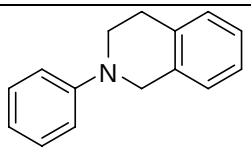
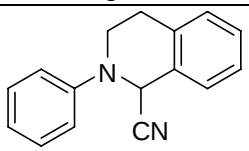
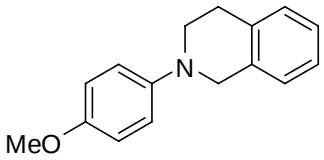
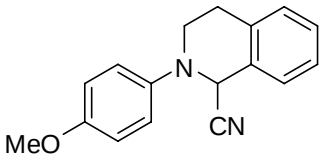
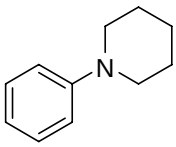
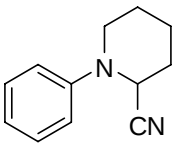
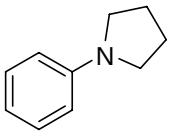
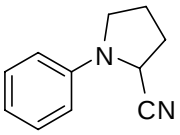
[a] *Conditions*: amine (1.0 mmol), $FeCl_2$ (0.10 mmol), Me_3SiCN (2.0 mmol), *t*BuOOH (2.5 mmol), MeOH (2.0 mL), r.t., dry N_2 atmosphere. [b] Yields of isolated products after column chromatography on silica gel. [c] The reaction mixture was heated to reflux. [d] $FeCl_2$ (20 mol %) and reflux.

The $FeCl_2$-catalyzed cross-coupling of tertiary amines with terminal alkynes using di-*tert*-butylperoxide as oxidant was recently described by Rao Volla and Vogel.[8] We found that under our conditions the presence of a para-ethynyl group at the phenyl ring did not disturb the high selectivity for the oxidative cyanation reaction at the *N*-methyl group (Table 2, entry 8).

N,N-Dimethyl-*p*-nitroso-aniline was converted after 12 h at room temperature in high yield to the corresponding *p*-nitro compound, illustrating the incompatibility of the NO group with the oxidative reaction conditions, in accord with the finding that introducing an α-cyano group at the thus formed *p*-NO_2 derivative requires higher reaction temperatures (Table 2, entry 13).

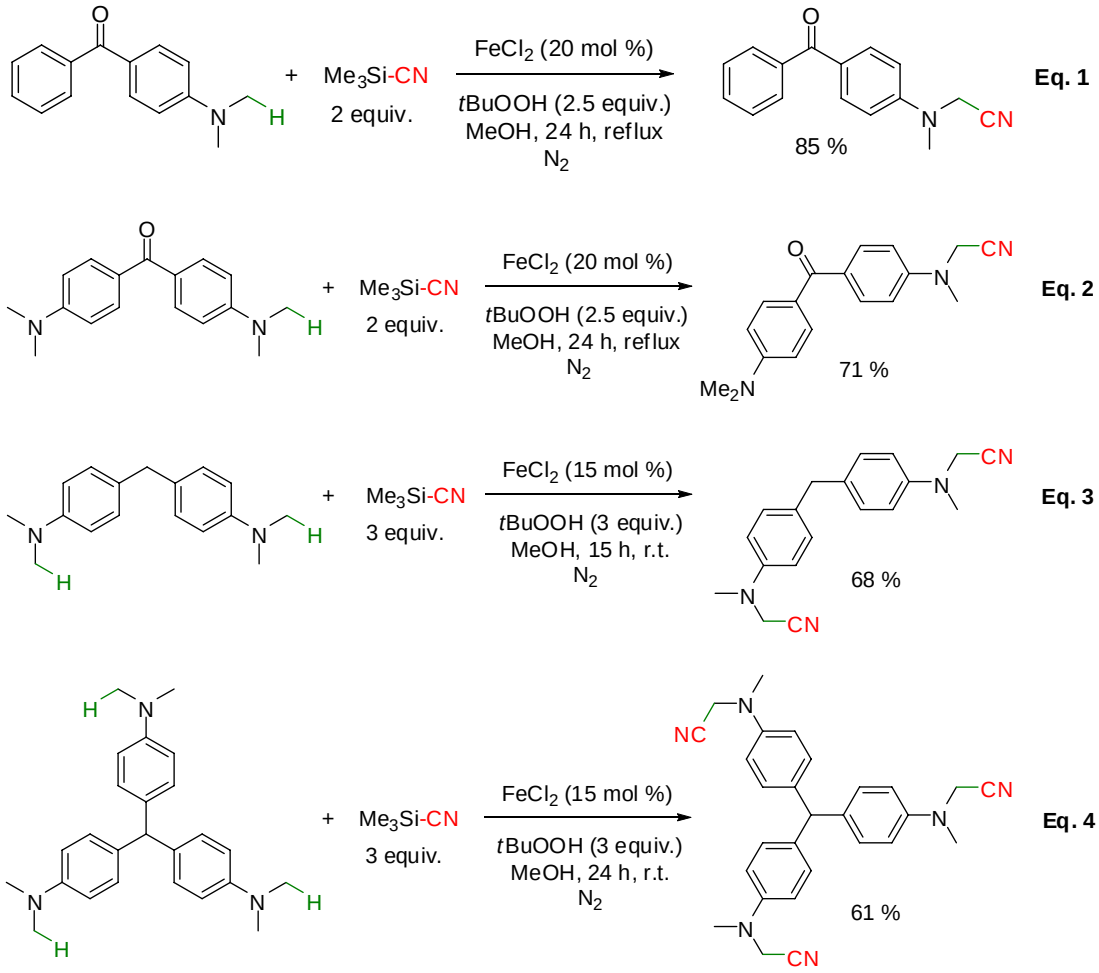
As shown in Table 3, the α-cyano derivatives of 2-aryl-1,2,3,4-tetrahydro-isoquinolines (aryl = phenyl,[19] *p*-anisyl) and *N*-phenyl-substituted cyclic amines could also be obtained in high yield under reaction conditions similar to those optimized for the conversion of **1**.

Table 3 $FeCl_2$-catalyzed oxidative cyanations of tertiary amines[a]

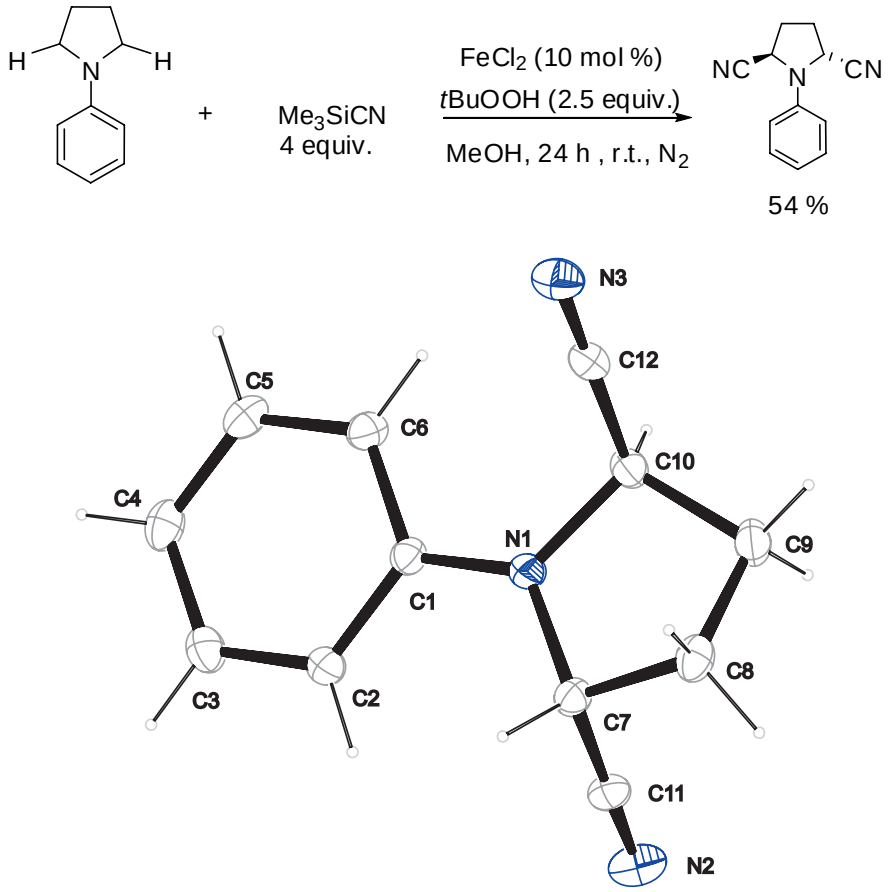
Entry	substrate	Time (h)	product	Yield[b] (%)
1		13		85
2		12		83
3		24[c]		~70[d]
4		24[c]		82

[a] *Conditions*: amine (1.0 mmol), $FeCl_2$ (0.10 mmol), Me_3SiCN (2.0 mmol), *t*BuOOH (2.5 mmol), MeOH (2.0 mL), r.t., dry N_2 atmosphere. [b] Yields of isolated products after column chromatography on silica gel.[c] Without solvent. [d] Contaminated by ca. 15 % of unknown byproducts that could not be separated by column chromatography.

(4-(Dimethylamino)phenyl)(phenyl)methanone was a good substrate for the catalytic system to afford the mono-cyanated product in 71 % yield under reflux (Eq. 1). Accordingly, bis(4-(dimethylamino)phenyl)methanone was expected to be easily converted to the double cyanated product. Disappointingly, the difunctionalized product did not form. Instead, the mono-cyanated product was isolated (Eq. 2). Fortunately, the double cyanated product was produced in 68 % yield even at room temperature from bis(4-(dimethylamino)phenyl)methane as substrate where the readily oxidizable benzylic C-H bonds remained intact during the reaction (Eq. 3).[20] Interestingly, tris(4-(dimethylamino)phenyl)methane generated the corresponding triple cyanated product with high selectivity (Eq. 4).

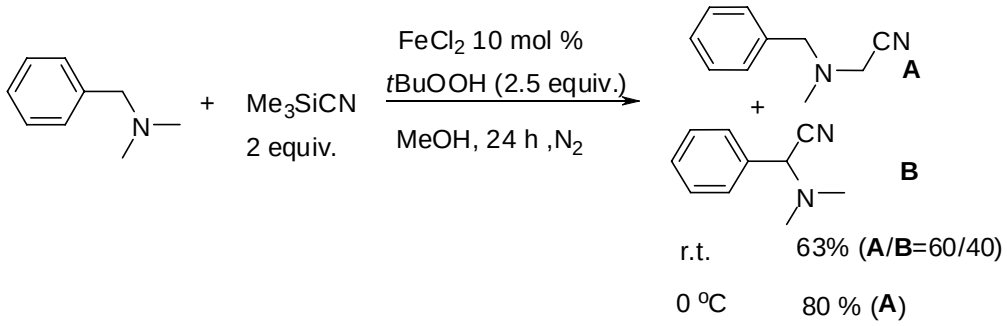


Furthermore, *N*-phenylpyrrolidine was two-fold cyanated to 1-phenylpyrrolidine-2,5-dicarbonitrile by using 4 equivalents of Me_3SiCN. The trans configuration of the product was revealed by a single crystal x-ray structure determination (Scheme 5). Interestingly, the 2,5-dicyanopyrrolidine moiety has been evaluated as a key part of inhibitors of dipeptidyl peptidase IV for the treatment of type 2 diabetes.[21]



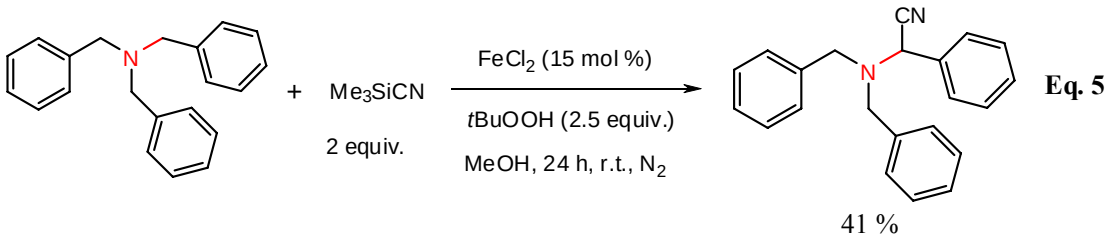
Scheme 5. Synthesis of *trans*-1-phenylpyrrolidine-2,5-dicarbonitrile and its single crystal structure (50 % probability level).

Metal-catalyzed α-cyanations of tertiary alkyl amines have not been described so far.[8,22] GC-MS analysis of the oxidative cyanation of *N,N*-dimethylbenzylamine at room temperature (24 h, 63 % conv.) indicated a C(sp^3)–H activation at both different α-positions adjacent to nitrogen with slight preference for the NCH_3 group over the $PhCH_2N$ moiety. When the reaction was performed at 0 °C, the selectivity was further shifted towards 2-(benzylmethylamino)acetonitrile (**A**), which was exclusively formed and isolated in high yield (80 %) (Scheme 6).



Scheme 6. Regioselective cyanation of *N,N*-dimethylbenzylamine.

Furthermore, tribenzylamine, which possesses three α-positions adjacent to nitrogen, was tested. A moderate yield of mono cyanated product was obtained due to steric hindrance, as shown in Eq. 5.

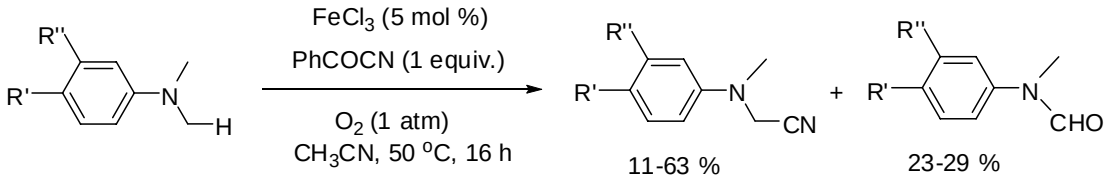


Eq. 5

2.2.3 Oxygen as Oxidant

Although *tert*-butylhydroperoxide is a highly effective oxidant in the above-mentioned catalytic system, it is potentially explosive. Thus, it was the aim of further investigations to select an equally effective but safer oxidant. Oxygen is an attractive, atom-economic, and environmentally benign oxidant due to the fact that it is cheap, widely available (20 vol % of air), and clean (only water as byproduct). According to the requirements of "green chemistry",[23] it has, therefore, been a long-standing goal to use molecular oxygen as oxidant.

As mentioned above (Scheme 1 of this chapter), oxygen was already applied in oxidative cyanations of tertiary amines with $RuCl_3$ as catalyst.[13a,13c] Already in 1993, Miura et al. described the reactions of *N,N*-dimethylanilines with iron(III) chloride as catalyst (5 mol %), O_2 as oxidant, and benzoyl cyanide as cyanide source (CH_3CN, 50 °C, 16 h) to furnish mainly α-cyano compounds accompanied by *N*-methylformanilides and traces of *N*-benzoyl-*N*-methylanilines with low selectivity (Scheme 7).[24]

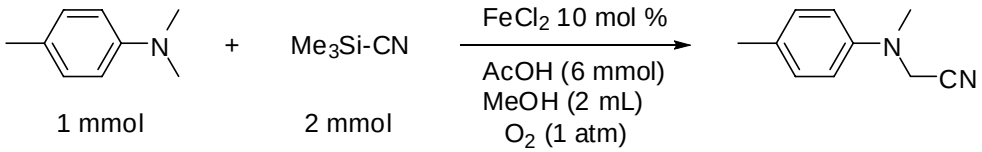


Scheme 7. $FeCl_3$-catalyzed oxidative cyanation of *N,N*-dimethyl-*p*-toluidine with oxygen as oxidant.

In this chapter, we describe the highly selective cyanation of various tertiary amines with molecular oxygen as the sole oxidant using $FeCl_2$ as catalyst in the presence of Me_3SiCN as cyanide source.

Initially, based on Murahashi's work,[13] good results were obtained with acetic acid as an additive, even at room temperature (Table 4, entries 1 and 2). Interestingly, a comparable

Table 4 O_2 as oxidant for the $FeCl_2$-catalyzed cyanation of *N,N*-dimethyl-*p*-toluidine



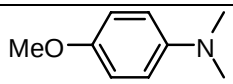
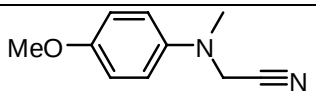
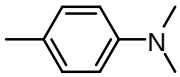
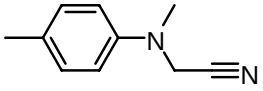
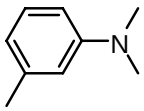
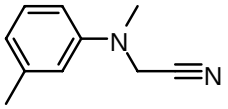
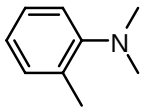
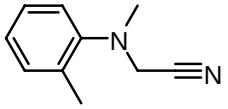
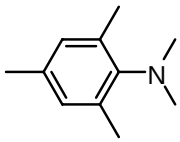
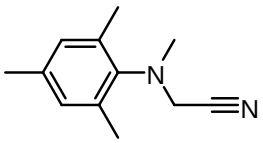
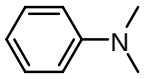
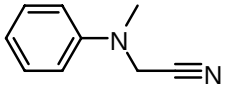
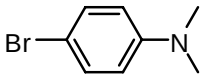
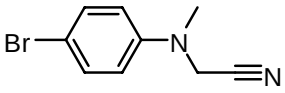
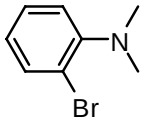
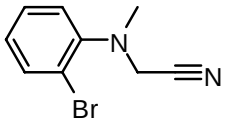
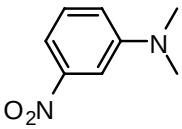
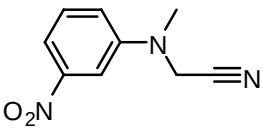
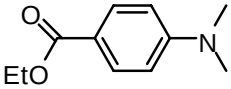
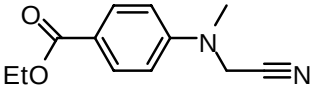
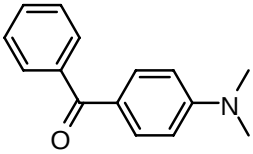
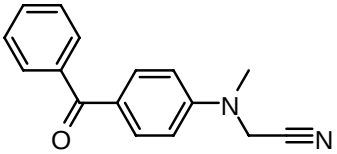
Entry	Solvent	Temperature	Time (h)	Yield (%)[a]
1	MeOH	reflux	12	61
2	MeOH	r.t.	24	83
3	CF_3CH_2OH	r.t.	24	31
4	MeOH[b]	r.t.	24	77

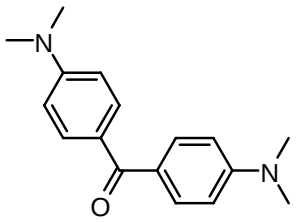
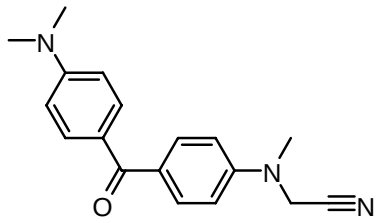
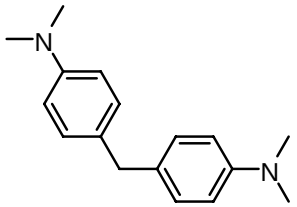
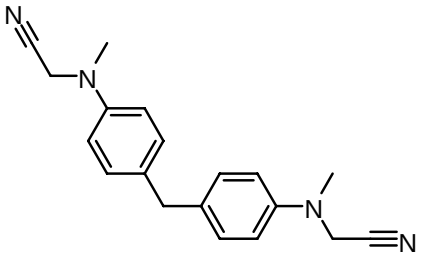
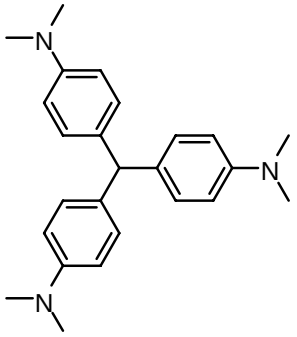
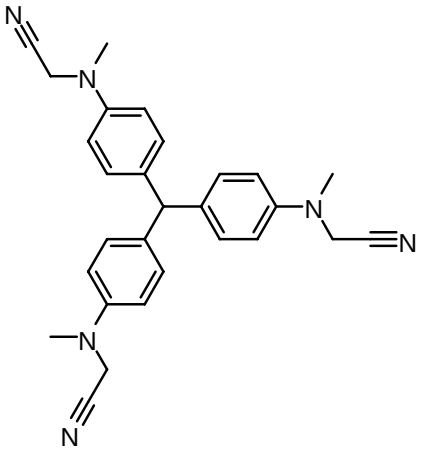
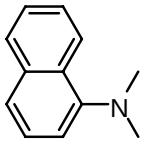
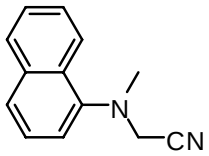
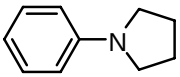
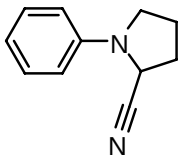
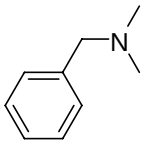
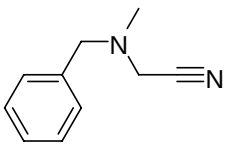
[a] Isolated yield. [b] Without AcOH.

result was also achieved, affording the desired product in 77 % in the absence of AcOH (Table 4, entry 4). A non-acid condition for cyanations is desirable with regard to safety aspects.

Next, we extended the scope of substrates under the optimized conditions: $FeCl_2$ (10 mol %) as catalyst, Me_3SiCN (2 equiv.) as cyanating reagent, 1 atm O_2 as oxidant, and MeOH as solvent. The results are summarized in Table 5. A variety of tertiary amines bearing either electron-donating or electron-withdrawing substituents were efficiently cyanated. Furthermore, the substrates with steric hindrance like 2-methyl-, 2,4,6-trimethyl-, and 2-bromo-substituted *N,N*-dimethylanilines were functionalized to the corresponding products in 63 %, 72 % and 45 % yields with high selectivity, respectively (Table 5, entries 4, 5 and 8). Notably, high selectivities for double and triple cyanations were achieved (Table 5, entries 13

Table 5 O_2 as oxidant for $FeCl_2$-catalyzed oxidative cyanation of tertiary amines with Me_3SiCN[a]

Entry	substrate	Time (h)	Product	Yield[b] (%)
1		60		72
2		24		77
3		60		75
4[c]		60		63
5[e]		72		72
6		72		62
7[c]		60		70
8[c,d]		72		45
9[c]		48		trace
10[d,f]		72		53
11[d,f]		72		61

12[d,f]		72		56
13		72 (3 equiv. Me_3SiCN)		48
14[e]		72 (3 equiv. Me_3SiCN)		41
15		72		52
16[c]		48		13
17		72		10

[a] Conditions: tertiary amine (1.0 mmol), $FeCl_2$ (0.1 mmol), and Me_3SiCN (2.0 mmol) in methanol (2.0ml) was stirred at room temperature for the indicated time under O_2 (1 atm), unless otherwise noted. In some cases, the low yields was attributed to the corresponding low conversions. [b] Yield of isolated product. [c] Reflux. [d] $FeCl_2$ (20 mol %). [e] $FeCl_2$ (15 mol %) and reflux. [f] O_2 (1 atm), *t*BuOOH (0.5 equiv.), reflux.

and 14). Unfortunately, *N,N*-dimethyl-3-nitroaniline, cyclic amines, and benzyl amine were not good substrates in the catalytic system with O_2 as oxidant (Table 5, entries 9, 16 and 17).

2.3 Conclusion

In summary, we have demonstrated that under oxidative conditions, environmentally benign iron salts activate C(sp^3)–H bonds adjacent to nitrogen in tertiary amines selectively to allow for efficient cross coupling reactions with cyanide at room temperature. Additionally, molecular oxygen can be used as oxidant to give α-aminonitriles in moderate to good yields with high selectivity. Compared to molecular oxygen as the oxidant, *tert*-butylhydroperoxide shows wider scope of substrates and higher efficiency but lower safety. Future studies will further explore the substrate scope, non-toxic cyanide sources, and selectivities of iron catalyzed C(sp^3)-H bond functionalizations.

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2.5 Experimental Section

2.5.1 General

All reactions were carried out under an atmosphere of dry nitrogen. ^{1}H and ^{13}C NMR spectra of solutions in $CDCl_3$ were recorded on 200, 300 or 400 MHz NMR spectrometers. Chemical shifts were expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals (δ_H 7.24 and δ_C 77.0 ppm). Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; m, multiplet. HRMS was performed on a Finnigan MAT 95Q mass spectrometer. Infrared spectra of neat substances were recorded on a Perkin-Elmer Spectrum BX II FT-IR spectrometer equipped with an ATR probe (diamond).

2.5.2 Materials

Commercially available tertiary amines were used as received. *N*,*N*-Dimethyl-*p*-anisidine,[S1] 1-phenylpiperidine,[S 2] 2-phenyl-1,2,3,4-tetrahydroisoquinoline[S2] and 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline[S2] were prepared according to literature procedures.

The following iron and copper salts were used: Iron(II) acetate (anhydrous, 97 %, Strem), iron(III) acetylacetonate (99.9 %, Aldrich), iron(III) bromide (99 %, ABCR), iron(II) chloride (98 %, Aldrich), iron(III) chloride (anhydrous, 97 %, Grüssing), iron(III) chloride hexahydrate (99 %), iron(II) fluoride (anhydrous, 99 %, Strem), iron(II) gluconate hydrate (purum p.a., Fluka), iron(II) sulfate (99 %), copper(I) bromide (98 %, Acros), and copper(II) bromide (> 99%, Acros).

Trimethylsilyl cyanide (98 %, Acros) and *tert*-butyl hydroperoxide (5.5 M solution in decane, purum, Aldrich) were purchased.

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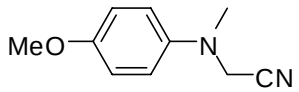
2.5.3 Iron-Catalyzed Cyanation of Tertiary Amines with *tert*-Butyl hydroperoxide as Oxidant

General Procedure A: Under an atmosphere of dry N_2, a 25 mL Schlenk flask was charged with iron(II) chloride (10 mol %, 13 mg). The tertiary amine (1.0 mmol), trimethylsilyl cyanide (2.0 mmol, 0.27 mL), and MeOH (2.0 mL) were added successively by syringe. To the mixture was added dropwise *tert*-butyl hydroperoxide (2.5 mmol, 0.47 mL, 5.5 M solution in decane) over a period of 5 min. The mixture was stirred at room temperature for the indicated time. At the end of the reaction, the reaction mixture was poured into a saturated aqueous NaCl solution (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (*n*-pentane/diethyl ether = 15:2, v/v).

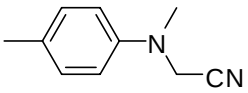
[(4-Methoxyphenyl)-methyl-amino]acetonitrile



Following *General Procedure* ***A***, 4-methoxy-*N,N*-dimethylaniline (153 mg, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 14 h to furnish the desired product (153 mg, 87 %).

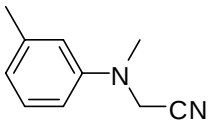
Known compound; the NMR spectroscopic data agree with those given in lit.[S3] δ_H ($CDCl_3$, 400 MHz) 2.90 (s, 3 H), 3.76 (s, 3 H), 4.06 (s, 2 H), 6.86 ppm (s, 4 H); δ_C ($CDCl_3$, 100 MHz) 39.9, 43.9, 55.5, 114.7, 115.4, 117.8, 142.1, 154.3 ppm; HRMS *m/z* (EI) 176.0944, $C_{10}H_{12}N_2O$ requires 176.0950.

(Methyl-*p*-tolyl-amino)acetonitrile



Following *General Procedure* ***A***, *N,N*-dimethyl-*p*-toluidine (147 μL, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 10 h to furnish the desired product (147 mg, 92 %).
Known compound; the NMR spectroscopic data agree with those given in lit.[S3] δ_H ($CDCl_3$, 300 MHz) 2.29 (s, 3 H), 2.96 (s, 3 H), 4.12 (s, 2 H), 6.80 (d, J = 8.5 Hz, 2 H), 7.12 ppm (d, J = 8.5 Hz, 2 H); δ_C ($CDCl_3$, 100 MHz) 20.3, 39.4, 42.7, 115.3, 115.4, 129.8, 129.9, 145.6 ppm; HRMS *m/z* (EI) 160.0990, $C_{10}H_{12}N_2$ requires 160.1001.

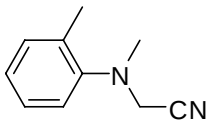
(Methyl-*m*-tolyl-amino)acetonitrile



Following *General Procedure* ***A***, *N,N*-dimethyl-*m*-toluidine (147 μL, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 10 h to furnish the desired product (142 mg, 89 %).
Known compound; the NMR spectroscopic data agree with those given in lit.[S3] δ_H ($CDCl_3$, 300 MHz) 2.31 (s, 3 H), 2.98 (s, 3 H), 4.25 (s, 2 H), 6.66-6.68 (m, 2 H), 6.74 (d, J = 6.0 Hz, 1 H), 7.16-7.22 ppm (m, 1 H); δ_C ($CDCl_3$, 100 MHz) 21.8, 39.2, 42.3, 112.0, 115.5, 115.6, 121.1, 129.2, 139.2,147.8 ppm; HRMS *m/z* (EI) 160.0990, $C_{10}H_{12}N_2$ requires 160.1001.

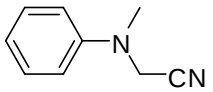
(S3) S. I. Murahashi, T. Nakae, H. Terai, N. Komiya, *J. Am. Chem. Soc*. **2008**, *130*, 11005–11012.

(Methyl-*o*-tolyl-amino)acetonitrile



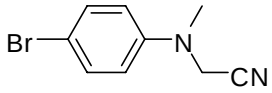
Following *General procedure* ***A***, *N,N*-dimethyl-*o*-toluidine (147 μL, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 24 h to furnish the desired product (121 mg, 76 %).
Known compound; the NMR spectroscopic data agree with those given in lit.[S3] δ_H ($CDCl_3$, 300 MHz) 2.29 (s, 3 H), 2.85 (s, 3 H), 3.84 (s, 2 H), 7.03-7.09 (m, 1 H), 7.17-7.22 ppm (m, 3 H); δ_C ($CDCl_3$, 100 MHz) 17.7, 41.0, 45.0, 115.6, 120.6, 124.9, 126.8, 131.3, 132.8, 148.4 ppm; HRMS *m/z* (EI) 160.0995, $C_{10}H_{12}N_2$ requires 160.1001.

(Methyl-phenyl-amino)acetonitrile



Following *General Procedure* ***A***, *N,N*-dimethylaniline (128 μL, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 13 h to furnish the desired product (131 mg, 90 %).
Known compound; the NMR spectroscopic data agree with those given in lit.[S3] δ_H ($CDCl_3$, 300 MHz) 3.00 (s, 3 H), 4.16 (s, 2 H), 6.85-6.94 (m, 3 H), 7.28-7.33 ppm (m, 2 H); δ_C ($CDCl_3$, 100 MHz) 39.3, 42.3, 114.9, 115.4, 120.2, 129.4, 147.7 ppm; HRMS *m/z* (EI) 146.0841, $C_9H_{10}N_2$ requires 146.0844.

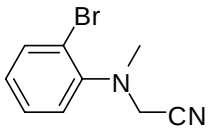
[(4-Bromophenyl)-methyl-amino]acetonitrile.



Following *General Procedure* ***A***, 4-bromo-*N,N*-dimethylaniline (202 mg, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 10 h to furnish the desired product (175 mg, 78 %).
Known compound; the NMR spectroscopic data agree with those given in lit.[S3] δ_H ($CDCl_3$, 300 MHz) 2.98 (s, 3 H), 4.13 (s, 2 H), 6.72 (d, J = 9.0 Hz, 2 H), 7.37-7.40 ppm (m, 2 H); δ_C

($CDCl_3$, 100 MHz) 39.3, 42.2, 112.6, 115.1, 116.4, 132.2, 146.7 ppm; HRMS *m/z* (EI) 223.9943, $C_9H_9BrN_2$ requires 223.9949.

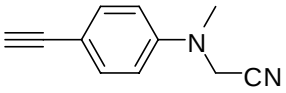
[(2-Bromophenyl)-methyl-amino]acetonitrile



Following *General Procedure* ***A***, 2-bromo-*N,N*-dimethylaniline (147 µL, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) for 24 h under reflux to furnish the desired product (190 mg, 85 %).

Viscous oil; δ_H ($CDCl_3$, 300 MHz) 2.92 (s, 3 H), 4.07 (s, 2 H), 6.98-7.04 (m, 1 H), 7.25-7.35 (m, 2 H), 7.55-7.58 ppm (m, 1 H); δ_C ($CDCl_3$, 100 MHz) 40.6, 44.8, 115.1, 119.7, 122.8, 126.3, 128.5, 133.9, 147.3 ppm; HRMS *m/z* (EI) 223.9942, $C_9H_9BrN_2$ requires 223.9949; Anal. Calcd for $C_9H_9BrN_2$: C, 48.03; H, 4.03; N, 12.45. Found: C, 48.10; H, 3.70; N, 12.41; *v* (neat/ATR probe) 2956, 2887, 2802, 2232 (C≡N), 1586, 1473, 1439, 1415, 1337, 1325, 1222, 1177, 1111, 1023, 987, 919, 871, 766, 752, 272, 722, 653 cm^{-1};

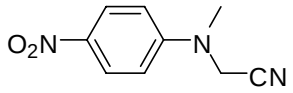
[(4-Ethynylphenyl)-methyl-amino]acetonitrile.



Following *General Procedure* ***A***, 4-ethynyl-*N,N*-dimethylaniline (150 mg, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) for 5 h under reflux to furnish the desired product (141 mg, 83 %).

Viscous oil; δ_H ($CDCl_3$, 200 MHz) 2.99 (s, 1 H), 3.03 (s, 3 H), 4.18 (s, 2 H), 6.75 (d, J = 9.0 Hz, 2 H), 7.42 ppm (d, J = 9.0 Hz, 2 H); δ_C ($CDCl_3$, 100 MHz) 37.7, 40.5, 76.0, 84.7, 113.5, 113.9, 115.1, 133.5, 148.5 ppm; HRMS *m/z* (EI) 170.0839, $C_{11}H_{10}N_2$ requires 170.0844; *v* (neat/ATR probe) 3279 (≡C-H), 3042, 2916, 2823, 2240 (C≡N), 2101 (C≡C), 1671, 1605, 1512, 1360, 1332, 1246, 1181, 1113, 997, 924, 819 cm^{-1}.

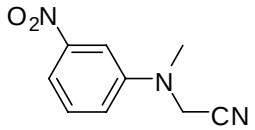
[Methyl-(4-nitrophenyl)-amino]acetonitrile.



Following *General Procedure* ***A***, *N,N*-dimethyl-4-nitroaniline (170 mg, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 24 h under reflux to furnish the desired product (86 mg, 45 %).

Known compound; the NMR spectroscopic data agree with those given in lit.[S4] δ_H ($CDCl_3$, 400 MHz) 3.17 (s, 3 H), 4.26 (s, 2 H), 6.79 (d, J = 8.0 Hz, 2 H), 8.19 ppm (d, J = 8.0 Hz, 2 H); δ_C ($CDCl_3$, 100 MHz) 39.3, 41.1, 112.3, 114.5, 126.0, 139.9, 152.0 ppm; HRMS *m/z* (EI) 191.0691, $C_9H_9N_3O_2$ requires 191.0695; mp 112.5-113.4 °C (lit.,[S4] 114 °C).

[Methyl-(3-nitrophenyl)-amino]acetonitrile

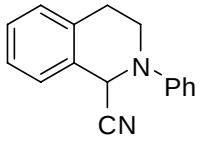


Following *General Procedure* ***A***, *N,N*-dimethyl-3-nitroaniline (170 mg, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 15 h under reflux to furnish the desired product (153 mg, 80 %).

δ_H ($CDCl_3$, 300 MHz) 3.11 (s, 3 H), 4.25 (s, 2 H), 7.09-7.13 (m, 1 H), 7.45 (t, J = 8.3 Hz, 1 H), 7.65-7.76 ppm (m, 2 H); δ_C ($CDCl_3$, 100 MHz) 39.3, 41.7, 108.7, 114.4, 114.7, 119.6, 130.3, 148.3, 149.3 ppm; HRMS *m/z* (EI) 191.0689, $C_9H_9N_3O_2$ requires 191.0695; Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.40; H, 4.73; N, 21.45; ν (neat/ATR probe) 3099, 3042, 2920, 2240 (C≡N), 1617, 1520, 1337, 1259, 1221, 1132, 1015, 881, 860, 789, 782, 737, 667 cm^{-1}; mp 99.3-99.5 °C (from Et_2O/pentane).

(S4) M. Barzoukas, D. Josse, P. Fremaux, J. Zyss, J. F. Nicoud and J. O. Morley, *J. Opt. Soc. Am. B* **1987**, *4*, 977–986.

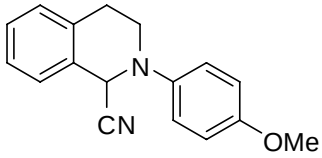
2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile



Following *General Procedure* ***A***, 2-phenyl-1,2,3,4-tetrahydroisoquinoline (210 mg, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 13 h to furnish the desired product (199 mg, 85 %).

Known compound; the NMR spectroscopic data agree with those given in lit.[S3] δ_H ($CDCl_3$, 200 MHz) 2.91-3.24 (m, 2 H), 3.41-3.55 (m, 1 H), 3.71-3.82 (m, 1 H), 5.50 (s, 1 H), 6.97-7.10 (m, 3 H), 7.24-7.39 ppm (m, 6 H); δ_C ($CDCl_3$, 100 MHz) 28.1, 44.1, 53.4, 117.6, 117.7, 121.9, 126.8, 127.1, 128.8, 129.3, 129.5, 129.6, 134.1, 148.1 ppm; HRMS *m/z* (EI) 234.1146, $C_{16}H_{14}N_2$ requires 234.1157.

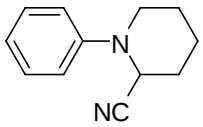
2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile



Following *General Procedure* ***A***, 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (239 mg, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 12 h to furnish the desired product (219 mg, 83 %).

Solid; δ_H ($CDCl_3$, 400 MHz) 2.91-2.96 (m, 1 H), 3.12-3.21 (m, 1 H), 3.40-3.47 (m, 1 H), 3.55-3.59 (m, 1 H), 3.80 (s, 3 H), 5.36 (s, 1 H), 6.90-6.94 (m, 2 H), 7.07-7.11 (m, 2 H), 7.22-7.33 ppm (m, 4 H); δ_C ($CDCl_3$, 100 MHz) 28.7, 44.9, 55.5, 55.6, 114.8, 117.6, 121.0, 126.7, 127.1, 128.6, 129.4, 129.6, 134.3, 142.6, 155.7 ppm; HRMS *m/z* (EI) 264.1250, $C_{17}H_{16}N_2O$ requires 264.1263; Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 76.88; H, 6.51; N, 10.43; ν (neat/ATR probe) 2996, 2933, 2837, 2221 (C≡N), 1647, 1510, 1465, 1454, 1259, 1245, 1206, 1179, 1030, 829, 733 cm^{-1}.

1-Phenylpiperidine-2-carbonitrile



Analogous to *General Procedure* ***A***, 1-phenylpiperidine (163 mg, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) without added solvent for 24 h to furnish the desired product (132 mg, 71 %).

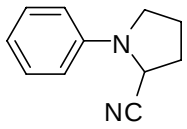
Known compound; the NMR spectroscopic data agree with those given in lit.[S3,S5] δ_H ($CDCl_3$, 400 MHz) 1.66-1.73 (m, 2 H), 1.84-1.87 (m, 2 H), 1.99-2.03 (m, 2 H), 3.00-3.06 (m, 1 H), 3.46 (d, J = 12 Hz, 1 H), 4.63 (s, 1 H), 6.98-7.02 (m, 3 H), 7.25-7.34 ppm (m, 2 H); δ_C ($CDCl_3$, 100 MHz) 20.1, 25.0, 29.1, 46.4, 51.9, 117.1, 118.1, 122.0, 129.2, 149.6 ppm; HRMS *m/z* (EI) 186.1153, $C_{12}H_{14}N_2$ requires 186.1157.

Additional NMR signals of unidentified byproducts: δ_H ($CDCl_3$, 400 MHz) 1.3-1.5 (m), 5.93 (s), 6.80-6.82 (m); δ_C ($CDCl_3$, 100 MHz) 16.0, 21.6, 22.3, 69.4, 86.9, 113.1, 117.4, 121.9, 129.4, 146.5, 150.6 ppm. One of the byproducts is tentatively assigned to the dicyanation product 1-phenylpiperidine-2,6-dicarbonitrile[S 6] based on HRMS [*m/z* (EI) 211.1106, $C_{13}H_{13}N_3$ requires 211.1109]. Because of superimposition of resonances, however, an unambiguous assignment of the signals in the NMR spectra was not possible.

(S5) E. Le Gall, J.-P. Hurvois, T. Renaud, C. Moinet, A. Tallec, P. Uriac, S. Sinbandhit and L. Toupet, *Liebigs Ann./Recueil* **1997**, 2089–2101.

(S6) K. Takahashi, T. Mikajiri, H. Kurita, K. Ogura, H. Iida, *J. Org. Chem.* **1985**, *50*, 4372–4375.

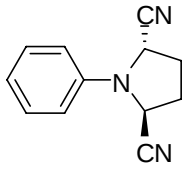
1-Phenylpyrrolidine-2-carbonitrile



Analogous to *General Procedure* ***A***, 1-phenylpyrrolidine (150 mg, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) without added solvent for 24 h to furnish the desired product (141 mg, 82 %).

Known compound; the NMR spectroscopic data agree with those given in lit.[S7] δ_H ($CDCl_3$, 200 MHz) 2.07-2.34 (m, 4 H), 3.26-3.38 (m, 2 H), 4.33-4.37 (m, 1 H), 6.58-6.63 (m, 2 H), 6.74 (t, J = 7.4 Hz, 1 H), 7.16-7.25 ppm (m, 2 H); δ_C ($CDCl_3$, 100 MHz) 23.9, 31.5, 47.4, 49.0, 112.6, 118.1, 119.2, 129.4, 145.1 ppm; HRMS *m/z* (EI) 172.0991, $C_{11}H_{12}N_2$ requires 172.1000.

1-Phenylpyrrolidine-2,5-dicarbonitrile



Under an atmosphere of dry nitrogen, a 25 ml Schlenk flask was charged with $FeCl_2$ (13 mg, 10 mol %). Then 1-phenylpyrrolidine (150 mg, 1.00 mmol), Me_3SiCN (0.54 ml, 4.0 mmol), and MeOH (2.0 ml) were added successively by syringe. To the mixture was added dropwise *t*BuOOH (2.5 mmol, 0.47 ml, 5.5 *M* solution in decane) over a period of 5 minutes. The mixture was stirred at room temperature for 24 h. Subsequently, the reaction mixture was poured into a saturated aqueous NaCl solution (20 ml) and extracted with dichloromethane (3 × 20 ml). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. After column chromatography on silica gel (*n*-pentane/diethyl ether = 3:1, v/v), 1-phenylpyrrolidine-2,5-dicarbonitrile was isolated as a colorless solid (106 mg, 54 %).

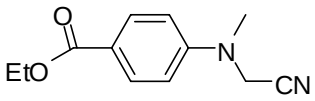
(S7) W. Liu, Y. Ma, Y. W. Yin, Y. F. Zhao, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 577–579.

The title compound (50 mg) was dissolved in 2 ml of a mixture of dichloromethane/*n*-pentane/ethyl ether mixture (2/1/1, v/v/v). The solvent was allowed to evaporate slowly at room temperature. The thus formed crystals were suitable for X-ray analysis.

Known compound (lit.[S8]); δ_H ($CDCl_3$, 400 MHz) 2.56-2.63 (m, 4 H), 4.57 (t, *J* 2.8 Hz, 2 H), 6.78-6.81 (m, 2 H), 6.96-6.99 (m, 1 H), 7.35-7.39 ppm (m, 2 H); δ_C ($CDCl_3$, 100 MHz) 30.4, 48.9, 113.4, 117.9, 120.5, 129.9, 141.8 ppm; *v* (neat/ATR probe) 3075, 3050, 3003, 2930, 2233, 1597, 1504, 1347, 1338, 1323, 1269, 1251, 1180, 1160, 966, 818, 745, 693 cm^{-1}; mp 149–151 ^oC.

Details of the crystal structure determination of *N*-phenylpyrrolidine-2,5-dicarbonitrile are reported in Chapter 2.5.5.

Ethyl 4-((cyanomethyl)(methyl)amino)benzoate

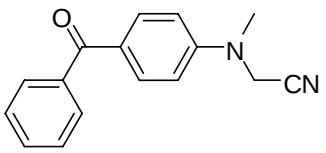


Following *General Procedure* ***A***, ethyl 4-(dimethylamino)benzoate (195 mg, 1.00 mmol,) reacted Me_3SiCN (270 µL, 2.00 mmol) for 24 h under reflux with $FeCl_2$ (20 mol %) to furnish the desired product (161 mg, 74 %).

δ_H ($CDCl_3$, 400 MHz) 1.35 (t, *J* = 7.2 Hz, 3 H), 3.07 (s, 3 H), 4.22 (s, 2 H), 4.32 (q, *J* = 7.2 Hz, 2 H), 6.78 (d, *J* = 9.2 Hz, 2 H), 7.96 ppm (d, *J* = 8.4 Hz, 2 H)); δ_C ($CDCl_3$, 100 MHz) 14.3, 39.0, 41.2, 60.5, 112.7, 115.1, 121.2, 131.3, 150.8, 166.3 ppm; HRMS (EI) calcd for $C_{12}H_{14}O_2N_2$ *m/z* 218.1055, found *m/z* 218.1048; *v* (neat/ATR probe) 2980, 2923, 2241, 1692, 1602, 1523, 1480, 1380, 1366, 1282, 1259, 1187, 1107, 1026, 931, 879, 834, 769, 698 cm^{-1}; mp 63.5-64.6 °C

(S8) K. Takahashi, H. Saitoh, K. Ogura, H. Iida, *Heterocycles*, **1986**, *24*, 2905–2910.

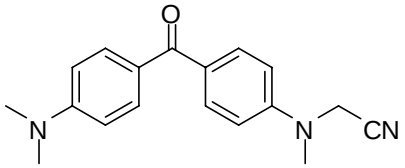
2-((4-Benzoylphenyl)(methyl)amino)acetonitrile



Following *General Procedure* ***A***, (4-(dimethylamino)phenyl)(phenyl)methanone (230 mg, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 24 h under reflux with $FeCl_2$ (20 mol %) to furnish the desired product (212 mg, 85 %).

δ_H ($CDCl_3$, 400 MHz) 3.12 (s, 3 H), 4.26 (s, 2 H), 6.83 (d, J = 9.2 Hz, 2 H), 7.43-7.47 (m, 2 H), 7.52-7.56 (t, J = 7.4 Hz, 1 H), 7.72-7.74 (m, 2 H), 7.83 ppm (d, J = 9.2 Hz, 2 H); δ_C ($CDCl_3$, 100 MHz) 39.1, 41.2, 112.6, 115.0, 128.1, 128.3, 129.6, 131.7, 132.5, 138.4, 150.7, 195.2 ppm; HRMS (EI) calcd for $C_{16}H_{14}ON_2$ *m/z* 250.1106, found *m/z* 250.1100; *v* (neat/ATR probe) 3064, 2979, 2238, 1642, 1599, 1518, 1480, 1365, 1324, 1287, 1200, 1114, 1000, 923, 835, 796, 770, 742, 702, 681 cm^{-1}; mp 109-110 °C.

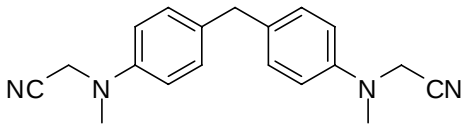
2-((4-(4-(Dimethylamino)benzoyl)phenyl)(methyl)amino)acetonitrile



Following *General Procedure* ***A***, bis(4-(dimethylamino)phenyl)methanone (271 mg, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 24 h under reflux with $FeCl_2$ (20 mol %) to furnish the desired product (208 mg, 71 %).

δ_H ($CDCl_3$, 400 MHz) 3.05 (s, 6 H), 3.10 (s, 3 H), 4.24 (s, 2 H), 6.67 (d, J = 8.8 Hz, 2 H), 6.83 (d, J = 8.4 Hz, 2 H), 7.74-7.77 ppm (m, 4 H); δ_C ($CDCl_3$, 100 MHz) 39.1, 40.0, 41.4, 110.5, 112.7, 115.2, 125.4, 130.1, 131.9, 132.4, 149.9, 153.0, 193.8 ppm; HRMS (EI) calcd for $C_{18}H_{19}ON_3$ *m/z* 293.1528, found *m/z* 293.1519; *v* (neat/ATR probe) 2906, 2819, 2231, 1587, 1527, 1479, 1428, 1369, 1321, 1285, 1177, 1150, 1065, 995, 921, 829, 819, 766, 747, 683 cm^{-1}; mp 133.1-134.5 °C.

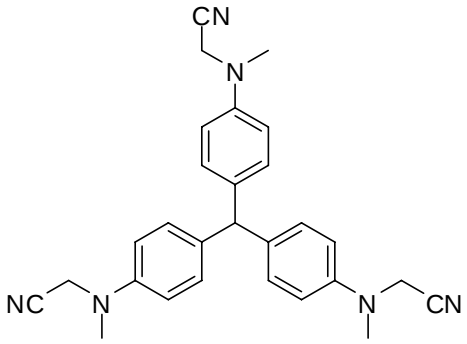
2,2'-(4,4'-Methylenebis(4,1-phenylene)bis(methylazanediyl))diacetonitrile



Analogous to *General Procedure* ***A***, bis(4-(dimethyl(amino)phenyl))methane (260 mg, 1.00 mmol,) reacted with Me_3SiCN (405 µL, 3.00 mmol) for 15 h with $FeCl_2$ (15 mol %) and *t*BuOOH (565 µL, 3.00 mmol) to furnish the desired product (206 mg, 68 %).

δ_H ($CDCl_3$, 400 MHz) 2.96 (s, 6 H), 3.84 (s, 2 H), 4.12 (s, 4 H), 6.79 (d, J = 8.6 Hz, 4 H), 7.10 ppm (d, J = 8.6 Hz, 4 H); δ_C ($CDCl_3$, 100 MHz) 39.4, 40.0, 42.6, 115.3, 115.4, 129.8, 133.4, 146.1 ppm; HRMS (EI) calcd for $C_{19}H_{20}N_4$ *m/z* 304.1688, found *m/z* 304.1687; *v* (neat/ATR probe) 3029, 2900, 2820, 2235, 1610, 1515, 1474, 1348, 1328, 1242, 1192, 1113, 997, 923, 793, 749, 689 cm^{-1}; mp 89.6-92.8 °C.

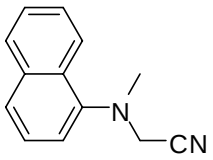
2,2',2''-(4,4',4''-Methanetriyltris(benzene-4,1-diyl)tris(methylazanediyl))triacetonitrile



Analogous to *General Procedure* ***A***, tris(4-(dimethyl(amino)phenyl))methane (378 mg, 1.00 mmol) reacted with Me_3SiCN (405 µL, 3.00 mmol) for 24 h with $FeCl_2$ (15 mol %) and *t*BuOOH (565 µL, 3.00 mmol) to furnish the desired product (273 mg, 61%).

δ_H ($CDCl_3$, 400 MHz) 2.97 (s, 9 H), 4.13 (s, 6 H), 5.35 (s, 1 H), 6.77 (d, J = 9.0 Hz, 6 H), 7.02 ppm (d, J = 9.0 Hz, 6 H); δ_C ($CDCl_3$, 100 MHz) 39.3, 42.4, 54.1, 114.9, 115.5, 130.2, 136.2, 146.1 ppm; HRMS (EI) calcd for $C_{28}H_{28}N_6$ *m/z* 448.2375, found *m/z* 448.2378; *v* (neat/ATR probe) 3034, 2887, 2814, 2237, 1608, 1514, 1474, 1429, 1356, 1320, 1183, 1110, 996, 926, 873, 845, 816, 796, 744 cm^{-1}; mp 159.5-160.7 °C.

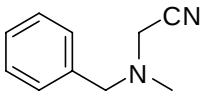
2-(Methyl(naphth-1-yl)amino)acetonitrile



Following *General Procedure* ***A***, *N,N*-dimethylnaphthalen-1-amine (173 mg, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 24 h to furnish the desired product (141 mg, 72 %).

δ_H ($CDCl_3$, 400 MHz) 3.04 (s, 3 H), 4.08 (s, 2 H), 7.32-7.34 (m, 1 H), 7.44 (t, J = 7.8 Hz, 1 H), 7.48-7.51 (m, 2 H), 7.65 (d, J = 8.4 Hz, 1 H), 7.85-7.87 (m, 1 H), 8.09-8.12 ppm (m, 1 H); δ_C ($CDCl_3$, 100 MHz) 41.3, 46.0, 115.3, 117.1, 122.6, 125.3, 125.6, 126.12, 126.13, 128.5, 128.6, 134.7, 146.2 ppm; HRMS (EI) calcd for $C_{13}H_{12}N_2$ *m/z* 196.1000, found *m/z* 196.0988; *v* (neat/ATR probe) 3051, 2989, 2948, 2880, 2235, 1594, 1576, 1508, 1462, 1448, 1396, 1260, 1128, 1073, 1040, 919, 875, 802, 772 cm^{-1}.

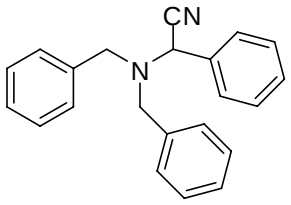
2-(Benzyl(methyl)amino)acetonitrile



Following *General Procedure* ***A***, benzyl-dimethylamine (152 μL, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 24 h at 0 ^oC to furnish the desired product (129 mg, 81 %).

δ_H ($CDCl_3$, 400 MHz) 2.42 (s, 3 H), 3.43 (s, 2 H), 3.59 (s, 2 H), 7.24-7.35 ppm (m, 5 H); δ_C ($CDCl_3$, 100 MHz) 42.3, 44.1, 60.1, 114.5, 127.8, 128.6, 129.0, 136.9 ppm; HRMS (EI) calcd for $C_{10}H_{12}N_2$ *m/z* 160.1000, found *m/z* 160.0996; *v* (neat/ATR probe) 3064, 3031, 2983, 2949, 2842, 2231, 1496, 1454, 1416, 1371, 1327, 1125, 1037, 1027, 983, 840, 740, 698 cm^{-1}.

2-(Dibenzylamino)-2-phenylacetonitrile



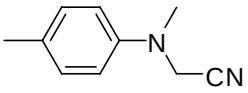
Analogous to *General Procedure* ***A***, tribenzylamine (290 mg, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) for 24 h with $FeCl_2$ (15 mol %) to furnish the desired product (128 mg, 41 %).

δ_H ($CDCl_3$, 400 MHz) 3.42 (d, ^2J = 13.6 Hz, 2 H), 3.89 (d, ^2J = 13.6 Hz, 2 H), 4.92 (s, 1 H), 7.27 (t, J = 6.8 Hz, 2 H), 7.33-7.43 (m, 11 H), 7.59 ppm (d, J = 8.8 Hz, 2 H); δ_C ($CDCl_3$, 100 MHz) 54.9, 57.3, 115.4, 127.6, 127.63, 128.6, 128.7, 128.8, 133.9, 137.7 ppm; HRMS (EI) calcd for $C_{22}H_{20}N_2$ *m/z* 312.1626, found *m/z* 312.1606; *v* (neat/ATR probe) 3061, 3033, 2925, 2803, 2235, 1493, 1452, 1372, 1113, 1076, 1027, 966, 924, 744, 694 cm^{-1}.

2.5.4 Iron-Catalyzed Cyanation of Tertiary Amines with Oxygen as Oxidant

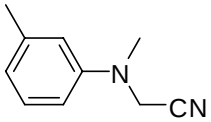
General Procedure B: $FeCl_2$ (10 mol %, 13 mg) was put into a 25 mL side-armed round-bottom flask with a magnetic stir bar. After the flask was evacuated and back filled with oxygen (1 atm) with a balloon, the tertiary amine (1.00 mmol), Me_3SiCN (270 μL, 2.00 mmol), and MeOH (2.0 mL) were added successively by syringe. The mixture was stirred at room temperature (or reflux) for the indicated time. At the end of the reaction, the mixture was poured into brine (20 ml) and extracted with CH_2Cl_2 (3 × 20 mL). The organic solvent was removed by rotary evaporation, and the crude product was purified by column chromatography on silica gel *n*-pentane/diethyl ether = 15:2, v/v).

(Methyl-*p*-tolyl-amino)acetonitrile



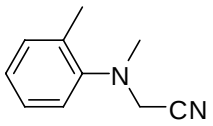
Following *General Procedure* ***B***, *N,N*-dimethyl-*p*-toluidine (147 μL, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 24 h to furnish the desired product (123 mg, 77 %).

(Methyl-*m*-tolyl-amino)acetonitrile



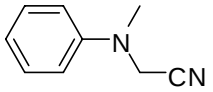
Following *General Procedure* ***B***, *N,N*-dimethyl-*m*-toluidine (147 μL, 1.00 mmol) reacted with Me_3SiCN (270 μL, 2.00 mmol) for 60 h to furnish the desired product (119 mg, 75 %).

(Methyl-*o*-tolyl-amino)acetonitrile



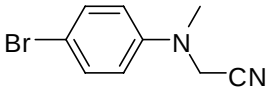
Following *General Procedure* ***B***, *N,N*-dimethyl-*o*-toluidine (147 µL, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) under reflux for 60 h to furnish the desired product (100 mg, 63 %).

(Methyl-phenyl-amino)acetonitrile



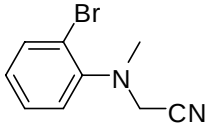
Following *General Procedure* ***B***, *N,N*-dimethylaniline (128 µL, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) for 72 h to furnish the desired product (90 mg, 62 %).

[(4-Bromophenyl)-methyl-amino]acetonitrile



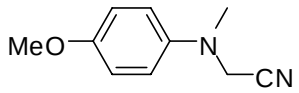
Following *General Procedure* ***B***, 4-bromo-*N,N*-dimethylaniline (202 mg, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) under reflux for 60 h to furnish the desired product (156 mg, 70 %).

[(2-Bromophenyl)-methyl-amino]acetonitrile



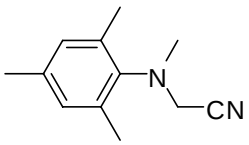
Following *General Procedure* ***B***, 2-bromo-*N,N*-dimethylaniline (147 µL, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) under reflux in the presence of $FeCl_2$ (20 mol %) for 72 h to furnish the desired product (100 mg, 45 %).

[(4-Methoxyphenyl)-methyl-amino]acetonitrile



Following *General Procedure* ***B***, 4-methoxy-*N,N*-dimethylaniline (153 mg, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) for 60 h to furnish the desired product (126 mg, 72 %).

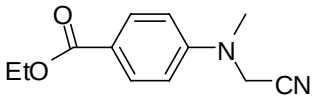
2-(Mesityl(methyl)amino)acetonitrile



Following *General Procedure* ***B***, *N,N*,2,4,6-pentamethylaniline (184 µL, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) for 72 h with $FeCl_2$ (15 mol %) under reflux to furnish the desired product (135 mg, 72 %).

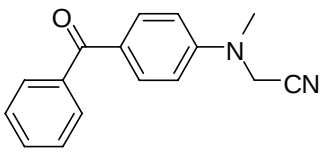
δ_H ($CDCl_3$, 400 MHz) 2.27 (s, 3 H), 2.30 (s, 6 H), 2.96 (s, 3 H), 3.93 (s, 2 H), 6.87 (s , 2 H); δ_C ($CDCl_3$, 100 MHz) 18.7, 20.6, 40.2, 43.8, 117.5, 129.6, 135.7, 136.7, 144.0 ppm; HRMS (EI) calcd for $C_{12}H_{16}N_2$ *m/z* 188.1313, found *m/z* 188.1307; ν(neat/ATR probe)/cm^{-1} 2919, 2860, 2802, 2237, 1486, 1451, 1376, 1201, 1106, 994, 928, 853, 732.

Ethyl 4-((cyanomethyl)(methyl)amino)benzoate



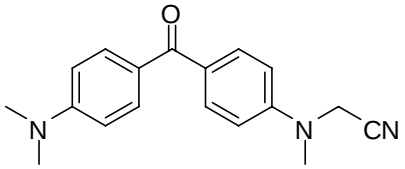
Following *General Procedure* ***B***, ethyl 4-(dimethylamino)benzoate (195 mg, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) under reflux for 72 h with $FeCl_2$ (20 mol %) and *t*BuOOH (94 µL, 0.50 mmol) to furnish the desired product (115 mg, 53 %).

2-((4-Benzoylphenyl)(methyl)amino)acetonitrile



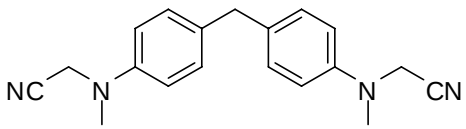
Following *General Procedure* ***B***, (4-(dimethylamino)phenyl)(phenyl)methanone (230 mg, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) under reflux for 72 h with $FeCl_2$ (20 mol %) and *t*BuOOH (94 µL, 0.50 mmol) to furnish the desired product (152 mg, 61 %).

2-((4-(4-(Dimethylamino)benzoyl)phenyl)(methyl)amino)acetonitrile



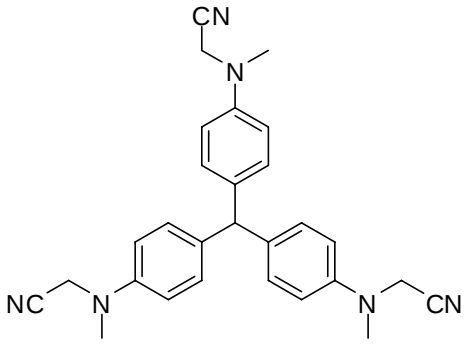
Following *General Procedure* ***B***, bis(4-(dimethylamino)phenyl)methanone (271 mg, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) under reflux for 72 h with $FeCl_2$ (20 mol %) and *t*BuOOH (94 µL, 0.50 mmol) to furnish the desired product (164 mg, 56 %).

2,2'-(4,4'-Methylenebis(4,1-phenylene)bis(methylazanediyl))diacetonitrile



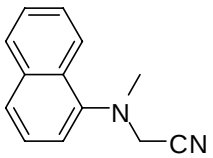
Following *General Procedure* ***B***, bis(4-(dimethylamino)phenyl)methane (260 mg, 1.00 mmol) reacted with Me_3SiCN (405 µL, 3.00 mmol) for 72 h to furnish the desired product (145 mg, 48 %).

2,2',2''-(4,4',4''-Methanetriyltris(benzene-4,1-diyl)tris(methylazanediyl))triacetonitrile



Following *General Procedure* ***B***, tris(4-(dimethylamino))phenyl)methane (378 mg, 1.00 mmol) reacted with Me_3SiCN (405 µL, 3.00 mmol) under reflux for 72 h with $FeCl_2$ (15 mol %) to furnish the desired product (183 mg, 41%).

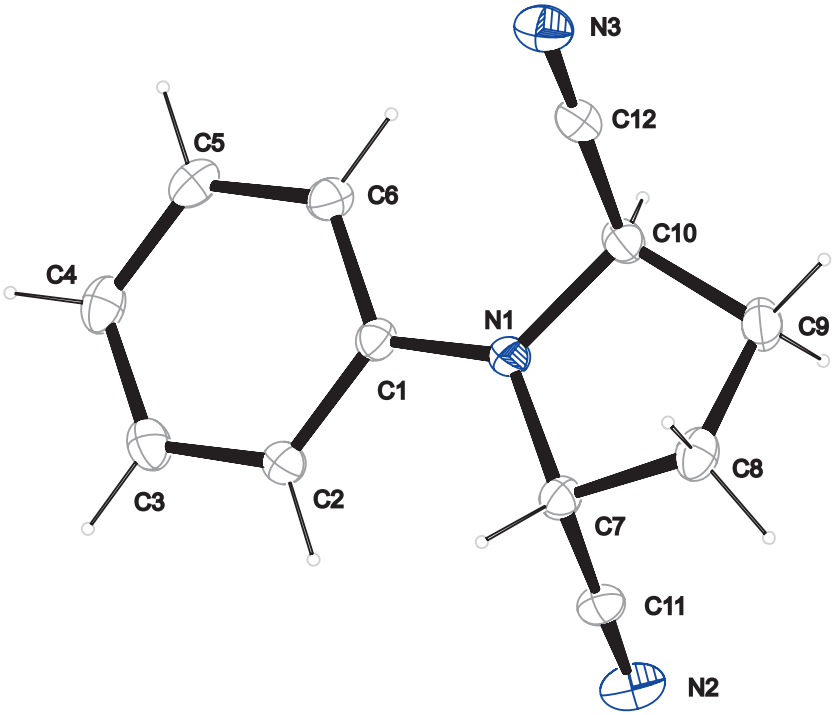
2-(Methyl(naphth-1-yl)amino)acetonitrile



Following *General Procedure* ***B***, *N,N*-dimethylnaphthalen-1-amine (173 mg, 1.00 mmol) reacted with Me_3SiCN (270 µL, 2.00 mmol) for 72 h to furnish the desired product (102 mg, 52 %).

2.5.5 X-Ray Crystal Structure Analysis of 1-Phenylpyrrolidine-2,5-dicarbonitrile

The data collection was performed on a Oxford Diffraction XCalibur diffractometer. The structure was solved by direct methods with SIR97[S9] and refined with SHELXL-97.[S10]



X-ray-sructure of 1-phenylpyrrolidine-2,5-dicarbonitrile

(S9) A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115–119.

(S10) G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112–122.

1-Phenylpyrrolidine-2,5-dicarbonitrile. Crystallographic data.

net formula	$C_{12}H_{11}N_3$
M_r/g mol^{-1}	197.236
crystal size/mm	0.33 × 0.18 × 0.15
T/K	200(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	orthorhombic
space group	*Pbca*
a/Å	9.18070(10)
b/Å	14.5693(2)
c/Å	15.7576(2)
α/°	90
β/°	90
γ/°	90
V/Å^3	2107.68(5)
Z	8
calc. density/g cm^{-3}	1.24316(3)
μ/mm^{-1}	0.077
absorption correction	none
refls. measured	16161
R_{int}	0.0223
mean σ(I)/I	0.0158
θ range	3.41–27.49
observed refls.	2109
x, y (weighting scheme)	0.0490, 0.5393
hydrogen refinement	constr
refls in refinement	2413
parameters	136
restraints	0
$R(F_{obs})$	0.0391
$R_w(F^2)$	0.1070
S	1.055
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.142
min electron density/e Å^{-3}	−0.181

Chapter 3

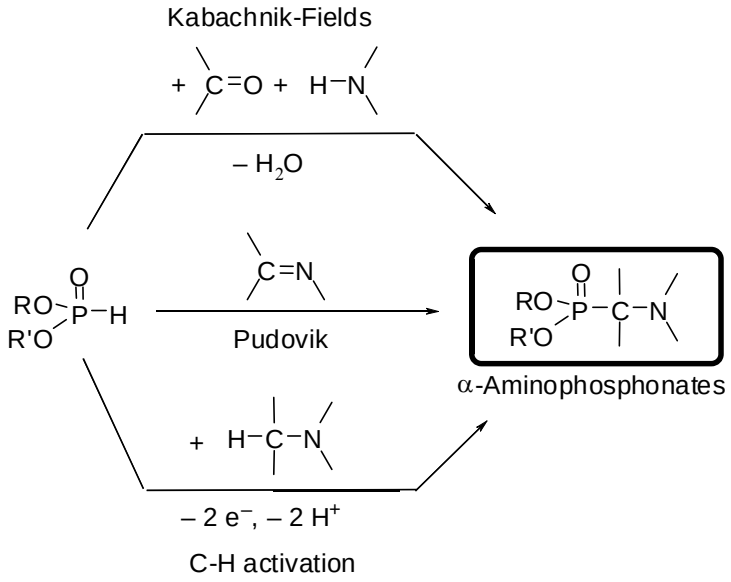
Iron-Catalyzed Dehydrogenative Phosphonation of *N,N*-Dialkylanilines

Wei Han, Armin R. Ofial, *Chem. Commun.* **2009**, 6023-6025;
Wei Han, Peter Mayer, Armin R. Ofial, *Adv. Synth. Catal.* **2010**, *352*, 1667-1676.

3.1 Introduction

α-Aminophosphonates and related α-aminophosphonic acids are structural analogues of α-amino acids.[1–3] They carry a tetrahedral phosphonic acid moiety that mimics the transition state of nucleophilic substitution reactions at the carboxyl group of natural amino acids,[4] which makes them efficient competitors for the active sites of enzymes and other cell receptors.[1,3] As a consequence, the chemical and, even more important, biological properties of aminophosphonates and related phosphonopeptides have been studied extensively.[1–4] Furthermore, α-aminophosphonates have found a multitude of applications in medicinal, agricultural, and industrial chemistry.[1–8]

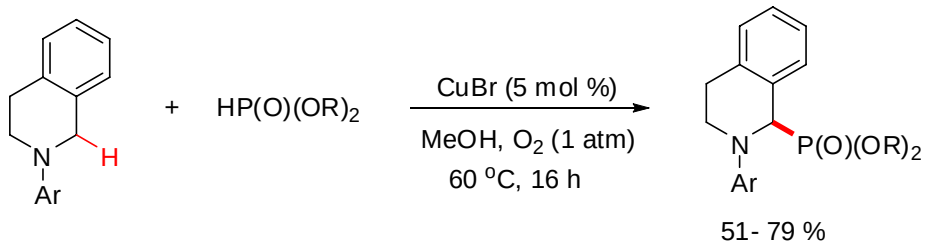
The standard procedures for the syntheses of α-aminophosphonates mainly rely on the Kabachnik–Fields reaction or the Pudovik reaction (Scheme 1).[1,2] The Kabachnik–Fields reaction is a three-component reaction of a dialkyl phosphonate, a carbonyl compound, and a primary or secondary amine.[9,10] Additions of phosphorus compounds with a labile H-P bond to unsaturated compounds are summarized as Pudovik reactions. Hence, the Pudovik reaction gives rise to the formation of α-aminophosphonates if an imine is employed as π-system.[11] Continuous efforts are being made to improve the synthesis of α-aminophosphonates[12] and recent advances of the Kabachnik–Fields and the Pudovik reactions comprise stereoselective[13] and catalytic enantioselective[14,15] syntheses as well as the use of microwave techniques.[16]



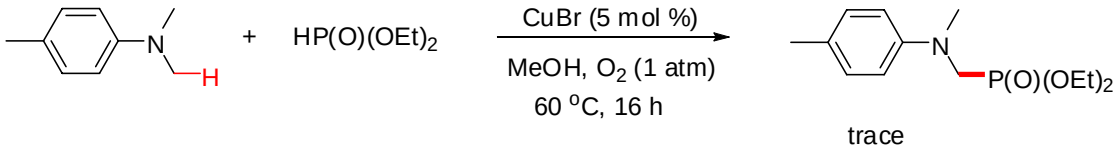
Scheme 1. Synthetic routes to α-aminophosphonates.

Selective activation of C(sp^3)-H bonds for subsequent cross-coupling reactions is an attractive concept that has strongly developed during the last decade because it removes the need for reactant prefunctionalization.[17] As it is known that metal catalysts, such as copper[18] or iron salts,[19–23] are capable of activating C(sp^3)-H bonds adjacent to nitrogen in tertiary amines under oxidative conditions, we were curious whether the formation of α-aminophosphonates from unfunctionalized tertiary amine precursors could be achieved by a metal-catalyzed cross-coupling (Scheme 1, lower path).

During the course of our studies, Baslé and Li reported a novel cross-dehydrogenative coupling (CDC),[18] in which a CuBr-catalyzed phosphonation of the benzylic position in N-aryltetrahydroisoquinolines (MeOH, 60 °C) with dialkyl H-phosphonates was performed under aerobic conditions (Scheme 2).[24] However, in our hands, CuBr/O_2 was inefficient for the analogous phosphonation of the NMe_2 group in *N,N*-dimethyl-*p*-toluidine (Eq. 1).[25]



Scheme 2. Copper-catalyzed oxidative phosphonation of tetrahydroisoquinoline derivatives by Baslé and Li.[24]



Eq. 1

The few studies on the double activation of C(sp^3)-H bonds in the α- and α'-positions to nitrogen of tertiary amines have so far concentrated on its use for subsequent C-C bond forming reactions.[18d,23,26] Methods for efficient and selective α,α'-bisphosphonations of tertiary amines are presently still lacking.

In this chapter, we report the selective synthesis of α-aminophosphonates under mild conditions by oxidation of tertiary amines in the presence of an inexpensive and non-toxic iron salt without designed ligands. Moreover, the usefulness of the catalyst system described in this work is substantiated by the finding that direct α,α'-bisphosphonations of Ar-$N(CH_3)_2$ groups are feasible when both the oxidant and the phosphonation agent are employed in excess.

3.2 Results and Discussion

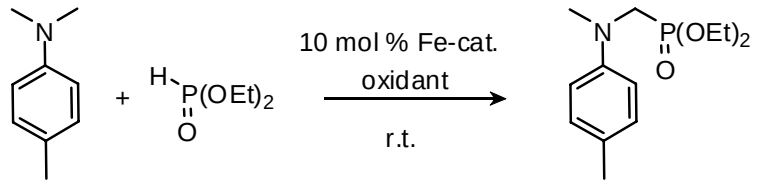
3.2.1 α-Phosphonation

The conditions tested in order to optimize the catalyst system for the α-phosphonations are listed in Table 1.[25] We had chosen *N,N*-dimethyl-*p*-toluidine (**1a**) as standard substrate and found that the combination of catalytic amounts of $FeCl_2$ (10 mol%) with 2.5 equivalents of *tert*-butyl hydroperoxide as oxidant in methanol[27] was more efficient than other catalyst/oxidant/solvent combinations that were investigated. By using two equivalents of diethyl phosphonate (**2a**), the optimum yield of the α-aminophosphonate **3a** (Table 1, entry 1) was already obtained at ambient temperature (84 % yield of isolated **3a**).[25] Different iron and copper salts were tested as catalysts (Table 1, entries 1–9), but only $FeCl_3$ and $FeBr_3$ were found to perform with comparable catalytic activity as $FeCl_2$ under otherwise analogous reaction conditions (Table 1, entries 5 and 6).

Replacing *t*BuOOH by other organic peroxides resulted in low yields of **3a**, (Table 1, entries 10–12). Noteworthy however, the use of dioxygen as oxidant in combination with $FeCl_2$ as catalyst delivered **3a** in 61 % yield after 36 h reaction time (Table 1, entry 13), but

gave only traces of **3a** when CuBr was employed as the catalyst[24] (Table 1, entry 14). Substitution of the standard solvent methanol by other alcohols, dichloromethane, or acetonitrile reduced the yields of **3a** to below 50 % (Table 1, entries 15–19).

Table 1. Optimization of the catalytic system for the α-phosphonation of *N,N*-dimethyl-*p*-toluidine (**1a**) with diethyl H-phosphonate (**2a**).[a]



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

Entry	Catalyst	Oxidant	Solvent	*t*/h	Yield[b] / %
1	$FeCl_2$	*t*BuOOH[c]	MeOH	15	84
2	FeF_2	*t*BuOOH[c]	MeOH	15	43
3	$Fe(OAc)_2$	*t*BuOOH[c]	MeOH	15	19
4	$Fe(ClO_4)_2 \cdot H_2O$	*t*BuOOH[c]	MeOH	15	55
5	$FeBr_3$	*t*BuOOH[c]	MeOH	15	66
6	$FeCl_3$	*t*BuOOH[c]	MeOH	15	76
7	None	*t*BuOOH[c]	MeOH	15	trace
8	CuCl	*t*BuOOH[c]	MeOH	15	51
9	CuBr	*t*BuOOH[c]	MeOH	15	46
10	$FeCl_2$	$(t\text{BuO})_2$	MeOH	15	trace
11	$FeCl_2$	Benzoyl peroxide	MeOH	15	37
12	$FeCl_2$	Cumylhydroperoxide	MeOH	15	27
13	$FeCl_2$	O_2 (1 atm)	MeOH	36	61
14	CuBr	O_2 (1 atm)	MeOH	24	trace
15	$FeCl_2$	*t*BuOOH[c]	EtOH	15	34
16	$FeCl_2$	*t*BuOOH[c]	*i*PrOH	15	26
17	$FeCl_2$	*t*BuOOH[c]	*t*BuOH	15	21
18	$FeCl_2$	*t*BuOOH[c]	CH_2Cl_2	15	29
19	$FeCl_2$	*t*BuOOH[c]	CH_3CN	15	47

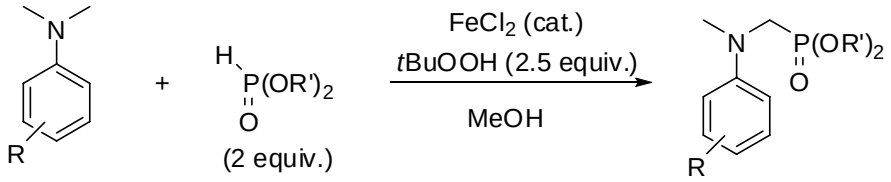
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), oxidant (2.5 mmol), and solvent (2.0 mL), dry N_2 atmosphere, room temperature (r.t.) was 23 ± 2 °C. [b] Yield of isolated product after column chromatography on silica gel. [c] A 5.5 M solution in decane was used.

The optimized reaction conditions (Table 1, entry 1) could be successfully applied for the reactions of different aliphatic dialkyl *H*-phosphonates. Similar reaction times for diethyl (**2a**), dimethyl (**2b**), di-isopropyl (**2c**), and di-*n*-butyl phosphonates (**2d**) indicate that the reactivities of these dialkyl phosphonates are almost independent of the alkyl moieties (Table

2, entries 1–5). Only when dibenzyl phosphonate (**2e**), was employed, reflux conditions were required to achieve a high degree of conversion (Table 2, entry 6).

For the reactions listed in Table 2, which were carried out in methanolic solution, we have not observed an exchange of the alkyl groups. Nevertheless, the reaction of *N*,*N*-dimethyl-*p*-toluidine (**1a**) with bis(2,2,2-trifluoroethyl) phosphonate (**2f**) generated the mixed ester **4** in high yield (Scheme 3). The formation of **4** can be rationalized by the substitution of one of the 2,2,2-trifluoroethoxy groups by a methoxy group that originates from the solvent methanol.

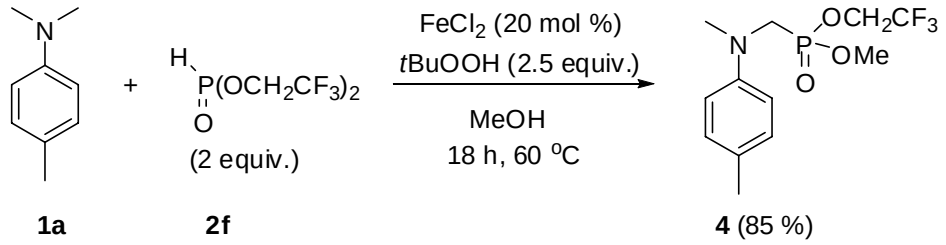
Table 2. α-Phosphonation of ring-substituted *N*,*N*-dimethylanilines.



1 **2** **3**

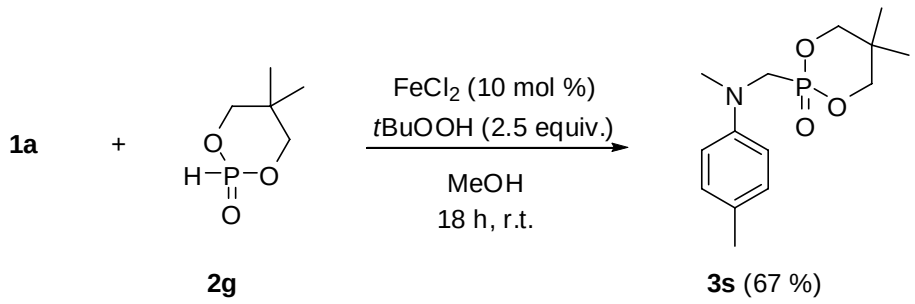
Entry	R	R'[a]	$FeCl_2$/ mol-%	*t*/h	*T*/ °C	Yield[b]/ %	δ_C (NCH_2P)/ ppm	$^1J_{C,P}$/ Hz
1	4-CH_3 (**1a**)	Et (**2a**)	10	15	r.t.[c]	**3a** (84)	50.3	162
2		Et (**2a**)[d]	10	15	r.t.[c]	**3a** (63)[d]		
3		Me (**2b**)	10	24	r.t.[c]	**3b** (78)	49.8	162
4		*i*Pr (**2c**)	10	15	r.t.[c]	**3c**(74)	51.2	166
5		*n*Bu (**2d**)	15	18	r.t.[c]	**3d** (63)	50.2	161
6		CH_2Ph (**2e**)	20	20	reflux	**3e** (79)	50.7	159
7	4-OCH_3 (**1b**)	Et (**2a**)	15	18	r.t.[c]	**3f** (83)	51.2	162
8		Me (**2b**)	15	36	r.t.[c]	**3g** (77)	50.7	162
9		*i*Pr (**2c**)	15	18	r.t.[c]	**3h** (80)	52.0	166
10	H (**1c**)	Et (**2a**)	20	14	r.t.[c]	**3i** (71)	49.9	162
11	4-Br (**1d**)	Et (**2a**)	15	24	r.t.[c]	**3j** (80)	49.8	162
12		Me (**2b**)	15	24	60	**3k** (84)	49.1	161
13		*i*Pr (**2c**)	15	24	60	**3l** (68)	50.5	164
14	4-C≡CH (**1e**)	Et (**2a**)[e]	30	24	reflux	**3m** (trace)	—	—
15	4-COPh (**1f**)	Et (**2a**)[e]	30	24	reflux	**3n** (65)	48.9	161
16	4-CO_2Et (**1g**)	Et (**2a**)	30	24	reflux	**3o** (61)	48.8	160
17	4-COOH (**1h**)	Et (**2a**)	30	24	reflux	**3p** (78)	48.8	160
18	3-NO_2 (**1i**)	Et (**2a**)	30	36	reflux	**3q** (57)	49.3	161
19	4-NO_2 (**1j**)	Et (**2a**)	30	24	reflux	**3r** (trace)	—	—

[a] Reactants **1**, **2**, and *t*BuOOH were used in a molar ratio of 1.0:2.0:2.5 if not indicated otherwise.
[b] Yields of isolated products after column chromatography on silica gel.
[c] Room temperature (r.t.) was 23 ± 2 °C.
[d] In the presence of 1.0 equiv. of 3,5-di-*tert*-butyl-4-hydroxytoluene.
[e] In the presence of 3 equiv. of **2a**.



Scheme 3. Phosphonation and transesterification in the reaction of **1a** with **2f** in methanol (in $CDCl_3$: $\delta_C(NCH_2P) = 50.3$ ppm, $^1J_{C,P} = 162$ Hz).

The reaction of the cyclic phosphonate 5,5-dimethyl-1,3,2-dioxaphosphorinan-2-one (**2g**) with **1a** furnished **3s** in moderate yield already at room temperature (Scheme 4), analogous to the behavior of the acyclic dialkyl phosphonates **2a**–**d**. Precipitation from a CH_2Cl_2/*n*-pentane/ethyl acetate mixture (10/10/1, v/v/v) delivered crystals of **3s** that were suitable for X-ray analysis (Figure 1)[28] (for crystallographic data, see Chapter 3.5.7).



Scheme 4. Formation of *N*-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphorinan-2-yl-methyl)-*N*-methyl-*p*-toluidine (**3s**) from **1a** with **2g** in methanol (r.t. was 23 ± 2 °C).

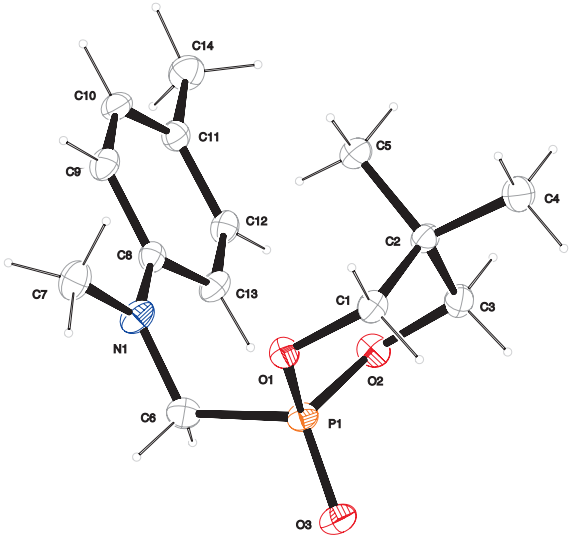


Figure 1. Crystal structure determination of *N*-(5,5-dimethyl-2-oxo-2λ^5-[1,3,2]-dioxaphosphorinan-2-yl-methyl)-*N*-methyl-*p*-toluidine (**3s**) (the shown thermal ellipsoids are drawn at the 50 % probability level; in $CDCl_3$: $\delta_C(NCH_2P)$ = 50.6 ppm, $^1J_{C,P}$ = 159 Hz).

The phosphonations of methyl-, methoxy-, bromo-, and 3-nitro-substituted substrates show that several functional groups are tolerated as ring substitutents in the *N,N*-dimethylanilines (Table 2, entries 1–13 and 18). Whereas the use of 4-ethynyl- (**1e**) and 4-nitro-*N,N*-dimethylaniline (**1j**) did not allow us to isolate a phosphonation product,[29] the *p*-benzoyl substituted *N,N*-dimethylaniline **1f** was phosphonated in the presence of 3 equivalent of **2a** (65 % yield, Table 2, entry 15). Furthermore, the linkage of *p*-carboxyl groups to the aniline substrates either as ethyl ester in **1g** (Table 2, entry 16) or as free carboxylic acid in **1h** (Table 2, entry 17) was compatible with the phosphonation reaction and gave acceptable yields of **3o** (61 %) and **3p** (78 %), respectively.

Michler's ketone **5** (Table 3, entry 1) was chosen as a model for studying the relative reactivities of the N-CH_3 group as part of either a $N(CH_3)_2$ or an $N(CH_3)CH_2P(O)(OEt)_2$ unit. In the presence of 4 equivalents of **2a**, the symmetrically substituted tetraethyl bis-phosphonate **7** was obtained as the major product (51 %) together with the mono-phosphonation product **6** (34 %). This result indicates that the first phosphonation of a $N(CH_3)_2$ is much faster than a second phosphonation at the same amino group.

Employing the more activated 4,4'-bis(dimethylaminophenyl)methane (**8**) in the presence of 1.5 equivalents of **2a** produced already a 4:3-mixture of the mono- and bis-phosphonation products **9** and **10**, respectively, which could be separated by column chromatography (Table

3, entry 2). Finally, the symmetrical bis-phosphonation product **10** (76 %) formed selectively when 4 equivalents of **2a** were used (Table 3, entry 3). Competing C–H bond activation at the central benzylic methylene group was not observed.[30–32]

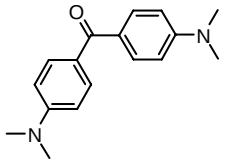
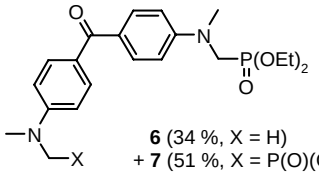
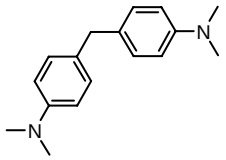
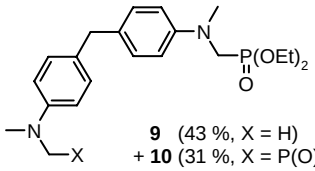
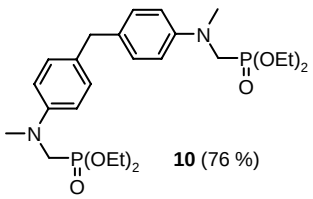
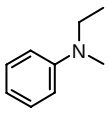
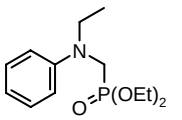
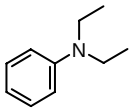
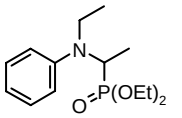
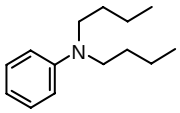
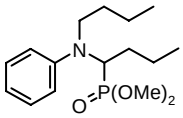
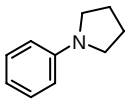
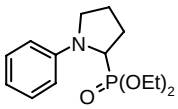
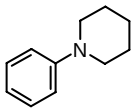
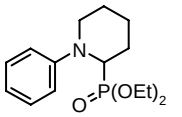
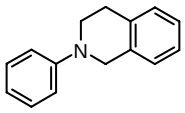
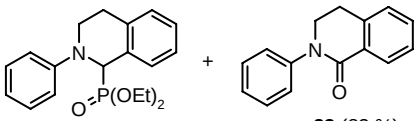
N-Ethyl-*N*-methylaniline (**11**) allows one to address the chemoselectivity of the oxidative phosphonation reaction (Table 3, entry 4). The high yield of **12** (83 %) demonstrates that preferential oxidation of the *N*-methyl group takes place.[27a,33]

Nevertheless, formation of **14** and **16** from *N*,*N*-diethylaniline (**13**) and *N*,*N*-dibutylaniline (**15**), respectively, as well as the successful α-phosphonation of the heterocycles in *N*-phenyl-pyrrolidine (**17**) and *N*-phenyl-piperidine (**19**) (Table 3, entries 5–8) proved that the scope of the $FeCl_2$-catalyzed phosphonation reaction can be extended also to other tertiary amines, beyond those that carry NMe groups.

Though *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**21**) was almost quantitatively converted under the reaction conditions, we were not able to isolate the expected α-aminophosphonate **22**.[34] Instead, we obtained the lactam 2-phenyl-3,4-dihydro-2H-isoquinolin-1-one (**23**)[35] owing to oxidation of the benzylic position of the substrate (Table 3, entry 9). A successful phosphonation of *N*-aryl-tetrahydroisoquinolines (i.e., **21** → **22**) with CuBr as catalyst under aerobic conditions has been reported.[24]

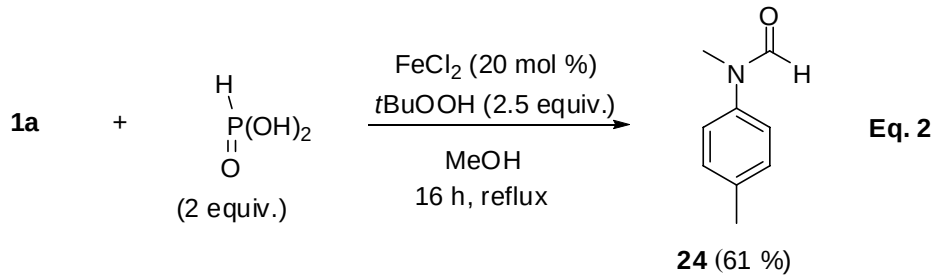
The products of the phosphonation reactions were characterized by NMR spectroscopic methods which unambiguously indicate the formation of a carbon-phosphorus bond. As noted in Table 2 and Schemes 3 and 4, the ^{13}C NMR chemical shifts for the NCH_2P carbon atom in **3** and **4** are in a narrow range of 48.8–52.0 ppm with characteristic $^1J_{C,P}$ coupling constants from 159 to 164 Hz. In the dialkyl phosphonates listed in Table 2, the ^{31}P nuclei resonate between 22.2 and 24.8 ppm. Slight changes in the electronic environment of the phosphorus atom are detected in the presence of a trifluoroethoxy group (**4**: δ_P = 26.1 ppm) or a 2-oxo-[1,3,2]dioxaphosphinane ring (**3s**: δ_P = 20.0 ppm).

Table 3. Oxidative $FeCl_2$ catalyzed α-phosphonations of *N,N*-dialkylanilines with the dialkyl phosphonates **2a,b** in methanol.

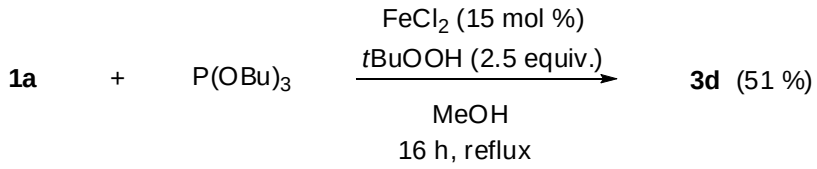
Entry	Amine		Conditions	Products (Yield/%)[a]
1		**5**	**2a** (4 equiv), *t*BuOOH (4 equiv.), $FeCl_2$ (20 mol-%), 24 h, reflux[b]	 **6** (34 %, X = H) + **7** (51 %, X = $P(O)(OEt)_2$)
2		**8**	**2a** (1.5 equiv.), *t*BuOOH (2.5 equiv.), $FeCl_2$ (15 mol-%), 24 h, 60 °C	 **9** (43 %, X = H) + **10** (31 %, X = $P(O)(OEt)_2$)
3		**8**	**2a** (4 equiv.), *t*BuOOH (4 equiv.), $FeCl_2$ (15 mol-%), 24 h, 60 °C	 **10** (76 %)
4		**11**	**2a** (2 equiv.), *t*BuOOH (2.5 equiv.), $FeCl_2$ (20 mol-%), 24 h, 60 °C	 **12** (83 %)
5		**13**	**2a** (2 equiv.), *t*BuOOH (2.5 equiv.), $FeCl_2$ (20 mol-%), 24 h, 60 °C[c]	 **14** (59 %)[c]
6		**15**	**2b** (2 equiv.), *t*BuOOH (2.5 equiv.), $FeCl_2$ (30 mol-%), 24 h, 60 °C[c]	 **16** (47 %)[c]
7		**17**	**2a** (3 equiv.), *t*BuOOH (2.5 equiv.), $FeCl_2$ (30 mol-%), 24 h, reflux	 **18** (73 %)
8		**19**	**2a** (3 equiv.) *t*BuOOH (2.5 equiv.), $FeCl_2$ (30 mol-%), 24 h, reflux	 **20** (81 %)
9		**21**	**2a** (2 equiv.) *t*BuOOH (2.5 equiv.), $FeCl_2$ (20 mol-%), 24 h, reflux	 **22** (trace) + **23** (83 %)

[a] Yields of isolated products after column chromatography on silica gel.
[b] In the presence of **2a** (2 equiv.) and *t*BuOOH (2.5 equiv.) **6** and **7** were isolated in 41 % and 27 % yield, respectively (20 mol-% $FeCl_2$, 24 h, reflux).
[c] Not optimized.

Our attempts to directly synthesize an α-aminophosphonic acid by combining **1a** with phosphorous acid $HP(O)(OH)_2$ and *tert*-butylhydroperoxide failed and delivered *N*,4'-dimethylformanilide (**24**) (Eq. 2).[36,37]



Trialkylphosphites might be considered as alternative P-nucleophiles. Indeed, the reaction of tributylphosphite with **1a** (Scheme 5) furnished **3d** in a yield comparable to that of the analogous reaction (at r.t.) of **1a** with dibutyl phosphonate (**2d**) but required elevated reaction temperatures.

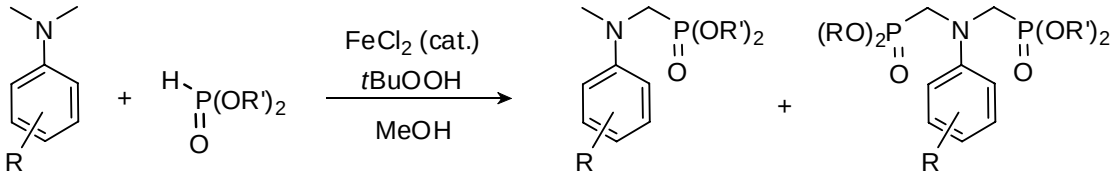


Scheme 5. Iron-catalyzed formation of α-aminophosphonate **3d** from **1a** and tributylphosphite (2 equiv.).

3.2.2 α,α'-Bisphosphonations[38]

Metal-catalyzed oxidative cross coupling reactions offer the potential for two-fold functionalizations of the α,α'-positions of tertiary amines. Nevertheless, only few one-pot

Table 4. α-Mono- and α,α'-bis-phosphonation of *N,N*-dimethyl-*p*-toluidine (**1b**) and *N,N*-dimethyl-mesidine (**1l**).



1 **2** **3** **25**

Entry	R	R'	mol-% $FeCl_2$	*t*/h	*T*/°C	Products (Yield/%)[a]
1	4-CH_3 (**1a**)	Et (**2a**) (2 equiv)[c]	10	15	r.t.[b]	**3a** (84)
2		Et (3 equiv)[c]	20	24	60	**3a** (61) + **25a** (18)
3		Et (5 equiv)[d]	20	24	60	**3a** (45) + **25a** (43)
4		Et (10 equiv)[d]	20	24	60	**3a** (24) + **25a** (40)
5	2,4,6-$(CH_3)_3$ (**1l**)	Et (**2a**) (2 equiv)[c]	10	24	60	**3t** (39) + **25b** (56)
6		Et (4 equiv)[d]	20	24	reflux	**3t** (19) + **25b** (65)
7		Et (10 equiv)[d]	20	24	reflux	**3t** (17) + **25b** (59)
8		*i*Pr (**2c**) (5 equiv)[d]	20	24	reflux	**3u** (15)[e] + **25c** (69)
9		*n*Bu (**2d**) (2 equiv)	20	24	reflux	**3v** (41) + **25d** (35)
10		*n*Bu (5 equiv)[d]	20	24	reflux	**3v** (12) + **25d** (80)
11		*n*Bu (10 equiv)[d]	20	24	reflux	**3v** (11) + **25d** (65)

[a] Yields of isolated products after column chromatography on silica gel.
[b] Room temperature (r.t.) was 23 ± 2 °C.
[c] In the presence of 2.5 equiv of *t*BuOOH.
[d] In the presence of 5 equiv of *t*BuOOH.
[e] It was not possible to isolate **3u**. Therefore, the yield of **3u** was estimated from the isolated yield of **25c** and the product ratio **3u**/**24c** obtained from the GC-MS of the crude product.

procedures of such reactions that avoid the isolation of mono-functionalized intermediates have been reported.[18d,23]

As shown in Table 4, the reactions of **1a** (entries 1–4) and *N,N*-dimethyl-mesidine (**1l**, entries 5–7) in the presence of excess diethyl H-phosphonate (**2a**) and oxidant delivered mixtures of mono-phosphonated (**3a** and **3t**) and bisphosphonated products (**25a** and **25b**).

Maximum yields of **25a** and **25b** were reached when 4 to 5 equivalents of phosphonate **2a** were used. The presence of 10 equivalents of **2a** reduced the overall yield and the yield of the two-fold functionalized products **25**.

N,*N*-Dimethyl-mesidine (**1l**) was slightly more prone to undergo α,α'-bisphosphonations than **1a**, and the isolated yields of the amino-α,α'-bisphosphonates **25** reached levels between 65 and 80 % with different dialkyl phosphonates, even in the presence of sterically demanding isopropyl groups (Table 4, entries 6, 8–11). The higher acidity of the NCH_3 groups in the radical cation $\mathbf{1l}^{\cdot+}$ than in $\mathbf{1a}^{\cdot+}$ has been discussed earlier in the context of anodic oxidations. Genies and co-workers rationalized the different regioselectivities of $\mathbf{1a}^{\cdot}$ and $\mathbf{1l}^{\cdot}$ in radical dimerizations by the reduced delocalization of the unpaired electron in the radical cation $\mathbf{1l}^{\cdot+}$ because of the twist between the plane of the aromatic ring and the plane containing the nitrogen and the carbons of the α-methyl groups.[39]

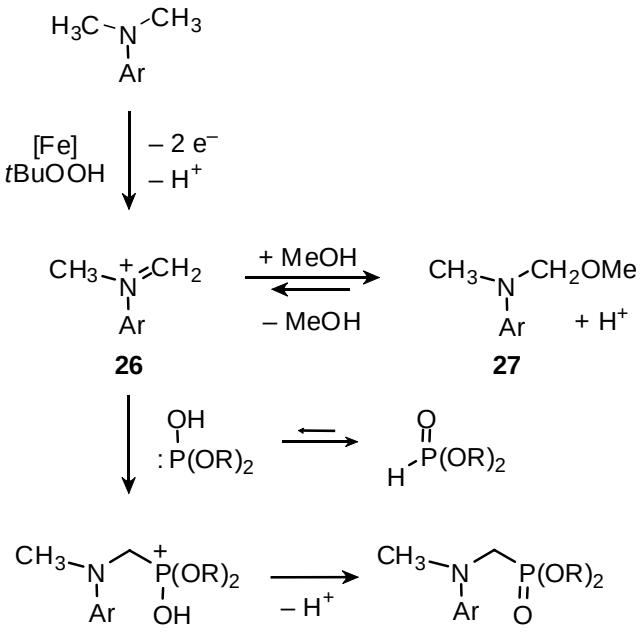
Later, the groups of Dinnocenzo, Fari, and Gould quantified Genies' assumption and calculated a twist angle of 42° between the aryl ring and the dimethylamino group in the radical cation $\mathbf{1l}^{\cdot+}$ (B3LYP/6-31G*), significantly larger than the 9° twist angle of the parent *N*,*N*-dimethyl-aniline radical cation $\mathbf{1c}^{\cdot+}$.[40]

3.2.3 Mechanism

Numerous iron complexes have been used to mimic enzymatic oxidations which involve the activation of C-H bonds under mild and selective conditions. Investigations by different groups have shown that in the presence of hydroperoxides a variety of rather complex mechanistic scenarios can be derived for these iron-catalyzed reactions, which have been reviewed.[41] In particular the question whether radical or non-radical species are formed as intermediates in Fe^{2+}/ROOH systems has given rise to controversial discussions.

To gain some insight into the initial C–H activation at the tertiary amines that is required for the subsequent phosphonation, we have studied our standard reaction in the presence of a radical scavenger. With *N*,*N*-dimethyl-*p*-toluidine (**1a**) as substrate, the addition of one equivalent of 3,5-di(*tert*-butyl)-4-hydroxy-toluene (BHT) to the $FeCl_2$ (10 mol-%)/*t*BuOOH/$HP(O)(OEt)_2$ mixture reduced the yield of the α-aminophosphonate **3a** only slightly (63 % yield, Table 2, entry 2). A similar lowering of the yield in the presence of BHT was reported earlier by Miura for analogous $FeCl_3$-catalyzed oxidations of tertiary amines[21] via iminium intermediates. The only partially suppressed phosphonation reaction in the presence of the radical inhibitor BHT may, on the one hand, indicate that the oxidation of carbon-centered radicals to iminium ions is faster than the trapping by the radical inhibitor. On the other hand, Li and coworkers concluded that a free radical process is not a requirement

for the benzylic alkylation of the tetrahydroisoquinoline **21** with nitromethane when a CuBr/*t*BuOOH catalyst/oxidant combination, that is related to our $FeCl_2$/*t*BuOOH system, was used because comparable yields were obtained in the absence and in the presence of 2 equivalents of BHT.[18d] As an alternative to the radical mechanism, Li suggested an ionic



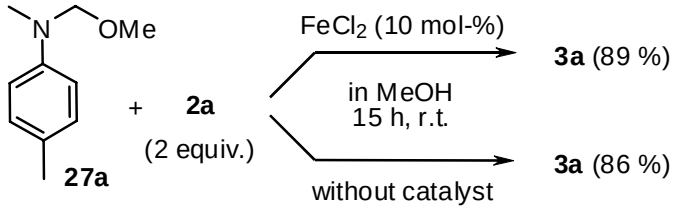
Scheme 6. Plausible mechanism for the formation of α-aminophosphonates from tertiary aromatic amines and dialkyl phosphonates under oxidative conditions.

mechanism. Further studies on the iron-catalyzed oxidation of tertiary amines are, therefore, needed to clarify the mechanism of the formation of the iminium ions **26** that are ultimately trapped by nucleophiles (Scheme 6).

The *N*-aryl substituted iminium ions **26** are sufficiently reactive[42] to be intercepted by the nucleophilic solvent methanol.[43] Under the acidic reaction conditions, the thus formed *N*,*O*-acetals **27** are in equilibrium with the corresponding iminium ions **26**.

As tetravalent dialkyl H-phosphonates $HP(O)(OR)_2$ are in equilibrium with their dialkyl phosphite tautomers $P(OH)(OR)_2$,[2,44,45] the formation of the carbon-phosphorus bond can be explained by the reaction of the iminium ion with $P(OH)(OR)_2$.

N,*O*-Acetals derived from aliphatic amines react with dialkyl *H*-phosphonates also under neutral conditions in benzene or THF solution.[10,46] Therefore, we tested whether acid catalysis is necessary to convert the *N*,*O*-acetal **27a**[47] into the corresponding iminium ion which then reacts with diethyl phosphonate (**2a**) to the α-aminophosphonate **3a** (Scheme 7).



Scheme 7. Reactions of the *N*,*O*-acetal **27a** with **2a** in the presence of catalytic amounts of $FeCl_2$ (10 mol-%) and without $FeCl_2$.

Under analogous reactions conditions, the isolated yields of **3a** from the reaction of **27a** with **2a** were independent (within experimental error) of the presence of $FeCl_2$. This result indicates that in methanol the *N*,*O*-acetal/iminium ion equilibrium[48] sufficiently provides electrophiles that can react with the nucleophilic dialkyl phosphite tautomers to the final product. The presence of acid catalysts is not necessary for this step.

3.3 Conclusions

In summary, the use of the environmentally benign iron salt $FeCl_2$ in combination with *tert*-butylhydroperoxide efficiently activated C(sp^3)–H bonds in α-position to nitrogen of *N*,*N*-dialkylanilines for a subsequent C–P bond formation. Substrates with various functional groups tolerated the oxidative reaction conditions and reacted with acylic or cyclic dialkyl phosphonates to give α-aminophosphonates in moderate to good yields.

The formation of different types of dimers, often found in other oxidations that generate radical cations of *N*,*N*-dimethyl anilines,[49] as well as competing activation of C(sp^3)–H bonds in benzylic positions were not observed. Only *N*-phenyl tetrahydroisoquinoline was oxidized to the corresponding lactam,[50] instead of being phosphonated.

The efficient α,α'-bisphosphonation of *N*,*N*-dimethyl-*p*-toluidine and *N*,*N*-dimethyl-mesidine in the presence of an excess of dialkyl phosphonates and oxidant is one of the few examples for a one-pot double functionalization with initial C(sp^3)–H activation.[18d,23,26] It is the first time that sequential C(sp^3)–H activation at two different carbons attached to the same nitrogen has been used for the formation of carbon-phosphorus bonds.

Mechanistic studies clarifying the nature of the catalytically active iron species[19e,51] as well as the roles of the *N*,*O*-acetal/iminium ion equilibrium and the $HP(O)(OR)_2/P(OH)(OR)_2$ tautomerism should be carried out in future work.

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3.5 Experimental Section

3.5.1 General

All reactions were carried out under an atmosphere of dry nitrogen. ^{1}H (400 or 600 MHz), ^{13}C (100.6 or 150.9 MHz), ^{31}P (162 MHz), and ^{19}F NMR (376 MHz) NMR spectra of solutions in $CDCl_3$ were recorded on 400 or 600 MHz NMR spectrometers. Chemical shifts were expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals (δ_H 7.24 and δ_C 77.0 ppm). Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. HRMS was performed on a Finnigan MAT 95Q mass spectrometer. Infrared spectra of neat substances were recorded on a Perkin-Elmer Spectrum BX II FT-IR spectrometer equipped with an ATR probe (diamond).

3.5.2 Materials

Commercially available tertiary amines were used as received. *N*,*N*-Dimethyl-*p*-anisidine and *N*-(methoxymethyl)-*N*,4-dimethylaniline were prepared according to literatures procedure [S1] and [S2], respectively.

The following iron and copper salts were used: Iron(II) acetate (anhydrous, 97 %, Strem), iron(III) bromide (99 %, ABCR), iron(II) chloride (98 %, Aldrich), iron(II) fluoride (99 %, Strem), iron(II) perchlorate hydrate (98 %, Aldrich), iron(III) chloride (anhydrous, 97 %, Acros), copper(I) bromide (98 %, Acros), and copper(I) chloride (98 %, Merck).

Dialkyl phosphonates (Aldrich) and *tert*-butyl hydroperoxide (5.5 M solution in decane, purum, Aldrich) were purchased.

[S1] J. A. Hodges, R. T. Raines, *Org. Lett*. **2006**, *8*, 4695–4697.

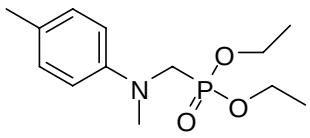
[S2] Y. M Shen, Z. Tan, D. Chen, X. B. Feng, C.-C. Cheng, C. L. Zhu, *Tetrahedron* **2009**, *65*, 158-163.

3.5.3 Typical Procedure for the Iron Catalyzed Phosphonation of Tertiary Amines

Under an atmosphere of dry N_2, a 25 mL Schlenk flask was charged with iron(II) chloride (10 mol-%, 13 mg). The tertiary amine (1.0 mmol), dialkyl phosphonate (2.0 mmol), and MeOH (2.0 mL) were added successively by syringe. To the mixture was added dropwise *tert*.-butyl hydroperoxide (0.47 mL of a 5.5 M solution in decane, 2.5 mmol) over a period of 5 min. The mixture was stirred at room temperature for the indicated time. At the end of the reaction, the reaction mixture was poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (*n*-pentane/ethyl acetate/triethylamine). Products of double phosphonation generally required longer retention times than mono-phosphonation products.

3.5.4 Phosphonated Tertiary Amines

Diethyl [methyl(*p*-tolyl)amino]methylphosphonate (3a)



3a

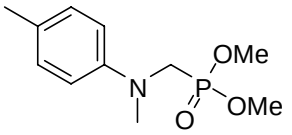
Following the *Typical Procedure*, 4-methyl-*N,N*-dimethylaniline (147 µL, 1.00 mmol) reacted with diethyl phosphonate (272 µL, 2.00 mmol) for 15 h to furnish **3a** (227 mg, 84 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 15:4:1).

Known compound; the ^{1}H NMR spectroscopic data agree with those given in ref.[S3] Viscous oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.24 (t, J = 7.0 Hz, 6 H), 2.22 (s, 3 H), 2.97 (s, 3 H), 3.63 (d, $^2J_{H,P}$ = 7.8 Hz, 2 H), 4.00–4.10 (m, 4 H), 6.71 (d, J = 8.4 Hz, 2 H), 7.01 ppm (d, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 16.4 (d, $J_{C,P}$ = 5.7 Hz), 20.1, 39.3, 50.3 (d, $^1J_{C,P}$ = 162 Hz), 62.0 (d, $J_{C,P}$ = 7.0 Hz), 113.2 (d, $J_{C,P}$ = 1.1 Hz), 126.7 (d, $J_{C,P}$ = 0.8 Hz), 129.5, 147.4 ppm (d, $J_{C,P}$ = 2.9 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 23.83 ppm; IR (ATR):

[S3] G. Bidan, M. Genies, *Tetrahedron* **1981**, *37*, 2297–2301.

ν = 2981, 2907, 2868, 2819, 1678, 1616, 1520, 1477, 1443, 1391, 1360, 1244, 1230, 1188, 1164, 1100, 1046, 1019, 957, 861, 801, 774, 715, 692 cm^{-1}.

Dimethyl [methyl(*p*-tolyl)amino]methylphosphonate (3b)

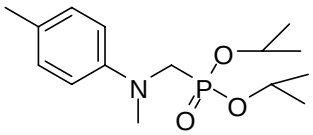


3b

Following the *Typical Procedure*, 4-methyl-*N,N*-dimethylaniline (147 µL, 1.00 mmol) reacted with dimethyl phosphonate (188 µL, 2.00 mmol) for 24 h to furnish **3b** (190 mg, 78 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 15:4:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.22 (s, 3 H), 2.97 (s, 3 H), 3.66 (d, $^{2}J_{H,P}$ = 7.6 Hz, 2 H), 3.69 (d, $J_{H,P}$ = 10.4 Hz, 6 H), 6.71 (d, J = 8.6 Hz, 2 H), 7.02 ppm (d, J = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.1, 39.3, 49.8 (d, $^{1}J_{C,P}$ = 162 Hz), 52.6 (d, $J_{C,P}$ = 7.0 Hz), 113.2 (d, $J_{C,P}$ = 1 Hz), 126.9 (d, $J_{C,P}$ = 0.9 Hz), 129.6 (d, $J_{C,P}$ = 0.4 Hz), 147.2 ppm (d, $J_{C,P}$ = 2.8 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 26.08 ppm; HRMS *m/z* (ESI+) 244.1091, $[C_{11}H_{19}NO_3P]^+$ requires 244.1097; IR (ATR): ν = 2954, 2919, 2853, 1676, 1616, 1520, 1450, 1360, 1230, 1184, 1107, 1022, 869, 800, 714, 692 cm^{-1}.

Di-*iso*-propyl [methyl(p-tolyl)amino]methylphosphonate (3c)



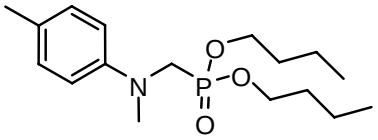
3c

Following the *Typical Procedure*, 4-methyl-*N,N*-dimethylaniline (147 µL, 1.00 mmol) reacted with diisopropyl phosphonate (340 µL, 2.00 mmol) for 15 h to furnish **3c** (221 mg, 74 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 15:2:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.21 (d, J = 6.0 Hz, 6 H), 1.29 (d, J = 6.0 Hz, 6 H), 2.22 (s, 3 H), 2.98 (s, 3 H), 3.56 (d, $^{2}J_{H,P}$ = 8.4 Hz, 2 H), 4.66–4.74 (m, 2 H), 6.72 (d, J = 8.2 Hz, 2 H), 7.00 ppm (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.2, 23.9 (d, $J_{C,P}$ = 4.9 Hz), 24.1 (d, $J_{C,P}$ = 3.6 Hz), 39.3, 51.2 (d, $^{1}J_{C,P}$ = 166 Hz), 70.8 (d, $J_{C,P}$ = 7.3 Hz),

113.4 (d, $J_{C,P}$ = 1.0 Hz), 126.6, 129.4, 147.7 ppm (d, $J_{C,P}$ = 3.6 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 22.11 ppm; HRMS *m/z* (EI) 299.1643, $C_{15}H_{26}NO_3P$ requires 299.1650; IR (ATR): ν = 2978, 2930, 2873, 1680, 1617, 1520, 1467, 1453, 1384, 1374, 1359, 1247, 1230, 1179, 1142, 1104, 978, 898, 886, 853, 801, 755, 718, 690 cm^{-1}.

_N_-(Dibutoxyphosphorylmethyl)-_N_-methyl-_p_-toluidine (3d)

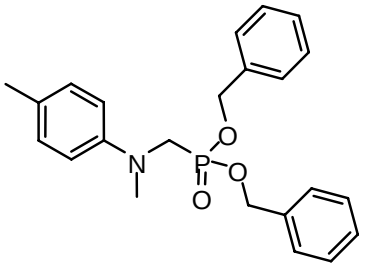


3d

Following the *Typical Procedure*, 4-methyl-*N,N*-dimethylaniline (147 µL, 1.00 mmol) reacted with dibutyl phosphonate (407 µL, 2.00 mmol) in the presence of $FeCl_2$ (15 mol %) for 18 h to furnish **3d** (220 mg, 63 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 10:1:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.87 (t, *J* = 7.4 Hz, 6 H), 1.27–1.35 (m, 4 H), 1.52–1.58 (m, 4 H), 2.22 (s, 3 H), 2.97 (s, 3 H), 3.64 (d, $^2J_{H,P}$ = 7.6 Hz, 2 H), 3.94–4.03 (m, 4 H), 6.71 (d, *J* = 8.4 Hz, 2 H), 7.01 ppm (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.5, 18.6, 20.2, 32.6, 39.3, 50.2 (d, $^1J_{C,P}$ = 161 Hz), 65.8 (d, $J_{C,P}$ = 7.3 Hz), 113.3 (d, $J_{C,P}$ = 1.2 Hz), 126.7 (d, $J_{C,P}$ = 0.8 Hz), 129.5, 147.4 ppm (d, $J_{C,P}$ = 2.7 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 23.97 ppm; HRMS (ESI+): *m/z* = 350.1856 [M + $^{23}Na^+$], calcd. for [$C_{17}H_{30}NO_3P$ + $^{23}Na^+$]: 350.1856; IR (ATR): ν = 2959, 2934, 2873, 1618, 1572, 1521, 1465, 1380, 1360, 1246, 1230, 1189, 1020, 977, 905, 856, 801, 735 cm^{-1}.

_N_-(Dibenzyloxyphosphorylmethyl)-_N_-methyl-_p_-toluidine (3e)

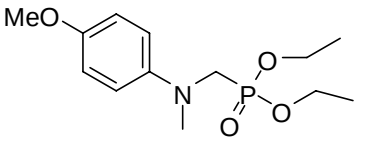


3e

Following the *Typical Procedure*, 4-methyl-*N,N*-dimethylaniline (147 µL, 1.00 mmol) reacted with dibenzyl phosphonate (552 mg, 2.00 mmol) in the presence of $FeCl_2$ (20 mol %) under reflux for 20 h to furnish **3e** (312 mg, 79 %) after column chromatography (*n*-pentane/ethyl acetate 10:3).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.25 (s, 3 H), 2.95 (s, 3 H), 3.69 (d, $^2J_{H,P}$ = 7.6 Hz, 2 H), 4.97 (d, *J* = 8.4 Hz, 4 H), 6.72 (d, *J* = 7.6 Hz, 2 H), 7.01 (d, *J* = 7.6 Hz, 2 H), 7.25–7.31 (m, 10 H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.2, 39.4, 50.7 (d, $^1J_{C,P}$ = 159 Hz), 67.6 (d, $J_{C,P}$ = 7.0 Hz), 113.3, 126.9, 128.0, 128.3, 128.5, 129.6, 136.2 (d, $J_{C,P}$ = 5.8 Hz), 147.2 ppm (d, $J_{C,P}$ = 2.6 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 24.81 ppm; HRMS (EI): *m/z* = 395.1649, calcd for $C_{23}H_{26}NO_3P$: 395.1650; IR (ATR): ν = 3064, 3031, 2950, 2892, 1616, 1519, 1497, 1454, 1377, 1359, 1246, 1188, 1105, 988, 877, 800, 731, 694 cm^{-1}.

Diethyl [(4-methoxyphenyl)(methyl)amino]methylphosphonate (3f)

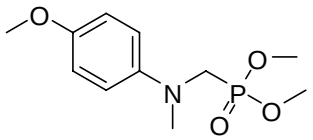


3f

Following the *Typical Procedure*, 4-methoxy-*N,N*-dimethylaniline (153 mg, 1.00 mmol) reacted with diethyl phosphonate (272 µL, 2.00 mmol) in the presence of $FeCl_2$ (15 mol %) for 18 h to furnish **3f** (239 mg, 83 %) after column chromatography (n-pentane/ethyl acetate/triethylamine 15:4:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (t, *J* = 7.2 Hz, 6 H), 2.95 (s, 3 H), 3.59 (d, $^{2}J_{H,P}$ = 8.0 Hz, 2 H), 3.72 (s, 3 H), 4.01–4.11 (m, 4 H), 6.76–6.81 ppm (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.4 (d, $J_{C,P}$ = 5.6 Hz), 39.7, 51.2 (d, $^{1}J_{C,P}$ = 162 Hz), 55.7, 62.1 (d, $J_{C,P}$ = 7.0 Hz), 114.5, 114.9 (d, $J_{C,P}$ = 0.9 Hz), 144.3 (d, $J_{C,P}$ = 3.8 Hz), 152.3 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 23.92 ppm; HRMS *m/z* (ESI+) 288.1351, $[C_{13}H_{23}NO_4P]^+$ requires 288.1359; IR (ATR): ν = 2982, 2934, 2907, 2834, 1512, 1466, 1443, 1408, 1391, 1366, 1296, 1242, 1182, 1164, 1099, 1019, 956, 861, 815, 773, 687 cm^{-1}.

Dimethyl [(4-methoxyphenyl)(methyl)amino]methylphosphonate (3g)

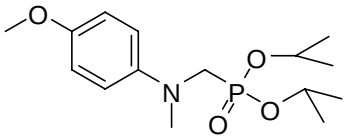


3g

Following the *Typical Procedure*, 4-methoxy-*N,N*-dimethylaniline (153 mg, 1.00 mmol) reacted with dimethyl phosphonate (188 µl, 2.00 mmol) in the presence of $FeCl_2$ (15 mol %) for 36 h to furnish **3g** (199 mg, 77 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 15:4:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.95 (s, 3 H), 3.62 (d, $^{2}J_{H,P}$ = 7.6 Hz, 2 H), 3.69 (d, $J_{H,P}$ = 10.4 Hz, 6 H), 3.72 (s, 3 H), 6.76–6.81 ppm (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* = 39.9, 50.7 (d, $^{1}J_{C,P}$ = 162 Hz), 52.7 (d, $J_{C,P}$ = 7.0 Hz), 55.6, 114.6, 115.0, 144.0 (d, $J_{C,P}$ = 3.7 Hz), 152.5 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 26.30 ppm; HRMS *m/z* (EI) 259.0970, $C_{11}H_{18}NO_4P$ requires 259.0973; IR (ATR): ν = 2954, 2835, 1511, 1464, 1409, 1358, 1299, 1242, 1180, 1106, 1019, 869, 813, 790, 687 cm^{-1}.

Di-*iso*-propyl [(4-methoxyphenyl)(methyl)amino]methylphosphonate (3h)

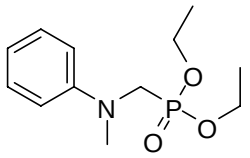


3h

Following the *Typical Procedure*, 4-methoxy-*N,N*-dimethylaniline (153 mg, 1.00 mmol) reacted with diisopropyl phosphonate (340 µL, 2.00 mmol) in the presence of $FeCl_2$ (15 mol %) for 18 h to furnish **3h** (252 mg, 80 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 15:3:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.21 (d, *J* = 6.4 Hz, 6 H), 1.29 (d, *J* = 6.0 Hz, 6 H), 2.96 (s, 3 H), 3.52 (d, $^2J_{H,P}$ = 8.0 Hz, 2 H), 3.72 (s, 3 H), 4.66–4.74 (m, 2 H), 6.79 ppm (s, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.0 (d, $J_{C,P}$ = 4.9 Hz), 24.2 (d, $J_{C,P}$ = 3.6 Hz), 39.9, 52.0 (d, $^1J_{C,P}$ = 166 Hz), 55.7, 70.7 (d, $J_{C,P}$ = 7.3 Hz), 114.4, 115.0, 144.6 (d, $J_{C,P}$ = 4.2 Hz), 152.2 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 22.06 ppm; HRMS *m/z* (EI) 315.1580, $C_{15}H_{28}NO_4P$ requires 315.1599; IR (ATR): ν = 2978, 2934, 2834, 1512, 1466, 1385, 1374, 1297, 1242, 1180, 1141, 1104, 1037, 978, 898, 887, 853, 815, 754, 687 cm^{-1}.

Diethyl [methyl-phenyl-amino]methylphosphonate (3i)

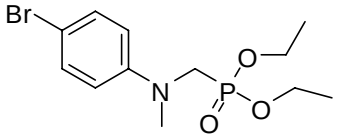


3i

Following the *Typical Procedure*, *N,N*-dimethylaniline (128 µL, 1.00 mmol) reacted with diethyl phosphonate (272 µL, 2.00 mmol) in the presence of $FeCl_2$ (20 mol %) for 14 h to furnish **3i** (182 mg, 71 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 15:4:1).

Known compound (ref.[S4]). Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (t, *J* = 7.2 Hz, 6 H), 3.01 (s, 3 H), 3.68 (d, $^{2}J_{H,P}$ = 8.0 Hz, 2 H), 4.01–4.11 (m, 4 H), 6.73 (t, *J* = 7.4 Hz, 1 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 7.19–7.23 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.4 (d, $J_{C,P}$ = 5.7 Hz), 39.2, 49.9 (d, $^{1}J_{C,P}$ = 162 Hz), 62.1 (d, $J_{C,P}$ = 7.0 Hz), 112.9 (d, $J_{C,P}$ = 1.1 Hz), 117.5, 129.0, 149.3 ppm (d, $J_{C,P}$ = 2.2 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 23.46 ppm; HRMS *m/z* (EI) 257.1170, $C_{12}H_{20}NO_3P$ requires 257.1181; IR (ATR): ν = 2981, 2930, 2907, 1677, 1599, 1506, 1365, 1296, 1244, 1197, 1162, 1099, 1048, 1019, 956, 860, 778, 747, 691 cm^{-1}.

Diethyl [(4-bromophenyl)(methyl)amino]methylphosphonate (3j)



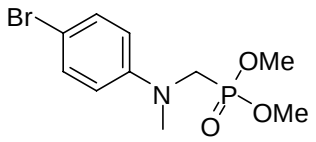
3j

Following the *Typical Procedure*, 4-bromo-*N,N*-dimethylaniline (202 mg, 1.00 mmol) reacted with diethyl phosphonate (272 µL, 2.00 mmol) in the presence of $FeCl_2$ (15 mol %) for 24 h to furnish **3j** (268 mg, 80 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 15:4:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (t, *J* = 7.0 Hz, 6 H), 2.99 (s, 3 H), 3.64 (d, $^{2}J_{H,P}$ = 7.6 Hz, 2 H), 3.99–4.11 (m, 4 H), 6.66 (d, *J* = 9.0 Hz, 2 H), 7.27 ppm (d, *J* = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.4 (d, $J_{C,P}$ = 5.6 Hz), 39.3, 49.8 (d, $^{1}J_{C,P}$ = 162 Hz), 62.2 (d, $J_{C,P}$ = 7.0 Hz), 109.5 (d, $J_{C,P}$ = 1.2 Hz), 144.5 (d, $J_{C,P}$ = 1.1 Hz), 131.6, 148.1 (d, $J_{C,P}$ = 1.6 Hz) ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 22.97 ppm; HRMS *m/z* (EI) 335.0277, $C_{12}H_{19}{}^{79}BrNO_3P$ requires 335.0286; IR (ATR): ν = 2982, 2906, 2821, 1679, 1591, 1496, 1368, 1239, 1196, 1163, 1099, 1046, 1018, 956, 860, 806, 750, 694 cm^{-1}.

[S4] (*a*) B. E. Ivanov, S. S. Krokhina, *Russ. Chem. Bull.* **1967**, 405–407 (*Izv. Akad. Nauk SSSR, Ser. Khim.* **1971**, 424–426); (*b*) B. E. Ivanov, S. S. Krokhina, *Russ. Chem. Bull.* **1971**, 2629–2632 (*Izv. Akad.Nauk SSSR, Ser. Khim.* **1971**, 2773–2776); (*c*) F. Effenberger, H. Kottmann, *Tetrahedron* **1985**, *41*, 4171–4182.

Dimethyl [(4-bromophenyl)(methyl)amino]methylphosphonate (3k)

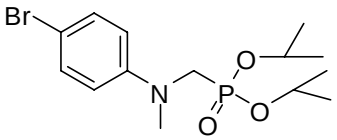


3k

Following the *Typical Procedure*, 4-bromo-*N,N*-dimethylaniline (202 mg, 1.00 mmol) reacted with dimethyl phosphonate (188 µL, 2.00 mmol) in the presence of $FeCl_2$ (15 mol %) at 60 °C for 24 h to furnish **3k** (258 mg, 84 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 15:4:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.96 (s, 3 H), 3.64 (d, $^2J_{H,P}$ = 8.0 Hz, 2 H), 3.67 (dd, $J_{H,P}$ = 10.8 Hz, J = 0.4 Hz, 6 H), 6.62 (d, J = 9.0 Hz, 2 H), 7.25 ppm (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 39.2, 49.1 (d, $^1J_{C,P}$ = 161 Hz), 52.6 (d, $J_{C,P}$ = 6.9 Hz), 109.5 (d, $J_{C,P}$ = 1.2 Hz), 114.3 (d, $J_{C,P}$ = 1.2 Hz), 131.7, 147.9 ppm (d, $J_{C,P}$ = 1.6 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 25.43 ppm; HRMS *m/z* (EI) 306.9972, $C_{10}H_{15}{}^{79}BrNO_3P$ requires 306.9973; IR (ATR): ν = 2953, 2903, 2851, 1591, 1496, 1367, 1310, 1238, 1194, 1107, 1080, 1020, 869, 801, 754, 713, 692 cm^{-1}.

Diisopropyl [(4-bromophenyl)(methyl)amino]methylphosphonate (3l)



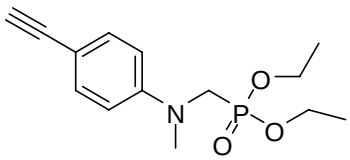
3l

Following the *Typical Procedure*, 4-bromo-*N,N*-dimethylaniline (202 mg, 1.00 mmol) reacted with diisopropyl phosphonate (340 µL, 2.00 mmol) in the presence of $FeCl_2$ (15 mol %) at 60 °C for 24 h to furnish **3l** (247 mg, 68 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 15:3:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.18 (d, J = 6.0 Hz, 6 H), 1.27 (d, J = 6.4 Hz, 6 H), 2.97 (s, 3 H), 3.56 (d, $^2J_{H,P}$ = 8.4 Hz, 2 H), 4.63–4.71 (m, 2 H), 6.64 (d, J = 9.0 Hz, 2 H), 7.24 ppm (d, J = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 23.9 (d, $J_{C,P}$ = 4.8 Hz), 24.1 (d, $J_{C,P}$ = 3.6 Hz), 39.3, 50.5 (d, $^1J_{C,P}$ = 164 Hz), 70.9 (d, $J_{C,P}$ = 7.4 Hz), 109.1 (d, $J_{C,P}$ = 1.1

Hz), 114.5 (d, $J_{C,P}$ = 1.2 Hz), 131.5, 148.3 ppm (d, $J_{C,P}$ = 1.9 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 21.21 ppm; HRMS *m/z* (EI) 363.0586, $C_{14}H_{23}{}^{79}BrNO_3P$ requires 363.0599; IR (ATR): ν = 2978, 2933, 2822, 1681, 1592, 1496, 1385, 1372, 1245, 1195, 1179, 1142, 1104, 1080, 978, 899, 887, 853, 806, 735, 718 cm^{-1}.

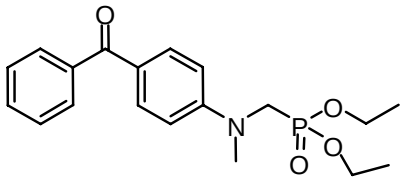
Diethyl ((4-ethynylphenyl)(methyl)amino)methylphosphonate (3m)



3m

Following the *Typical Procedure*, **1e** (230 mg, 1.00 mmol) reacted with diethyl phosphonate (408 µL, 3.00 mmol) in the presence of $FeCl_2$ (30 mol %) under reflux for 24 h to furnish **3m** in trace amount based on GC-MS.

Diethyl ((4-benzoylphenyl)(methyl)amino)methylphosphonate (3n).



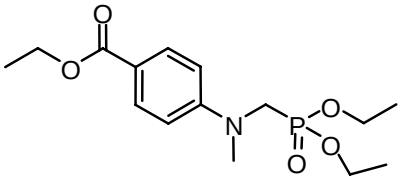
3n

Following the *Typical Procedure*, (4-(dimethylamino)phenyl)(phenyl)methanone (230 mg, 1.00 mmol) reacted with diethyl phosphonate (272 µL, 2.00 mmol) in the presence of $FeCl_2$ (20 mol %) under reflux for 20 h to furnish **3n** (285 mg, 79 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 5:10:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.25 (t, *J* = 6.9 Hz, 6 H), 3.12 (s, 3 H), 3.78 (d, $^2J_{H,P}$ = 9.0 Hz, 2 H), 4.04–4.09 (m, 4 H), 6.77 (d, *J* = 8.4 Hz, 2 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.50 (t, *J* = 6.9 Hz, 1 H), 7.69 (d, *J* = 7.8 Hz, 2 H), 7.77 ppm (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 16.5 (d, $J_{C,P}$ = 5.7 Hz), 39.3, 48.9 (d, $^1J_{C,P}$ = 160 Hz), 62.3 (d, $J_{C,P}$ = 6.9 Hz), 111.2 (d, $J_{C,P}$ = 0.9 Hz), 125.9 (d, $J_{C,P}$ = 0.9 Hz), 128.0, 129.4, 131.3, 132.5, 138.9, 152.1, 195.1 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 22.23 ppm; HRMS (EI): *m/z* = 361.1446,

calcd. for $C_{19}H_{24}NO_4P$: 361.1443; IR (ATR): ν = 2983, 2908, 1641, 1590, 1549, 1522, 1478, 1377, 1284, 1199, 1149, 1019, 960, 861, 790, 728, 700, 677 cm^{-1}.

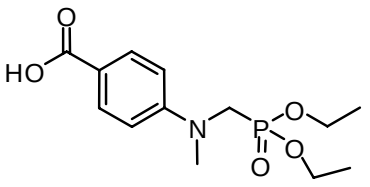
4-((Diethoxyphosphorylmethyl)(methyl)amino)benzoic acid ethyl ester (3o)



3o

Following the *Typical Procedure*, **1g** (195 mg, 1.00 mmol) reacted with diethyl phosphonate (272 µL, 2.00 mmol) in the presence of $FeCl_2$ (30 mol %) under reflux for 24 h to furnish **3o** (200 mg, 61 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 10:5:1). Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.19 (t, *J* = 7.2 Hz, 6 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 3.04 (s, 3 H), 3.70 (d, $^2J_{H,P}$ = 10.0 Hz, 2 H), 3.98–4.05 (m, 4 H), 4.21–4.27 (m, 2 H), 6.68 (d, *J* = 9.0 Hz, 2 H), 7.83 ppm (d, *J* = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3 (d, $J_{C,P}$ = 1.1 Hz), 16.3 (d, $J_{C,P}$ = 5.6 Hz), 39.1, 48.8 (d, $^1J_{C,P}$ = 160 Hz), 60.0, 62.1 (d, $J_{C,P}$ = 6.9 Hz), 111.2 (d, $J_{C,P}$ = 1.4 Hz), 118.4, 130.9, 151.9, 166.6 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 22.41 ppm; HRMS (EI): *m/z* = 329.1393, calcd. for $C_{15}H_{24}NO_5P$: 329.1392; IR (ATR): ν = 2982, 2932, 2908, 1698, 1602, 1563, 1523, 1478, 1444, 1376, 1367, 1278, 1245, 1184, 1104, 1046, 1017, 956, 861, 832, 767, 697 cm^{-1}.

4-((Diethoxyphosphorylmethyl)(methyl)amino)benzoic acid (3p)

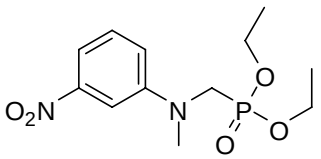


3p

Following the *Typical Procedure*, **1h** (167 mg, 1.00 mmol) reacted with diethyl phosphonate (272 µL, 2.00 mmol) in the presence of $FeCl_2$ (30 mol %) under reflux for 24 h to furnish **3p** (235 mg, 78 %) after column chromatography (*n*-pentane/ethyl acetate/acetic acid 15:6:1). Solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (t, *J* = 7.0 Hz, 6 H), 3.11 (s, 3 H), 3.79 (d, $^2J_{H,P}$ = 8.4 Hz, 2 H), 3.83 (s, 1 H), 4.05–4.10 (m, 4 H), 6.75 (d, *J* = 9.2 Hz, 2 H), 7.94 ppm (d, *J* = 9.2

Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.4 (d, $J_{C,P}$ = 5.6 Hz), 39.3, 48.8 (d, $^1J_{C,P}$ = 160 Hz), 62.5 (d, $J_{C,P}$ = 7.0 Hz), 111.3, 117.6, 131.8, 152.5, 171.4 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 22.47 ppm; HRMS (EI): *m/z* = 301.1064, calcd. for $C_{13}H_{20}NO_5P$: 301.1079; IR (ATR): ν = 2984, 2908, 2770, 1688, 1601, 1563, 1521, 1482, 1435, 1373, 1286, 1247, 1172, 1113, 1020, 962, 864, 830, 772, 694 cm^{-1}.

Diethyl [methyl(3-nitrophenyl)amino]methylphosphonate (3q)

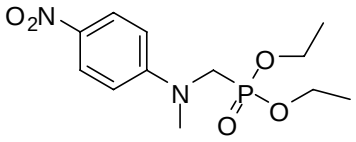


3q

Following the *Typical Procedure*, *N,N*-dimethyl-3-nitroaniline (170 mg, 1.00 mmol) reacted with diethyl phosphonate (272 μL, 2.00 mmol) in the presence of $FeCl_2$ (30 mol %) under reflux for 36 h to furnish **3q** (172 mg, 57 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 15:4:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (t, *J* = 7.0 Hz, 6 H), 3.08 (s, 3 H), 3.71 (d, $^2J_{H,P}$ = 8.0 Hz, 2 H), 4.02–4.10 (m, 4 H), 7.03–7.06 (m, 1 H), 7.29 (t, *J* = 8.2 Hz, 1 H), 7.49–7.55 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.4 (d, $J_{C,P}$ = 5.6 Hz), 39.4, 49.3 (d, $^1J_{C,P}$ = 161 Hz), 62.2 (d, $J_{C,P}$ = 7.0 Hz), 106.6 (d, $J_{C,P}$ = 1.0 Hz), 111.6, 118.1 (d, $J_{C,P}$ = 1.1 Hz), 129.5 (d, $J_{C,P}$ = 0.7 Hz), 149.1, 149.4 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 22.37 ppm; HRMS *m/z* (EI) 302.1019, $C_{12}H_{19}N_2O_5P$ requires 302.1032; IR (ATR): ν = 2983, 2908, 1618, 1571, 1524, 1497, 1444, 1415, 1371, 1344, 1297, 1232, 1204, 1163, 1099, 1047, 1018, 958, 882, 860, 783, 734, 669 cm^{-1}.

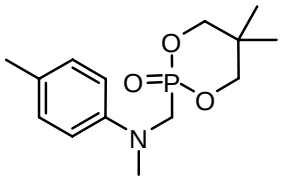
Diethyl (methyl(4-nitrophenyl)amino)methylphosphonate (3r)



3r

Following the *Typical Procedure*, **1j** (230 mg, 1.00 mmol) reacted with diethyl phosphonate (272 µL, 2.00 mmol) in the presence of $FeCl_2$ (30 mol %) under reflux for 24 h to furnish **3r** in trace amount based on GC-MS.

***N*-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphorinan-2-yl-methyl)-*N*-methyl-*p*-toluidine (3s)**



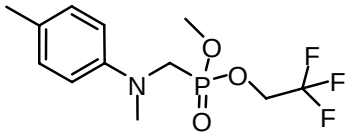
3s

Following the *Typical Procedure*, 4-methyl-*N,N*-dimethylaniline (147 µL, 1.00 mmol) reacted with **2g** (313 mg, 2.00 mmol) for 16 h to furnish **3s** (205 mg, 67 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 15:4:1).

Solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (s, 3 H, 5-CH_3^a), 1.03 (s, 3 H, 5-CH_3^b), 2.24 (s, 3 H, Ar-CH_3), 2.98 (s, 3 H, NCH_3), 3.76 (d, $^2J_{H,P}$ = 7.6 Hz, 2 H), 3.83 (pseudo t, J = 11.4 Hz, 2 H), 4.13 (pseudo t, J = 9.6 Hz, 2 H), 6.73 (d, J = 8.4 Hz, 2 H), 7.04 ppm (d, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.2 (q, Ar-CH_3), 21.2 (q, 5-CH_3^a), 21.5 (5-CH_3^b), 32.5 (sd, $J_{C,P}$ = 6.9 Hz, C-5), 39.6 (q, NCH_3), 50.6 (td, $^1J_{C,P}$ = 159 Hz, NCH_2P), 75.9 (td, $J_{C,P}$ = 7.1 Hz, C-4 and C-6), 113.1 (d), 127.2 (s), 129.7 (d), 147.2 ppm (sd, $J_{C,P}$ = 3.0 Hz), signal multiplicities were assigned on the basis of additional HSQC experiments; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 19.95 ppm; HRMS (ESI+): *m/z* = 306.1229 [M + $^{23}Na^+$], calcd. for [$C_{14}H_{22}NO_3P$ + $^{23}Na^+$] 306.1230; IR (ATR): ν = 2965, 2892, 2816, 1620, 1522, 1477, 1364, 1242, 1225, 1194, 1109, 1047, 1004, 963, 948, 918, 873, 842, 794, 715, 614 cm^{-1}; mp 105.5–106.5 °C.

Details of the crystal structure determination of **3s** are reported in Chapter 3.5.7.

Methyl 2,2,2-trifluoroethyl (methyl(*p*-tolyl)amino)methylphosphonate (4)



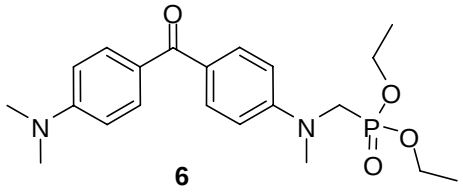
4

Following the *Typical Procedure*, 4-methyl-*N,N*-dimethylaniline (147 µL, 1.00 mmol) reacted with bis(2,2,2-trifluoroethyl) phosphonate (354 µL, 2.00 mmol) in the presence of $FeCl_2$ (20 mol %) at 60 °C for 18 h to furnish **4** (263 mg, 85 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 10:2:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.24 (s, 3 H), 2.98 (s, 3 H), 3.67–3.81 (m, 2 H), 3.74 (superimposed d, J = 10.8 Hz, 3 H), 4.04–4.15 (m, 1 H), 4.33–4.44 (m, 1 H), 6.73 (d, J = 8.7 Hz, 2 H), 7.05 ppm (d, J = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.2, 39.5, 50.3 (d, $^1J_{C,P}$ = 162 Hz), 52.6 (d, $J_{C,P}$ = 7.7 Hz), 62.2 (qd, $^2J_{C,F}$ = 37.3 Hz, $^2J_{C,P}$ = 6.0 Hz), 113.4 (d, $J_{C,P}$ = 1.2 Hz), 122.8 (qd, $^1J_{C,F}$ = 276 Hz, $^3J_{C,P}$ = 7.3 Hz), 127.5, 129.7, 147.0 ppm (d, $J_{C,P}$ = 3.0 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 26.10 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = –75.41 ppm (t, $J_{F,H}$ = 8.3 Hz); HRMS (ESI+): *m/z* = 310.0815 [M – H$^-$], calcd. for $C_{12}H_{16}F_3NO_3P^+$: 310.0814; IR (ATR): ν = 2957, 2699, 1612, 1516, 1459, 1420, 1352, 1285, 1163, 1077, 1046, 961, 820, 781, 727, 656, 614 cm^{-1}.

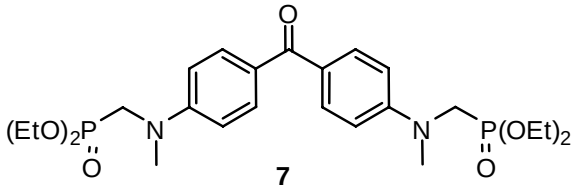
Diethyl ((4-(4-(dimethylamino)benzoyl)phenyl)(methyl)amino)methylphosphonate (6) and Tetraethyl(4,4'-carbonylbis(4,1-phenylene)bis(methylazanediyl))bis(methylene)-diphosphonate (7)

Following the *Typical Procedure*, bis(4-(dimethylamino)phenyl)methanone (271 mg, 1.00 mmol,) reacted with diethyl phosphonate (544 µL, 4.00 mmol) in the presence of $FeCl_2$ (20 mol %) and *t*BuOOH (768 µL, 4.00 mmol) under reflux for 24 h to furnish **6** (137 mg, 34 %) and **7** (275 mg, 51 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 10:20:2).



6

Viscous oil; R_f = 0.65; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.25 (t, J = 7.0 Hz, 6 H), 3.03 (s, 6 H), 3.11 (s, 3 H), 3.77 (d, $^2J_{H,P}$ = 8.4 Hz, 2 H), 4.03–4.12 (m, 4 H), 6.66 (d, J = 9.2 Hz, 2 H), 6.77 (d, J = 8.8 Hz, 2 H), 7.71–7.74 ppm (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.5 (d, $J_{C,P}$ = 5.6 Hz), 39.3, 40.1, 49.1 (d, $^1J_{C,P}$ = 160 Hz), 62.3 (d, $J_{C,P}$ = 7.0 Hz), 110.5, 111.2 (d, $J_{C,P}$ = 0.9 Hz), 126.0, 127.5 (d, $J_{C,P}$ = 0.9 Hz), 131.9, 132.2, 151.4 (d, $J_{C,P}$ = 0.9 Hz), 152.7, 193.9 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 22.57 ppm; HRMS (EI): *m/z* = 404.1852, calcd. for $C_{21}H_{29}N_2O_4P$: 404.1865; IR (ATR): ν = 2981, 2906, 2820, 1675, 1588, 1545, 1523, 1478, 1444, 1367, 1320, 1287, 1229, 1177, 1017, 944, 925, 860, 833, 767, 742, 728, 683 cm^{-1}.



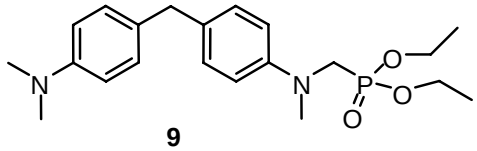
7

Viscous oil; R_f = 0.40; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (t, J = 7.0 Hz, 12 H), 3.09 (s, 6 H), 3.75 (d, $^2J_{H,P}$ = 8.4 Hz, 4 H), 4.00–4.07 (m, 8 H), 6.75 (d, J = 8.8 Hz, 4 H), 7.69 ppm (d, J = 8.8 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.4 (d, $J_{C,P}$ = 5.6 Hz), 39.2, 48.9 (d, $^1J_{C,P}$ = 160 Hz), 62.3 (d, $J_{C,P}$ = 7.1 Hz), 111.1, 127.1, 131.9, 151.4, 193.7 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 22.49 ppm; HRMS (EI): *m/z* = 540.2154, calcd. for $C_{25}H_{38}N_2O_7P_2$, found *m/z* 540.2157; IR (ATR): ν = 2983, 2908, 1676, 1592, 1548, 1524, 1478, 1374, 1288, 1180, 1100, 1044, 1017, 957, 927, 861, 820, 787, 767, 727, 683 cm^{-1}.

Diethyl ((4-(4-(dimethylamino)benzyl)phenyl)(methyl)amino)methylphosphonate (9) and Tetraethyl(4,4'-methylenebis(4,1-phenylene)bis(methylazanediyl))bis(methylene)-diphosphonate (10)

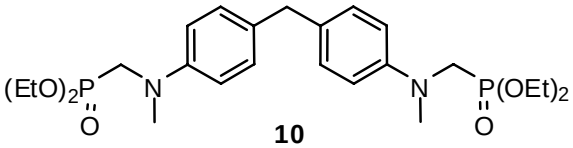
Following the *Typical Procedure*, bis(4-(dimethyl(amino)phenyl)methane (260 mg, 1.00 mmol) reacted with diethyl phosphonate (204 μL, 1.50 mmol) in the presence of $FeCl_2$ (15

mol %) at 60 °C for 24 h to furnish **9** (168 mg, 43 %) and **10** (162 mg, 31 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 10:15:2).



9

Viscous oil; R_f = 0.55; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (t, *J* = 7.0 Hz, 6 H), 2.88 (s, 6 H), 2.98 (s, 3 H), 3.65 (d, $^2J_{H,P}$ = 7.6 Hz, 2 H), 3.78 (s, 2 H), 4.02–4.10 (m, 4 H), 6.66 (d, *J* = 8.4 Hz, 2 H), 6.73 (d, *J* = 8.4 Hz, 2 H), 7.01–7.05 ppm (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.5 (d, $J_{C,P}$ = 5.7 Hz), 39.3, 39.8, 40.9, 50.3 (d, $^1J_{C,P}$ = 162 Hz), 62.1 (d, $J_{C,P}$ = 6.9 Hz), 112.9, 113.2 (d, $J_{C,P}$ = 1.1 Hz), 129.3, 129.4, 130.1, 131.1, 147.7 (d, $J_{C,P}$ = 2.8 Hz), 149.0 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 23.79 ppm; HRMS (EI): *m/z* = 390.2084, calcd. for $C_{21}H_{31}N_2O_3P$: 390.2072; IR (ATR): ν = 2980, 2903, 2801, 1613, 1516, 1477, 1408, 1391, 1342, 1247, 1227, 1186, 1162, 1098, 1049, 1020, 946, 860, 794 cm^{-1}.

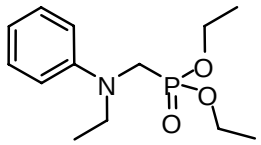


10

Viscous oil; R_f = 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (t, *J* = 7.0 Hz, 12 H), 2.97 (s, 6 H), 3.63 (d, $^2J_{H,P}$ = 7.6 Hz, 4 H), 3.76 (s, 2 H), 4.02–4.08 (m, 8 H), 6.71 (d, *J* = 8.6 Hz, 4 H), 7.00 ppm (d, *J* = 8.6 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.4 (d, $J_{C,P}$ = 5.7 Hz), 39.2, 39.7, 50.2 (d, $^1J_{C,P}$ = 161 Hz), 62.0 (d, $J_{C,P}$ = 7.0 Hz), 113.1 (d, $J_{C,P}$ = 1.1 Hz), 129.3, 130.9, 147.6 ppm (d, $J_{C,P}$ = 2.8 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 23.76 ppm; HRMS (EI): *m/z* = 526.2356, calcd. for $C_{25}H_{40}N_2O_6P_2$: 526.2362; IR (ATR): ν = 2982, 2905, 1613, 1569, 1516, 1477, 1441, 1391, 1365, 1225, 1363, 1099, 1047, 1017, 955, 860, 795, 725 cm^{-1}.

Following the *Typical Procedure*, bis(4-(dimethyl(amino)phenyl)methane (260 mg, 1.00 mmol) reacted with diethyl phosphonate (544 µL, 4.00 mmol) in the presence of $FeCl_2$ (15 mol %) and *t*BuOOH (768 µL, 4.00 mmol) at 60 °C for 24 h to furnish **10** (399 mg, 76 %) after column chromatography (*n*-pentane/ethyl acetate/triethylamine 10:15:2).

Diethyl (ethyl(phenyl)amino)methylphosphonate (12)

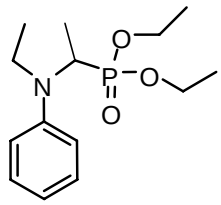


12

Following the *Typical Procedure*, *N*-ethyl-*N*-methylaniline (138 mg, 1.00 mmol) reacted with diethyl phosphonate (272 µL, 2.00 mmol) in the presence of $FeCl_2$ (20 mol %) at 60 °C for 24 h to furnish **12** (225 mg, 83 %) after column chromatography (*n*-pentane/diethyl ether/triethylamine 15:4:1).

Known compound; see ref.[S5]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.15 (t, *J* = 7.0 Hz, 3 H), 1.25 (t, *J* = 7.0 Hz, 6 H), 3.50 (q, *J* = 7.1 Hz, 2 H), 3.67 (d, $^2J_{H,P}$ = 8.0 Hz, 2 H), 4.02–4.13 (m, 4 H), 6.70 (t, *J* = 7.6 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 2 H), 7.18–7.23 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 10.7, 16.5 (d, $J_{C,P}$ = 5.6 Hz), 45.1, 47.1 (d, $J_{C,P}$ = 164 Hz), 62.2 (d, $J_{C,P}$ = 7.0 Hz), 112.8 (d, $J_{C,P}$ = 1.1 Hz), 116.9 (d, $J_{C,P}$ = 0.8 Hz), 129.1 (d, $J_{C,P}$ = 0.5 Hz), 147.7 ppm (d, $J_{C,P}$ = 1.4 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 23.76 ppm; HRMS (EI): *m/z* = 271.1330, calcd. for $C_{13}H_{22}NO_3P$: 271.1337; IR (ATR): ν = 2978, 2929, 2907, 2872, 1598, 1505, 1446, 1389, 1351, 1222, 1177, 1020, 958, 846, 774, 745, 691 cm^{-1}.

Diethyl 1-(ethyl(phenyl)amino)ethylphosphonate (14)



14

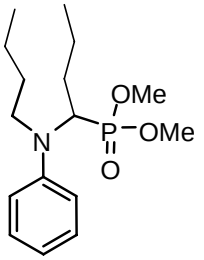
Following the *Typical Procedure*, *N,N*-diethylaniline (162 µL, 1.00 mmol) reacted with diethyl phosphonate (272 µL, 2.00 mmol) in the presence of $FeCl_2$ (20 mol %) at 60 °C for 24 h to furnish **14** (168 mg, 59 %) after column chromatography (*n*-pentane/diethyl ether/triethylamine 15:2:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13-1.19 (m, 6 H), 1.27 (t, *J* = 7.0 Hz, 3 H), 1.45 (dd, $J_{H,P}$ = 16.8 Hz, $J_{H,H}$ = 7.2 Hz, 3 H), 3.43-3.55 (m, 2 H), 3.93-3.99 (m, 1 H), 4.03-4.06 (m, 3 H), 4.14-4.23 (m, 1 H), 6.71 (t, *J* = 7.2 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 7.19-7.22 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.5 (d, $J_{C,P}$ = 5.4 Hz), 13.9 (d, $J_{C,P}$ = 2.0 Hz), 16.4 (d,

[S5] E. K. Fields, *J. Am. Chem. Soc.* **1952**, *74*, 1528–1531.

$J_{C,P}$ = 2.5 Hz), 16.5 (d, $J_{C,P}$ = 2.4 Hz), 39.9, 52.2 (d, $J_{C,P}$ = 156 Hz), 61.5 (d, $J_{C,P}$ = 7.4 Hz), 62.5 (d, $J_{C,P}$ = 7.1 Hz), 114.4 (d, $J_{C,P}$ = 1.4 Hz), 117.4, 129.0, 147.9 ppm (d, $J_{C,P}$ = 4.8 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 26.41 ppm; HRMS (EI): *m/z* = 285.1494, calcd. for $C_{14}H_{24}NO_3P$: 285.1494; IR (ATR): ν = 2978, 2932, 2905, 2872, 1597, 1500, 1447, 1390, 1376, 1348, 1241, 1198, 1040, 1019, 955, 746, 691 cm^{-1}.

Dimethyl 1-(butyl(phenyl)amino)butylphosphonate (16)

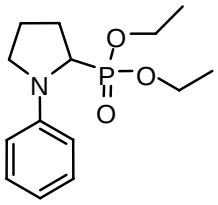


16

Following the *Typical Procedure*, *N,N*-dibutylaniline (234 μL, 1.00 mmol) reacted with dimethyl phosphonate (188 μL, 2.00 mmol) in the presence of $FeCl_2$ (30 mol %) at 60 °C for 24 h to furnish **16** (147 mg, 47 %) after column chromatography (*n*-pentane/ethyl acetate 15:10).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86-0.94 (m, 6 H), 1.31-1.38 (m, 3 H), 1.43-1.51 (m, 2 H), 1.54-1.63 (m, 1 H), 1.72-1.81 (m, 1 H), 1.87-1.97 (m, 1 H), 3.33 (t, *J* = 7.8 Hz, 2 H), 3.62-3.65 (m, 6 H), 4.00-4.10 (m, 1 H), 6.72 (t, *J* = 7.4 Hz, 1 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 7.20 ppm (t, *J* = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8 (d, $J_{C,P}$ = 1.6 Hz), 13.9, 20.0 (d, $J_{C,P}$ = 4.8 Hz), 20.3, 29.6 (d, $J_{C,P}$ = 1.4 Hz), 30.4 (d, $J_{C,P}$ = 6.4 Hz), 45.3, 52.1 (d, $J_{C,P}$ = 7.2 Hz), 52.9 (d, $J_{C,P}$ = 7.1 Hz), 57.6 (d, $J_{C,P}$ = 150 Hz), 114.8 (d, $J_{C,P}$ = 1.4 Hz), 117.6, 129.0, 148.9 ppm (d, $J_{C,P}$ = 2.6 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ 28.90 ppm; HRMS (EI): *m/z* = 313.1795, calcd. for $C_{16}H_{28}NO_3P$: *m/z* 313.1807; IR (ATR): ν = 2956, 2933, 2872, 1598, 1499, 1459, 1365, 1347, 1306, 1251, 1181, 1027, 819, 746, 692 cm^{-1}.

Diethyl 1-phenylpyrrolidin-2-ylphosphonate (18)

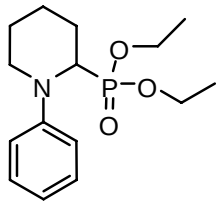


18

Following the *Typical Procedure*, 1-phenylpyrrolidine (150 mg, 1.00 mmol) reacted with diethyl phosphonate (408 µL, 3.00 mmol) in the presence of $FeCl_2$ (30 mol %) under reflux for 24 h to furnish **18** (206 mg, 73 %) after column chromatography (*n*-pentane/diethyl ether/ ethyl acetate 10:12:2).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.17 (t, *J* = 7.0 Hz, 3 H), 1.30 (t, *J* = 7.0 Hz, 3 H), 2.00–2.09 (m, 2 H), 2.31–2.39 (m, 2 H), 3.13-3.20 (m, 1 H), 3.57 (t, *J* = 8.2 Hz, 1 H), 3.88-3.94 (m, 1 H), 4.01–4.15 (m, 4 H), 6.71–6.80 (m, 3 H), 7.20–7.25 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.45 (d, $J_{C,P}$ = 3.8 Hz), 16.51 (d, $J_{C,P}$ = 4.2 Hz), 24.3, 27.8, 49.7 (d, $J_{C,P}$ = 2.3 Hz), 56.4 (d, $^1J_{C,P}$ = 168 Hz), 61.9 (d, $J_{C,P}$ = 7.5 Hz), 62.5 (d, $J_{C,P}$ = 7.1 Hz), 113.1 (d, $J_{C,P}$ = 0.7 Hz), 117.0 (d, $J_{C,P}$ = 0.9 Hz), 128.8 (d, $J_{C,P}$ = 0.7 Hz), 147.8 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 25.59 ppm; HRMS (EI): *m/z* = 283.1330, calcd. for $C_{14}H_{22}NO_3P$: 283.1337; IR (ATR): ν = 2979, 2930, 2906, 1598, 1503, 1479, 1456, 1391, 1359, 1334, 1244, 1160, 1046, 1018, 956, 746, 690 cm^{-1}.

Diethyl 1-phenylpiperidin-2-ylphosphonate (20).



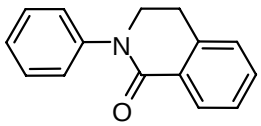
20

Following the *Typical Procedure*, 1-phenylpiperidine (163 mg, 1.00 mmol) reacted with diethyl phosphonate (408 µL, 3.00 mmol) in the presence of $FeCl_2$ (30 mol %) under reflux for 24 h to furnish **20** (259 mg, 81 %) after column chromatography (*n*-pentane/diethyl ether/ ethyl acetate 10:12:2).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.06 (t, *J* = 7.2 Hz, 3 H), 1.21 (t, *J* = 7.0 Hz, 3 H), 1.54–1.59 (m, 1 H), 1.64–1.72 (m, 2 H), 1.80–1.86 (m, 1 H), 1.94–2.13 (m, 2 H), 3.46–3.59 (m, 2 H), 3.72–3.82 (m, 1 H), 3.91–3.99 (m, 3 H), 4.20–4.26 (m, 1 H), 6.73 (t, *J* = 7.2 Hz,

1 H), 6.88 (d, J = 8.0 Hz, 2 H), 7.19 ppm (t, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.4 (qd, $J_{C,P}$ = 5.9 Hz), 20.4 (td, $J_{C,P}$ = 2.4 Hz), 24.7 (td, $J_{C,P}$ = 1.5 Hz), 25.1 (td, $J_{C,P}$ = 4.5 Hz), 44.2 (t), 54.5 (dd, $J_{C,P}$ = 144 Hz), 61.2 (td, $J_{C,P}$ = 7.4 Hz), 61.7 (td, $J_{C,P}$ = 7.0 Hz), 115.9 (dd, $J_{C,P}$ = 1.4 Hz), 118.3 (d), 128.9 (d), 150.7 ppm (sd, $J_{C,P}$ = 2.4 Hz), signal multiplicities were assigned on the basis of additional HSQC experiments; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 26.26 ppm; HRMS (ESI+): *m/z* = 320.1385 [M + $^{23}Na^+$], calcd. for [$C_{15}H_{24}NO_3P$ + $^{23}Na^+$]: 320.1860; IR (ATR): ν = 2979, 2936, 2867, 1597, 1578, 1497, 1444, 1385, 1248, 1162, 1049, 1018, 953, 752, 692 cm^{-1}.

2-Phenyl-3,4-dihydroisoquinolin-1(2H)-one (23)[S6]



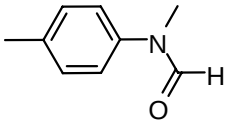
23

Following the *Typical Procedure*, 2-phenyl-1,2,3,4-tetrahydroisoquinoline (210 mg, 1.00 mmol) reacted with diethyl phosphonate (408 µL, 3.00 mmol) in the presence of $FeCl_2$ (20 mol %) under reflux for 24 h to furnish **23** (185 mg, 83 %) after column chromatography (*n*-pentane/ ethyl acetate / triethylamine 10:12:2).

Solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.13 (t, J = 6.4 Hz, 2 H), 3.98 (t, J = 6.4 Hz, 2 H), 7.22–7.26 (m, 2 H), 7.36–7.47 (m, 6 H), 8.14 ppm (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.6, 49.4, 125.3, 126.2, 126.9, 127.2, 128.7, 128.9, 132.0, 138.3, 143.1, 164.2 ppm; HRMS (EI): *m/z* = 223.0991, calcd. for $C_{15}H_{13}NO$: 223.0997; mp 94–97 °C (lit.:[S6a] mp 98–100 °C).

[S6] (a) C.-Y. Cheng, H.-B. Tsai, M.-S. Lin, *J. Heterocycl. Chem.* **1995**, *32*, 73–77; (b) M. Cherest, X. Lusinchi, *Tetrahedron* **1982**, *38*, 3471–3478.

***N*,4'-Dimethylformanilide (24)**



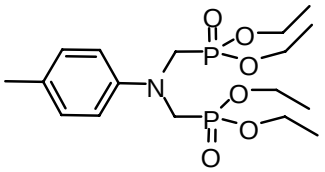
24

Following the *Typical Procedure*, 4-methyl-*N,N*-dimethylaniline (147 µL, 1.00 mmol) reacted with phosphonic acid (166 mg, 2.00 mmol) in the presence of $FeCl_2$ (20 mol %) under reflux for 16 h to furnish the desired product (91 mg, 61 %) after column chromatography (*n*-pentane/diethyl ether/ ethyl acetate 15:5:3).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.34 (s, 3 H), 3.27 (s, 3 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 8.40 ppm (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.8, 32.2, 122.5, 130.1, 136.3, 139.6, 162.3 ppm.

Known compound; the ^{1}H and ^{13}C NMR spectroscopic data agree with those given in ref.[S7].

***N*,*N*-Bis(diethoxyphosphorylmethyl)-*p*-toluidine (25a)**



25a

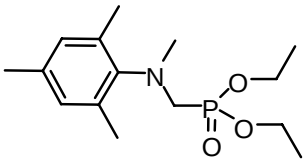
Analogous to the *Typical Procedure*, 4-methyl-*N,N*-dimethylaniline (147 µL, 1.00 mmol) reacted with diethyl phosphonate (680 µL, 5.00 mmol) in the presence of $FeCl_2$ (20 mol %) and *t*BuOOH (960 µL, 5.00 mmol) at 60 °C for 24 h to furnish **25a** (175 mg, 43 %) and **3a** (122 mg, 45 %) after column chromatography (*n*-pentane/ ethyl acetate/ triethylamine 10:10:2).

Viscous oil; R_f = 0.25; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (t, *J* = 7.0 Hz, 12 H), 2.21 (s, 3 H), 3.91 (d, $^2J_{H,P}$ = 6.0 Hz, 4 H), 4.00–4.07 (m, 8 H), 6.81 (d, *J* = 8.6 Hz, 2 H), 6.99 ppm (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.4 ($^3J_{C,P}$ = 5.7 Hz), 20.2, 46.8 ($^1J_{C,P}$ = 156.0 Hz), 62.1 ($^2J_{C,P}$ = 7.0 Hz), 113.6 (d, $J_{C,P}$ = 1.1 Hz), 127.4, 129.4, 145.3 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 23.70 ppm (virtual $J_{P,P}$ = 18.6 Hz), the virtual coupling between the

[S7] *Spectral Database of Organic Compounds* (SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/), National Institute of Advanced Industrial Science and Technology (AIST), Japan, 18.12.2009; SDBS No.: 51707.

two ^{31}P nuclei causes higher order signals in the ^{13}C NMR spectrum (at 16.4, 46.8, and 62.1 ppm) and NMR spectral synthesis[S8] was employed to calculate the coupling constants $J_{C,P}$ listed above; HRMS (EI): *m/z* = 407.1626, calcd. for $C_{17}H_{31}NO_6P_2$: 407.1627; IR (ATR): ν = 2982, 2909, 2869, 1617, 1574, 1521, 1478, 1388, 1247, 1162, 1018, 958, 880, 801, 774, 728 cm^{-1}.

_N_-(Diethoxyphosphorylmethyl)-_N_-methyl-mesidine (3t)



3t

Following the *Typical Procedure*, *N,N*-dimethylmesidine (184 µL, 1.00 mmol) reacted with diethyl phosphonate (272 µL, 2.00 mmol) at 60 °C for 24 h to furnish **3t** (116 mg, 39 %) and **25b** (243 mg, 56 %) after column chromatography (*n*-pentane/ ethyl acetate/ triethylamine 10:10:2).

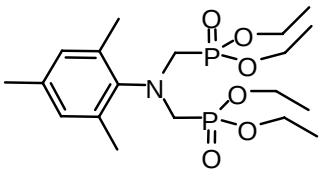
Known compound; the ^1H NMR spectroscopic data agree with those given in ref.[S9]

Viscous oil; ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.27 (t, *J* = 7.0 Hz, 6 H), 2.20 (s, 3 H), 2.27 (s, 6 H), 2.85 (s, 3 H), 3.41 (d, $^2J_{H,P}$ = 8.4 Hz, 2 H), 4.03–4.11 (m, 4 H), 6.79 ppm (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.4 (d, $J_{C,P}$ = 5.9 Hz), 18.6 (d, $J_{C,P}$ = 0.5 Hz), 20.6, 41.9 (d, $J_{C,P}$ = 0.7 Hz), 52.2 (d, $^1J_{C,P}$ = 166 Hz), 61.5 (d, $J_{C,P}$ = 6.9 Hz), 129.4, 134.8, 136.5, 146.7 ppm (d, $J_{C,P}$ = 8.5 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 25.13 ppm; HRMS (EI): *m/z* = 299.1644, calcd. for $C_{15}H_{26}NO_3P$: 299.1650; IR (ATR): ν = 2981, 2917, 2863, 2790, 1680, 1609, 1485, 1444, 1392, 1374, 1340, 1236, 1098, 1022, 959, 852, 781, 752 cm^{-1}.

[S8] D. S. Stephenson, G. Binsch, *J. Magn. Reson.* **1980**, *37*, 395–407.

[S9] G. Bidan, M. Genies, R. Renaud, *Electrochim. Acta* **1981**, *26*, 275–282.

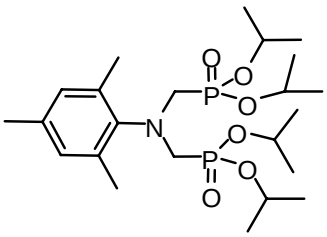
***N*,*N*-Bis(diethoxyphosphorylmethyl)mesidine (25b).**



25b

Analogous to the *Typical Procedure*, *N,N*-dimethylmesidine (184 µL, 1.00 mmol) reacted with diethyl phosphonate (544 µL, 4.00 mmol) in the presence of $FeCl_2$ (20 mol %) and *t*BuOOH (960 µL, 5.00 mmol) under reflux for 24 h to furnish **25b** (282 mg, 65 %) and **3t** (56 mg, 19 %) after column chromatography (*n*-pentane/ ethyl acetate/ triethylamine 10:10:2).
Viscous oil; R*f* = 0.35; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.14 (t, *J* = 7.0 Hz, 12 H), 2.15 (s, 3 H), 2.28 (s, 6 H), 3.64 (d, $J_{H,P}$ = 4.8 Hz, 4 H), 3.85–3.96 (m, 8 H), 6.73 ppm (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.2 ($^3J_{C,P}$ = 6.0 Hz), 19.0, 20.5, 48.5 ($^1J_{C,P}$ = 153.7 Hz), 61.5 ($^2J_{C,P}$ = 6.7 Hz), 129.5, 134.5, 135.7 (t, $J_{C,P}$ = 1.7 Hz), 143.8 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 25.20 ppm (virtual $J_{P,P}$ = 18.0 Hz), the virtual coupling between the two ^{31}P nuclei causes higher order signals in the ^{13}C NMR spectrum (at 16.2, 48.5, and 61.5 ppm) and NMR spectral synthesis[S8] was employed to calculate the coupling constants $J_{C,P}$ listed above; HRMS (EI): *m/z* = 435.1927, calcd. for $C_{19}H_{35}NO_6P_2$: 435.1940; IR (ATR): ν = 2983, 2909, 2869, 1609, 1483, 1444, 1392, 1368, 1224, 1162, 1019, 958, 879, 852, 778, 729 cm^{-1}.

***N*,*N*-Bis(diisopropoxyphosphorylmethyl)mesidine (25c).**

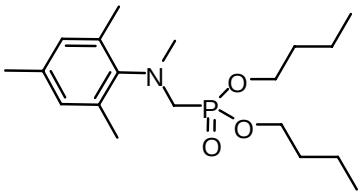


25c

Analogous to the *Typical Procedure*, *N,N*-dimethylmesidine (184 µL, 1.00 mmol) reacted with diisopropyl phosphonate (850 µL, 5.00 mmol) in the presence of $FeCl_2$ (20 mol %) and *t*BuOOH (960 µL, 5.00 mmol) under reflux for 24 h to furnish **25c** (339 mg, 69 %) and **3u** (49 mg, 15 %) after column chromatography (*n*-pentane/ ethyl acetate/ triethylamine 10:4:1).
Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.07 (d, *J* = 6.0 Hz, 12 H), 1.20 (d, *J* = 6.0 Hz, 12 H), 2.15 (s, 3 H), 2.28 (s, 6 H), 3.61 (d, $^2J_{H,P}$ = 4.0 Hz, 4 H), 4.54–4.59 (m, 4 H), 6.72 ppm (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.2, 20.6, 23.7 ($^3J_{C,P}$ = 4.6 Hz), 24.0 ($^3J_{C,P}$ = 3.9

Hz), 49.8 ($^1J_{C,P}$ = 154.1 Hz, $^3J_{C,P}$ = –0.7 Hz), 70.2 ($^2J_{C,P}$ = 7.1 Hz), 129.5, 134.1, 135.7 (t, $J_{C,P}$ = 1.9 Hz), 144.0 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 24.08 ppm (virtual $J_{P,P}$ = 21.1 Hz), the virtual coupling between the two ^{31}P nuclei causes higher order signals in the ^{13}C NMR spectrum (at 23.7, 24.0, 49.8, and 70.2 ppm) and NMR spectral synthesis[S8] was employed to calculate the coupling constants $J_{C,P}$ listed above; HRMS (EI): *m/z* = 491.2560, calcd. for $C_{23}H_{43}NO_6P_2$: 491.2566; IR (ATR): ν = 2959, 2934, 2874, 1608, 1484, 1465, 1380, 1227, 1201, 1062, 1020, 974, 907, 851, 795, 735 cm^{-1}.

_N_-(Dibutoxyphosphorylmethyl)-_N_-methyl-mesidine (3v)

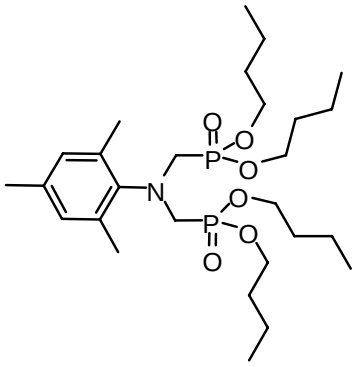


3v

Following the *Typical Procedure*, *N,N*-dimethylmesidine (184 µL, 1.00 mmol) reacted with dibutyl phosphonate (850 µL, 2.00 mmol) in the presence of $FeCl_2$ (20 mol %) under reflux for 24 h to furnish **3v** (145 mg, 41 %) and **25d** (191 mg, 35 %) after column chromatography (*n*-pentane/ ethyl acetate/ triethylamine 10:3:1).

Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (t, *J* = 7.4 Hz, 6 H), 1.30-1.39 (m, 4 H), 1.55-1.62 (m, 4 H), 2.20 (s, 3 H), 2.26 (s, 6 H), 2.84 (s, 3 H), 3.40 (d, $^2J_{H,P}$ = 8.4 Hz, 2 H), 3.95-4.01 (m, 4 H), 6.78 ppm (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.6, 18.69, 18.74, 20.6 (d, $J_{C,P}$ = 2.7 Hz), 32.6 (d, $J_{C,P}$ = 5.8 Hz), 42.0, 52.1 (d, $^1J_{C,P}$ = 166 Hz), 65.4 (d, $J_{C,P}$ = 7.1 Hz), 129.5, 134.9, 136.6, 146.7 ppm (d, $J_{C,P}$ = 8.2 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 25.33 ppm; HRMS (EI): *m/z* = 355.2269, calcd. for $C_{19}H_{34}NO_3P$: 355.2276; IR (ATR): ν = 2959, 2933, 2873, 1608, 1486, 1464, 1379, 1238, 1064, 1021, 975, 906, 852, 798, 731 cm^{-1}.

***N,N*-Bis(dibutoxyphosphorylmethyl)mesidine (25d)**



25d

Analogous to the *Typical Procedure*, *N,N*-dimethylmesidine (184 µL, 1.00 mmol) reacted with dibutyl phosphonate (1.02 mL, 5.00 mmol) in the presence of $FeCl_2$ (20 mol %) and TBHP (960 µL, 5.00 mmol) under reflux for 24 h to furnish **25d** (437 mg, 80 %) and **3v** (42 mg, 12 %) after column chromatography (*n*-pentane/ ethyl acetate/ triethylamine 10:4:1).
Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.77 (t, J = 7.4 Hz, 12 H), 1.14–1.23 (m, 8 H), 1.37–1.44 (m, 8 H), 2.10 (s, 3 H), 2.23 (s, 6 H), 3.59 (d, $J_{H,P}$ = 4.4 Hz, 4 H), 3.76–3.80 (m, 8 H), 6.68 ppm (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.3, 18.4, 18.9, 20.4, 32.2 ($^{3}J_{C,P}$ = 6.0 Hz), 48.3 ($^{1}J_{C,P}$ = 153.5 Hz), 65.1 ($^{2}J_{C,P}$ = 7.0 Hz), 129.4, 134.3, 135.6 (t, $J_{C,P}$ = 1.7 Hz), 143.5 ppm; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 25.40 ppm (virtual $J_{P,P}$ = 18.8 Hz), the virtual coupling between the two ^{31}P nuclei causes higher order signals in the ^{13}C NMR spectrum (at 32.2, 48.3, and 65.1 ppm) and NMR spectral synthesis[S8] was employed to calculate the coupling constants $J_{C,P}$ listed above; HRMS (EI): *m/z* = 547.3195, calcd. for $C_{27}H_{51}NO_6P_2$: 547.3192; IR (ATR): ν = 2981, 2907, 2868, 2819, 1616, 1520, 1477, 1443, 1391, 1360, 1295, 1244, 1230, 1188, 1164, 1100, 1046, 1019, 957, 861, 801, 774, 715, 692 cm^{-1}.

3.5.5 Reactions of the *N,O*-acetal 27a with 2a

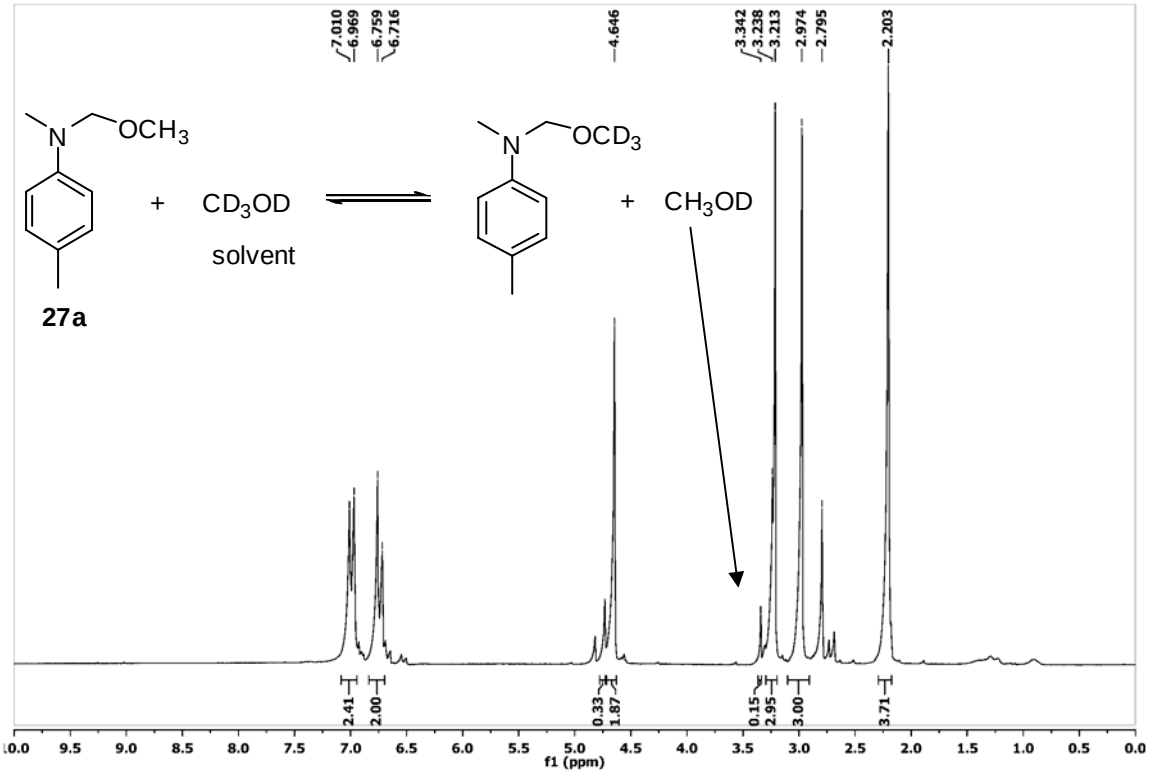
With $FeCl_2$: Under an atmosphere of dry N_2, a 25 mL Schlenk flask was charged with iron(II) chloride (10 mol-%, 6.5 mg). Then, **27a** (75 mg, 0.50 mmol), diethyl phosphonate **2a** (136 µL, 1.00 mmol,), and MeOH (1.0 mL) were added successively by syringe. The mixture was stirred at room temperature for 15 h. At the end of the reaction, the reaction mixture was poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (n-pentane/ethyl acetate/triethylamine 15:4:1) to give **3a** (120 mg, 89 %).

Without $FeCl_2$: Under an atmosphere of dry N_2, a 25 mL Schlenk flask was charged with the **27a** (75 mg, 0.50 mmol), diethyl phosphonate **2a** (136 µL, 1.00 mmol), and MeOH (1.0 mL). The mixture was stirred at room temperature for 15 h. At the end of the reaction, the reaction mixture was poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (*n*-pentane/ethyl acetate/triethylamine 15:4:1) to give **3a** (116 mg, 86 %).

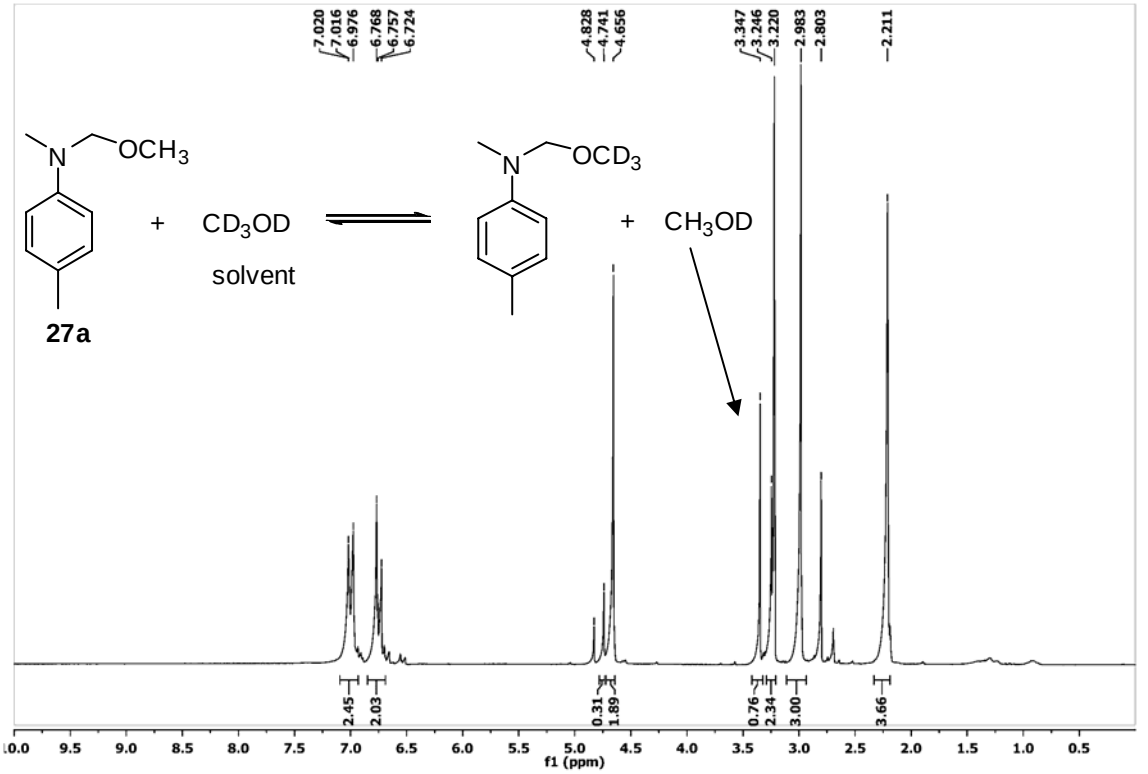
3.5.6 In Situ Experiment for Slow Formation of CH_3OD

27a (20 mg) and CD_3OD were mixed in a NMR tube at room temperature and the mixture was analyzed ^1H NMR after 2 min and 24 h, respectively. The formation of CH_3OD was followed by the increase spectroscopy of the resonance at 3.24 ppm, as shown in the ^1H NMR spectra below.

after **2 min**

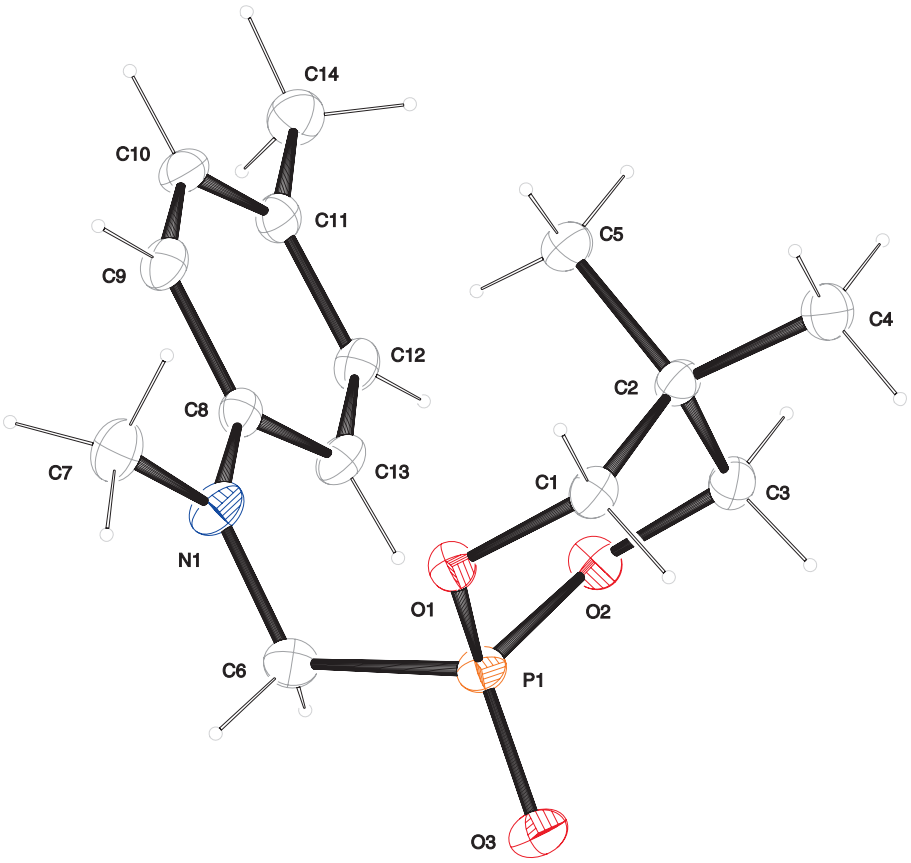


after **24 h**



3.5.7 X-ray Crystal Structure Analysis of 3s

The data collection was performed on a Oxford Diffraction XCalibur diffractometer. The structure was solved by direct methods with SIR97[S10] and refined with SHELXL-97.[S11] CCDC 761658 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



[S10] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32,* 115–119.

[S11] G. M. Sheldrick, *Acta Crystallogr. Sect. A: Found. Crystallogr.* **2008**, *64,* 112–122.

3s. Crystallographic data:

	3s
net formula	$C_{14}H_{22}NO_3P$
M_r/g mol^{-1}	283.303
crystal size/mm	0.41 × 0.17 × 0.06
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	monoclinic
space group	$P2_1/c$
a/Å	19.2608(9)
b/Å	6.3513(3)
c/Å	12.5159(7)
α/°	90
β/°	105.063(5)
γ/°	90
V/Å^3	1478.48(13)
Z	4
calc. density/g cm^{-3}	1.27277(11)
μ/mm^{-1}	0.190
absorption correction	'multi-scan'
transmission factor range	0.97751–1.00000
refls. measured	10157
R_{int}	0.0368
mean σ(I)/I	0.0492
θ range	4.38–26.34
observed refls.	1950
x,y (weighting scheme)	0.0524, 0
hydrogen refinement	constr
refls in refinement	2995
parameters	176
restraints	0
$R(F_{obs})$	0.0377
$R_w(F^2)$	0.0957
S	0.906
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.259
min electron density/e Å^{-3}	−0.230

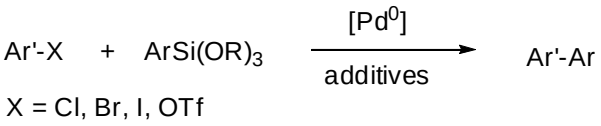
Chapter 4

Palladium-Catalyzed Direct Arylations of Azoles with Aryl Silicon and Tin Reagents

Wei Han, Peter Mayer, Armin R. Ofial, *Chem. Eur. J.* **2011**, *17*, 6904-6908.

4.1 Introduction

Biaryls Ar–Ar' are structural motifs found in many biologically active compounds, pharmaceuticals, agrochemicals, and functional materials.[1–4] Regioselective C–C bond formation between carbocyclic and/or heterocyclic arenes has, therefore, been a longstanding goal in synthetic organic chemistry and stimulated the development of numerous catalytic methods for the synthesis of biaryls. Generally, the classical Kumada, Negishi, Stille, and Suzuki couplings require the reaction of aryl halides or, more recently, sulfonates Ar–X with Grignard, organozinc, organotin, or organoboron reagents Ar'-Met.[5] Hiyama and Denmark developed cross-couplings of Ar–X with organosilicon compounds which are of particular interest because of the low toxicity and safe handling of the organosilanes (Scheme 1).[6] Furthermore, the low electronegativity difference between carbon and silicon provides an advantageously high degree of compatibility with functional groups.

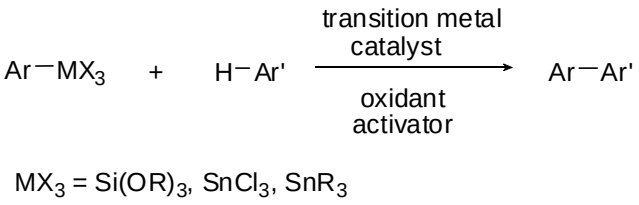


Scheme 1. Classical Hiyama reaction.

Yet, organosilicon reagents possess a lower nucleophilic reactivity than other organometallic reagents. Nevertheless, cleavage of C–Si bonds (306 kJ mol^{-1}) and formation of F–Si (595 kJ mol^{-1}) or O–Si bonds (444 kJ mol^{-1}) provides the thermodynamic driving force for the efficient activation of organosilanes by promotors (fluoride or hydroxide ions) for transmetalation reactions.[7]

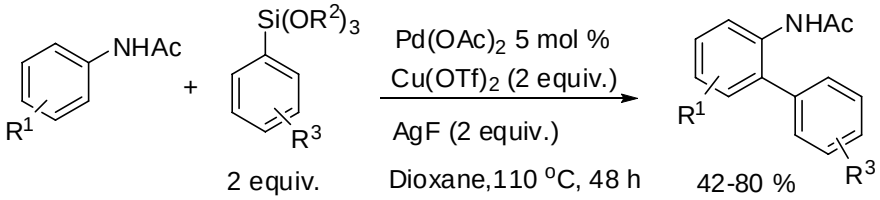
In recent years, transition metal-catalyzed direct C–H functionalization attracted considerable interest.[8,9] Direct arylations through cleavage of C–H bonds represent an environmentally and economically attractive strategy which avoids the extra introduction of functional groups at one of the potential coupling partners and hence provides a more direct access to the synthetic targets.[10,11]

So far, only few intermolecular direct oxidative arylations of $C(sp^2)$–H bonds with organoelement compounds using group 14 elements have been investigated (Scheme 2).[12–14]

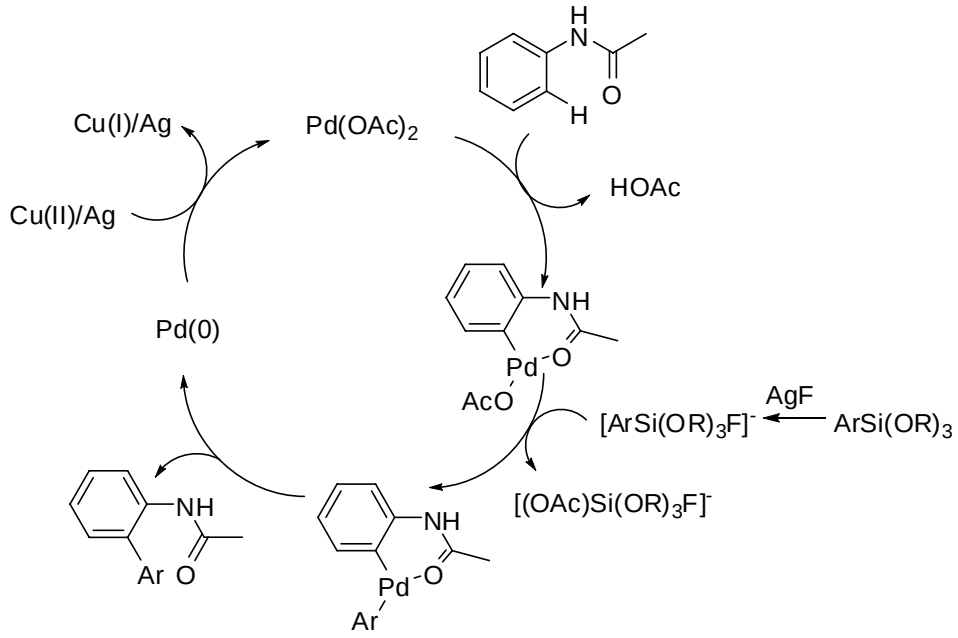


Scheme 2. Direct arylations with aryl silanes and stannanes.

The group of Shi[12a] reported on palladium-catalyzed direct arylations of acetanilides with trialkoxy(aryl)silanes (Scheme 3). In the transformation, the key to success is that $Cu(OTf)_2$ is helpful to inhibit the homocouplings of aryl silanes. In order to investigate the mechanism, a palladacycle was prepared which stoichiometrically reacted with arylsilanes to give the desired product. Additionally, it was found that electron-donating groups on the acetanilides favored the transformation. On the basis of these results, the authors proposed that the reaction starts by electrophilic attack of Pd(II) under the help of the acetamino group to form a palladacycle. In a transmetalation, the aryl group from the fluoride-activated silicon reagent is transferred to the palladacycle to give a diaryl palladium intermediate, which undergoes a reductive elimination to afford the product (Scheme 4).



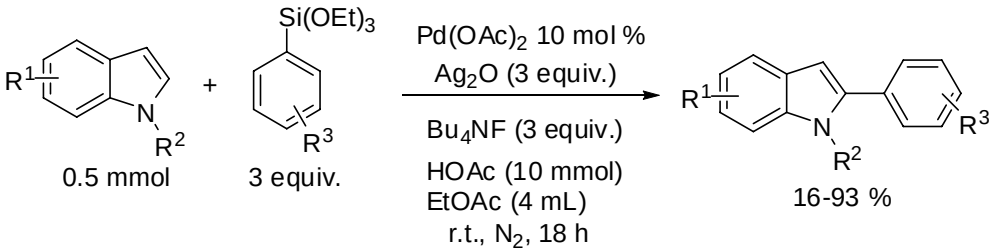
Scheme 3. Pd-catalyzed direct ortho arylation of acetanilides with aryl silicon reagents.



Scheme 4. Proposed mechanism for direct ortho-arylation of acetanilides with aryl silicon reagents.

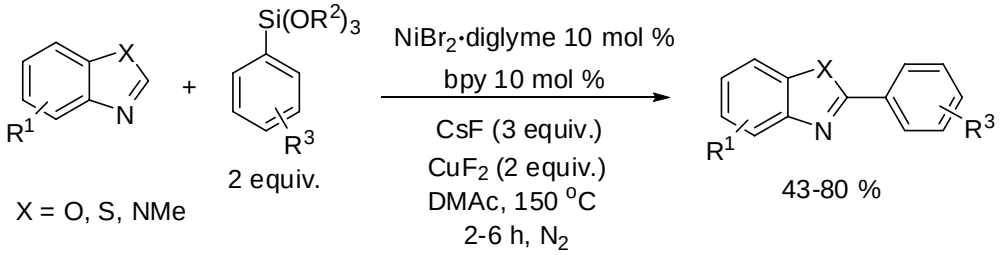
Subsequently, Loh[12b] and co-workers described a similar system to catalyze the direct arylation of cyclic enamides with arylsilanes which gave the cross-coupling products in moderate to excellent yields.

Methods for the derivatization of heterocyclic arenes find broad academic and industrial use due to their importance in medicinal chemistry and in materials science.[15] The regioselective arylation at the 2-position of indoles by arylsiloxanes was achieved by Zhang and coworkers already at room temperature by using $Pd(OAc)_2$ as the catalyst in combination with a Ag_2O/Bu_4NF mixture (3 equiv.) in acid solution (Scheme 5). The cross coupling of electron-rich indoles with electron-poor arylsiloxanes was found to be most effective under these conditions.[12c]

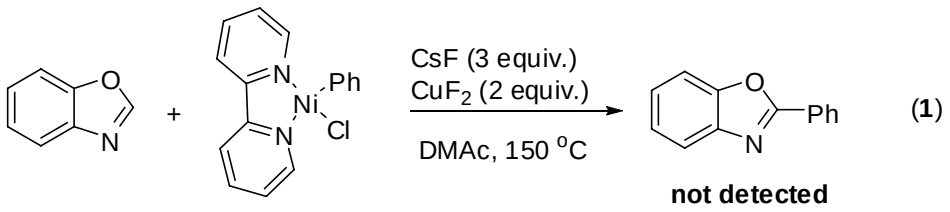


Scheme 5. Pd-catalyzed direct arylation of indoles with arylsiloxanes.

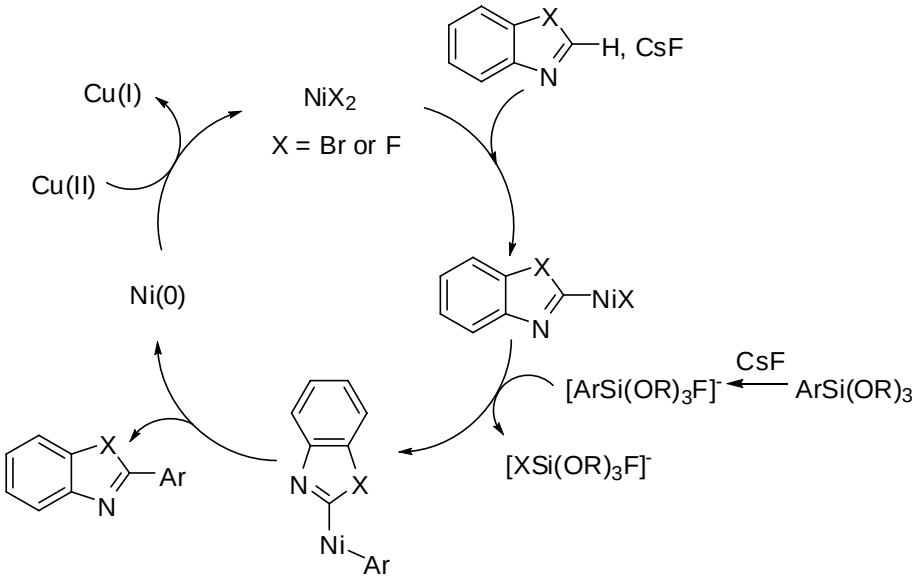
Recently, Miura and co-workers studied direct arylations and vinylations of azoles and 1,3,4-oxadiazoles by trialkoxy(aryl)- and trialkoxy(vinyl)silanes, respectively, using $NiBr_2$·diglyme/2,2'-bipyridine (bpy) as the catalyst (10 mol-%) in the presence of CuF_2 (2 equiv.) and CsF (3 equiv.) for the cross coupling under harsh conditions (Scheme 6).[13] The organonickel complex [PhNiCl(bpy)] was isolated and did not react with benzoxazole as shown in Eq. **1**, which implied [(heteroaryl)$Ni^{II}X$] rather than [(aryl)$Ni^{II}X$] (X = halide) as a key intermediate in the reaction. A plausible process of the transformation should initiate by nickelation of the heteroarene to give the [(heteroaryl)$Ni^{II}X$] intermediate. Then, the arylsilane transmetalates to the intermediate with the aid of CsF to yield [(heteroaryl)Ni^{II}(aryl)], which undergoes reductive elimination to furnish the desired product and releases Ni(0). The Ni(0) is reoxidized to Ni(II)X_2 with CuF_2 to complete the catalytic loop (Scheme 7).



Scheme 6. Nickel-catalyzed direct coupling of heteroarenes with organosilanes.

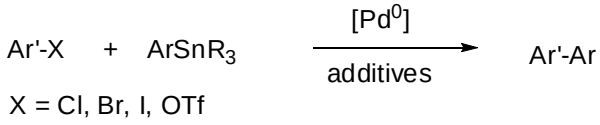


(**1**)



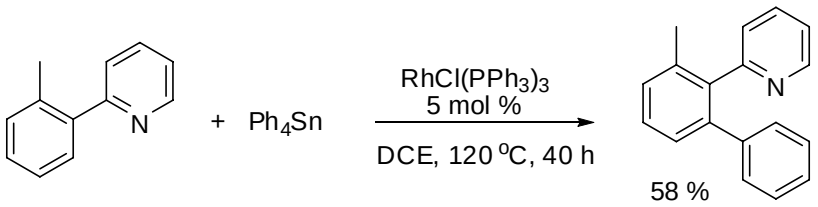
Scheme 7. Proposed mechanism for nickel-catalyzed direct coupling of heteroarenes with organosilanes.

The classical cross coupling between tin reagents and Ar–X is known as Stille reaction, as shown in Scheme 8.[16] However, methods for metal-catalyzed C–H arylation with organotin compounds are rare.



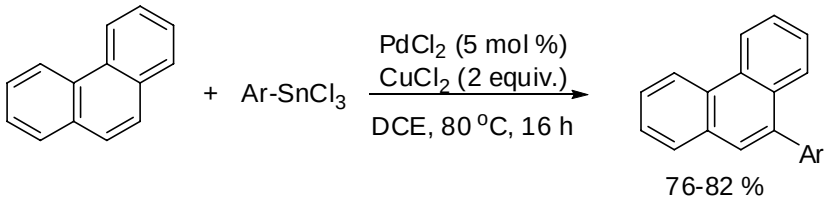
Scheme 8. Classical Stille reaction.

Oi, Inoue and co-workers reported the $RhCl(PPh_3)_3$-catalyzed direct *ortho*-arylation of 2-arylpyridines with tetraarylstannanes (Scheme 9).[14a] The transformation proceeded regioselectively as a result of the directing effect of the nitrogen atom.

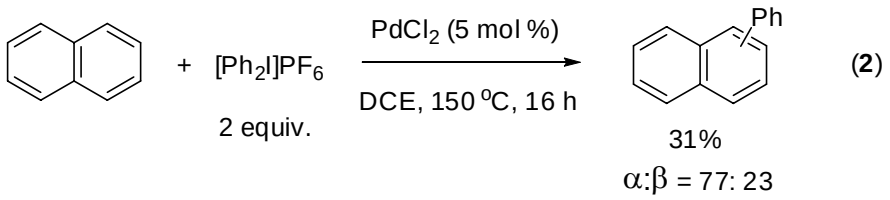


Scheme 9. Rhodium-catalyzed direct arylation of 2-*o*-tolylpyridine with tetraphenylstannane.

Recently, the same group described a C–H bond arylation of arenes with aryltin reagents using $PdCl_2$ as catalyst and $CuCl_2$ as oxidant (Scheme 10). [14b] Considering the fact that arylpalladium(IV) species can be generated via reaction of palladium(II) complexes with diaryliodonium salts, the authors performed the reaction between $[Ph_2I]PF_6$ and naphthalene in the presence of a catalytic amount of $PdCl_2$ which gave a comparable result as for the corresponding normal reaction (Eq. **2**). This implied that a arylpalladium(IV) intermediate is present in the course of the reaction.



Scheme 10. Pd-catalyzed arylation of phenanthrene with aryltintrichlorides.



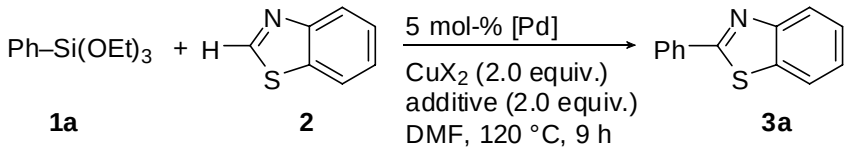
Herein, we report on a convenient, efficient and "ligand-free" palladium-catalyzed direct arylation of $C(sp^2)$–H at C-2 of various azoles with trialkoxy(aryl)silanes and aryl tin compounds.

4.2 Results and Discussion

4.2.1 Optimizing the Catalytic System

The reaction of triethoxy(phenyl)silane (**1a**) with benzothiazole (**2**) served as a model system to identify and optimize potential catalysts and the critical reaction parameters (Table 1). The palladium catalysts were examined first. $PdCl_2$ or $Pd(PPh_3)_2Cl_2$ afforded **3a** in moderate yields (Table 1, entries 1 and 2). The use of $Pd(OAc)_2$ as the catalyst provided an excellent yield (93 %) of **3a** under the same conditions (Table 1, entry 3).

Table 1. Optimization of the palladium-catalyzed direct C–H phenylation of **2** with triethoxy-(phenyl)silane (**1a**).[a]



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

Entry	Pd catalyst	CuX_2 / Additive	Yield[b] [%]
1	$PdCl_2$	$Cu(OAc)_2 \cdot H_2O$ / AgF	52
2	$Pd(PPh_3)_2Cl_2$	$Cu(OAc)_2 \cdot H_2O$ / AgF	40
3	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$ / AgF	93[c]
4	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$[d] / AgF	66[e]
5	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$	–
6	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$ / FeF_3	trace
7	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$ / KF	–
8	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$ / nBu$_4$NF·H_2O	10
9	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$ / CsF	–
10	$Pd(OAc)_2$	$Cu(OAc)_2 \cdot H_2O$ / CuF_2	57
11	$Pd(OAc)_2$	AgF	< 10
12	$Pd(OAc)_2$	$CuCl_2$ / AgF	57
13	$Pd(OAc)_2$	$CuBr_2$ / AgF	66
14	$Pd(OAc)_2$	$Cu(OTf)_2$ / AgF	trace
15	$Pd(OAc)_2$	CuF_2 / AgOAc	82

[a] A mixture of **1a** (0.50 mmol), **2** (0.25 mmol), Pd-catalyst (5 mol-%), CuX_2 (0.50 mmol), and additive (0.50 mmol) in solvent (2.5 mL) was stirred at 120 °C for 9 h under air. [b] Yield of isolated **3a**. [c] Without $Pd(OAc)_2$ as a catalyst, only trace amounts of **3a** were obtained. [d] Only 1 equivalent of $Cu(OAc)_2 \cdot H_2O$ (0.25 mmol) was used. [e] The formation of biphenyl from homocoupling of **1a** was observed.

Of the fluorides tested, AgF was most effective (Table 1, entry 3), followed by CuF_2 (Table 1, entries 3 and 10). Very poor results were obtained in the absence of fluoride, in the

presence of other fluoride sources (FeF_3, KF, nBu$_4$NF·H_2O, or CsF, see Table 1), or under the acid conditions used by Zhang and coworkers for the arylation of indoles with arylsiloxanes.[12c,17]

It has previously been reported that silver ions can serve as oxidants that oxidize Pd^0 to Pd^{II}, thus completing the catalytic cycle.[12,18] In fact, precipitation of Ag^0 was observed when the reaction had finished. However, when AgF was employed as the only oxidant a very low yield of **3a** was obtained (Table 1, entry 11). This observation showed that a proper co-oxidant was indispensable for the reaction to proceed smoothly. The use of 2 equivalents of $Cu(OAc)_2·H_2O$ proved to be the best choice (Table 1, entry 3). While $CuCl_2$ and $CuBr_2$ in combination with AgF still gave moderate results, the presence of $Cu(OTf)_2$ was ineffective (Table 1, entries 12–14). Decreasing the amount of $Cu(OAc)_2·H_2O$ to 1.0 equivalent (Table 1, entry 4) reduced the yield of **3a** to 66 % because of the triethoxy(phenyl)silane's homocoupling to biphenyl. Cross-coupling of **1a** with **2** by using the less expensive activator/oxidant combination CuF_2 and AgOAc produced **3a** in 82 % yield (Table 1, entry 15). This result shows that the source of Cu^{2+}, Ag^+, F^-, and acetate ions was not crucial for the success of the cross coupling, presumably because of the complete dissociation of the dissolved copper and silver fluorides and acetates in *N*,*N*-dimethylformamide (DMF).

As summarized in Figure 1, formation of **3a** by the direct C-2 phenylation of **2** by **1a** could be achieved in several solvents under conditions otherwise analogous to those in entry 3 of Table 1. However, the use of DMF gave the best results.

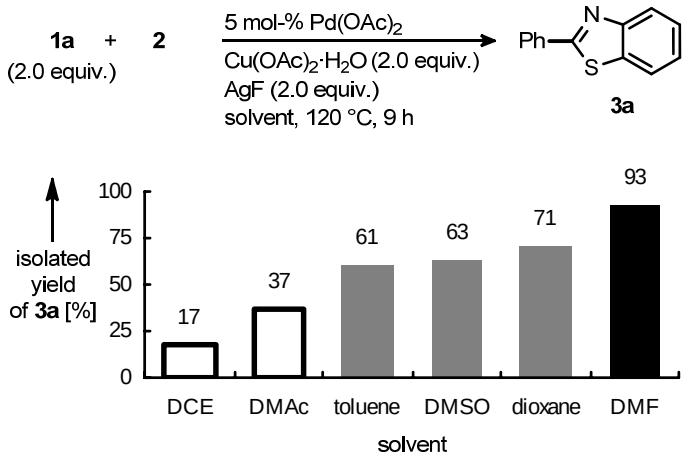


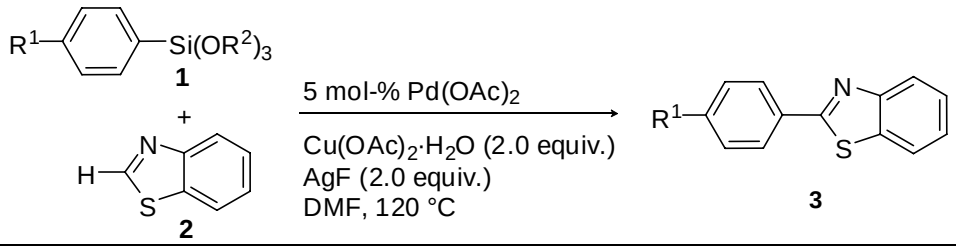
Figure 1. Solvent dependence of the cross coupling of **2** with **1a** to form **3a** (DCE = 1,2-dichloroethane, DMAc = *N*,*N*-dimethylacetamide, DMSO = dimethylsulfoxide).

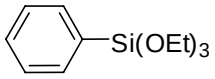
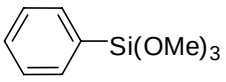
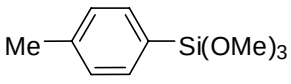
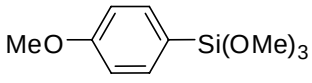
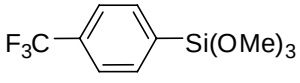
4.2.2 Scope and Limitations

With the optimized conditions in hand (*cf.* Table1, entry 3), we explored the scope of this cross coupling method by using commercially available trialkoxy(aryl)silanes as reaction partners for benzothiazole (**2**) (Table 2).

Triethoxy(phenyl)silane (**1a**) reacted at a similar rate as the trimethoxy-substituted silane **1a'**, consistent with previous reports on palladium-catalyzed direct arylations of

Table 2. Palladium-catalyzed direct C–H arylation of benzothiazole (**2**) with various trialkoxy(aryl)silanes **1**.[a]

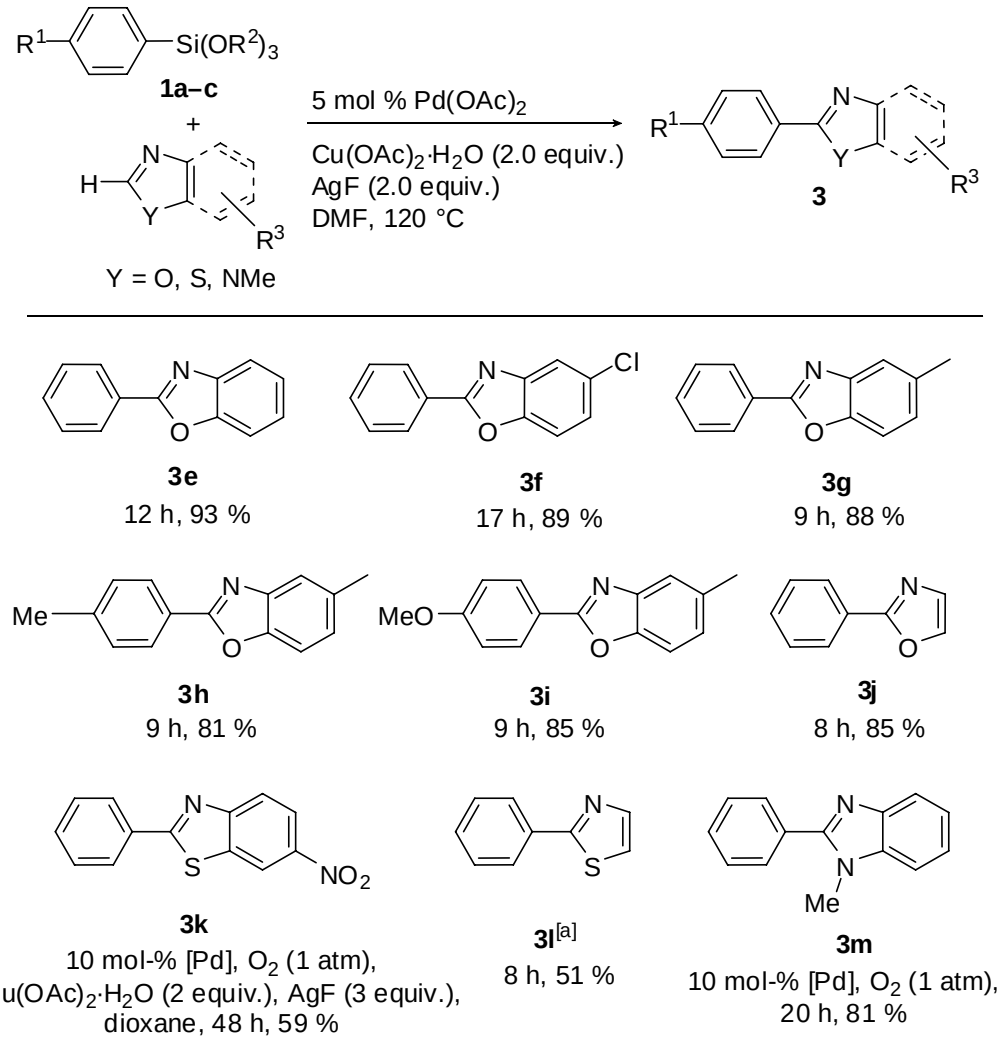


Trialkoxy(aryl)silane **1**		*t* [h]	Product **3**	Yield[b] [%]
	**1a**	9	**3a**	93
	**1a'**	12	**3a**	91
	**1b**	12	**3b**	86
	**1c**	20	**3c**	83
	**1d**	18	**3d**	87

[a] A mixture of **1** (0.50 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (0.50 mmol), and AgF (0.50 mmol) in DMF (2.5 mL) was stirred at 120 °C for the given time under air. [b] Yields of isolated products.

acetanilides, enamides, and indoles, respectively, with arylsilanes.[12] Variation of the substituents R^1 at the aryl ring of **1** was unproblematic, and electron-rich and electron-deficient aryl(trimethoxy)silanes coupled with **2** to generate **3a**–**d** in high yields and without the necessity to exclude moisture.

Next, the couplings of the organosilicon compounds **1a**–**c** with different azoles were

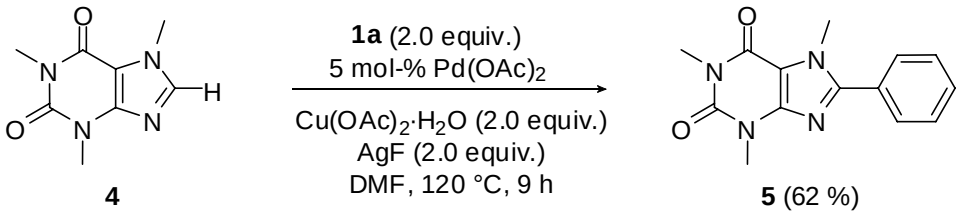


Scheme 11. Products of the palladium-catalyzed direct coupling of trialkoxy (aryl)silanes **1a-c** (2.0 equiv.) with various azoles (yields of isolated products). [a] Additionally 2,2'-bithiazole was isolated (22 % yield).

examined (Scheme 11). Benzoxazoles carrying electron-donating or electron-withdrawing groups cross coupled regioselectively at C-2 with the aryl silanes **1a**–**c** to form **3e**–**i** in

excellent yields. The chloro substituent in 5-position of the heteroaryl part of **3f** offers the potential for further functionalization. Also the parent oxazole was phenylated by **1a** at C-2 to yield **3j** (85 %).

Different from the results in Table 2, which demonstrate that benzothiazole (**2**) is an effective coupling partner for silanes **1a**–**d**, the more electron-poor 6-nitrobenzothiazole required coupling in 1,4-dioxane as the solvent under an O_2 atmosphere in the presence of 10 mol-% Pd-catalyst and an enhanced amount of fluoride (3.0 equiv.) to furnish **3k** in an acceptable yield (59 %). The reaction of parent thiazole with **1a** afforded 2-phenylthiazole (**3*l***) as the major product (51 %) which was accompanied by the homocoupling product 2,2'-bithiazole (22 % yield).[19] The successful transformation of 1-methyl-benzimidazole by arylsilane **1a** to **3m** encouraged us to extend our studies to further heterocycles that contain an imidazole unit. For example, caffeines with an aryl moiety at C-8 are of interest as potent and selective antagonists at human adenosine receptors and have therefore been the targets of recent metal-catalyzed direct arylations.[10*l*,20,21] Indeed, the direct coupling between **4** and triethoxy(phenyl)silane (**1a**) furnished 8-phenyl caffeine (**5**) in 62 % yield (Scheme 12). Crystallizing **5** from a pentane/ethyl acetate/diethyl ether solvent mixture delivered crystals adequate for single crystal X-ray analysis (Figure 2).[22]



Scheme 12. Formation of 8-phenyl caffeine (**5**) by palladium-catalyzed direct phenylation of caffeine (**4**) with **1a**.

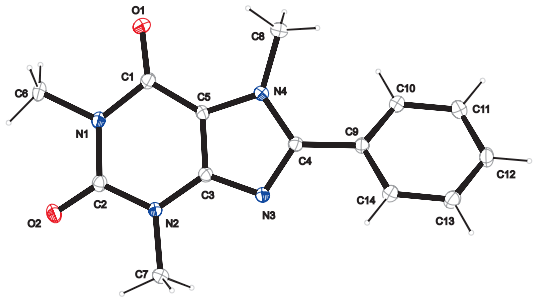
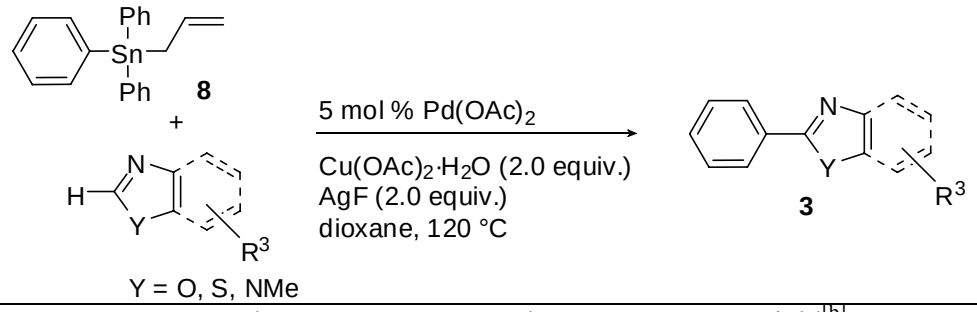
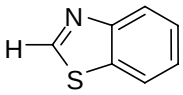
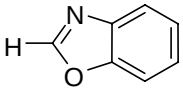
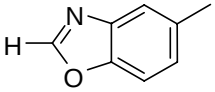
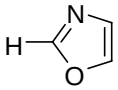
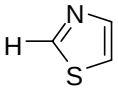
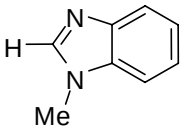


Figure 2. X-ray single crystal structure of 8-phenyl caffeine (**5**). The shown thermal ellipsoids in the crystal structure of **5** are drawn at the 50% probability level. The twist angle between the least squares planes of the phenyl and the xanthine rings is 33.50 (7)°.

Thus far in this work, the transfer of aryl groups originating from aryl silicon reagents was studied. Moreover, aryl tin compounds were found to be capable of transferring a phenyl group to C-2 of azoles under oxidative conditions. With 1,4-dioxane as the solvent instead of DMF, but under conditions otherwise identical to those optimized for the reactions of azoles with trialkoxy(aryl)silanes, allyltriphenylstannane (**8**) turned out to be a selective phenylation reagent for the thiazoles and oxazoles listed in Table 3. The analogous reaction of **8** with *N*-methyl-benzimidazole gave only poor results, however. Competing allylation by **8** was not observed for any of the azoles listed in Table 3.

Table 3. Palladium-catalyzed direct C–H phenylation of azoles **2** with allyltriphenylstannane (**8**).[a]



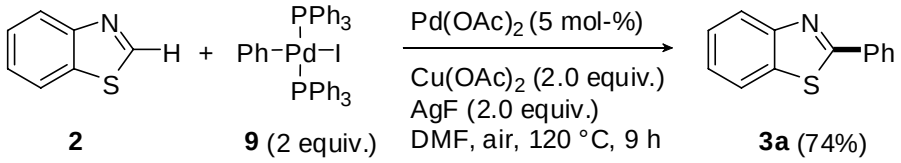
Azole	*t* [h]	Product **3**	Yield[b] [%]
	24	**3a**	58
	18	**3e**	79 (62)[c]
	24	**3g**	71 (40)[d]
	24	**3j**	76
	48	***3l***	65[e]
	24	**3m**	35[f]

[a] A mixture of **8** (0.50 mmol), (benz)azole (0.25 mmol), $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (0.50 mmol), and AgF (0.50 mmol) in 1,4-dioxane (2.5 mL) was stirred at 120 °C for the given time under air. [b] Yields of isolated products. [c] By using Ph_3SnCl instead of **8**. [d] In DMF as the solvent. [e] In addition, 2,2'-bithiazole was isolated (30 % yield). [f] By using $Pd(OAc)_2$ (10 mol %) and an O_2 atmosphere (balloon).

4.2.3 Mechanism

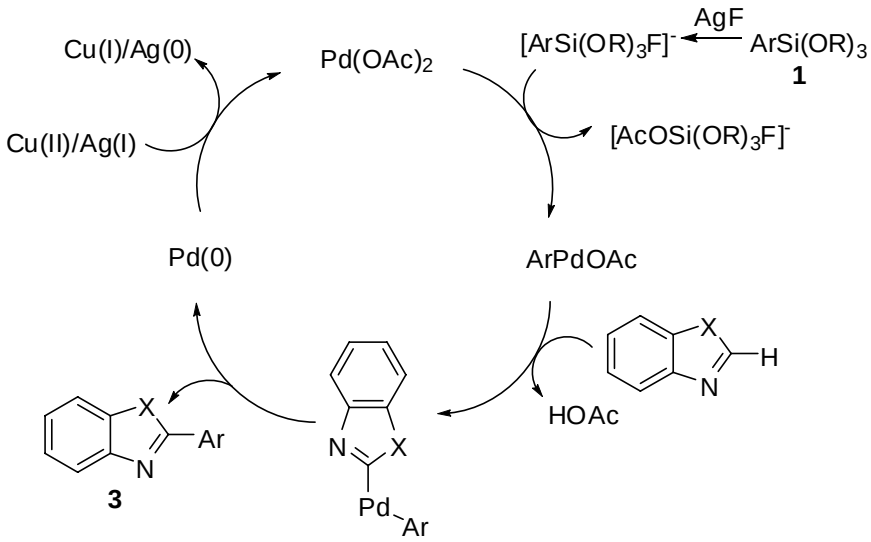
To obtain insight into the nickel-catalyzed version of the direct C-H arylation of azoles with trialkoxy(aryl)silanes, Miura and coworkers studied the reaction of the isolated [PhNiCl(bpy)] complex with a mixture of benzoxazole and CsF (3 equiv.) with or without CuF_2 (2 equiv.).[13]

They reported for both experiments, that the formation of 2-phenyl-benzoxazole (**3e**) was not detected (see Eq. **1**). On this basis, they assumed that not [(aryl)$Ni^{II}X$] but rather [(heteroaryl)$Ni^{II}X$] are the key intermediates in the catalytic cycle. The situation is less clear in our case because benzothiazole (**2**) has previously been shown to readily undergo direct arylation with the isolated complex [*trans*-$PhPdI(PPh_3)_2$] (**9**) (Scheme 13).[23]



Scheme 13. Direct phenylation of **2** by the aryl palladium complex **9**.

It is reasonable to assume, therefore, that the catalytic cycle starts with a fluoride ion-assisted transmetalation of the silicon compound **1** (or the tin reagent **8**) with PdX_2 to form an [(aryl)$Pd^{II}X$] species, as depicted in Scheme 14. Subsequent C–H bond cleavage at the azole generates a mixed aryl heteroaryl palladium complex which undergoes reductive elimination to deliver the 2-arylated azoles **3** (or **5**) and a Pd^0 complex. To complete the catalytic cycle, the Pd^0 complex is reoxidized by Ag^+/Cu^{2+} ions. However, at present, we cannot exclude a reversal of the two initial steps. In this alternative scenario, the formation of a [(heteroaryl)$Pd^{II}X$] complex by C-H bond cleavage at the azole precedes the transmetalation by hypervalent aryl silicon or tin intermediates.



Scheme 14. Plausible mechanism.

It has previously been assumed that the scope of palladium catalysis for direct Hiyama-type arylation is limited to substrates carrying an acetamido group that assists by chelation in the crucial cyclopalladation step of the catalytic cycle.[13] Our results, in accord with the findings by Zhang for arylations of indoles,[12c] suggest that the use of a proper solvent (such as DMF or, alternatively, 1,4-dioxane) is also capable of effectively stabilizing the intermediate Pd complexes.

4.3 Conclusion

A facile and robust method has been developed for the direct C–H arylation at the C-2 position of azoles with trialkoxy(aryl)silanes **1**. Alternatively, allyltriphenylstannane (**8**) can be employed to achieve the 2-phenylation of azoles. Neither the assistance of a directing group nor anhydrous conditions or the presence of additional ligands for the palladium catalyst are necessary for the preparation of heterocycle-containing biaryls in good to excellent yields. The synthesis of druglike and/or pharmaceutically relevant molecules in a single step from commercially available starting materials underscores the utility of this process. Detailed mechanistic investigations and expanded applications of the methodology are in progress.

4.4 References

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[19] The analogous reaction of **1a** with the more electron-rich 4,5-dimethylthiazole yielded almost exclusively 4,4',5,5'-tetramethyl-2,2'-bithiazole (after 20 h, 86 % yield) from homocoupling. For copper-catalyzed homocouplings of heteroarenes, see: Y. Li, J. Jin, W. Qian, W. Bao, *Org. Biomol. Chem.* **2010**, *8*, 326-330.

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[21] a) H. A. Chiong, O. Daugulis, *Org. Lett.* **2007**, *9*, 1449-1451; b) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404-12405; c) H.-Q. Do, R. M. K. Khan, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 15185-15192; d) D. Zhao, W. Wang, S. Lian, F. Yang, J. Lan, J. You, *Chem. Eur. J.* **2009**, *15*, 1337-1340; e) L. Ackermann, A. Althammer, S. Fenner, *Angew. Chem.* **2009**, *121*, 207-210; *Angew. Chem. Int. Ed.* **2009**, *48*, 201-204; f) D. Zhao, W. Wang, F. Yang, J. Lan, L. Yang, G. Gao, J. You, *Angew. Chem.* **2009**, *121*, 3346-3350; *Angew. Chem. Int. Ed.* **2009**, *48*, 3296-3300.

[22] CCDC 771685 contains the supplementary crystallographic data for 8-phenyl-caffeine (**5**) reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[23] W. Han, P. Mayer, A. R. Ofial, *Angew. Chem. Int. Ed.* **2011**, *50*, 2178-2182.

4.5 Experimental Section

4.5.1. General

All reactions were carried out under air atmosphere. ^{1}H and ^{13}C NMR spectra of solutions in $CDCl_3$ were recorded on 400 MHz NMR spectrometers. Chemical shifts were expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals (δ_H 7.24 and δ_C 77.0 ppm). Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; m, multiplet. HRMS was performed on a Finnigan MAT 95Q mass spectrometer. Infrared spectra of neat substances were recorded on a Perkin-Elmer Spectrum BX II FT-IR spectrometer equipped with an ATR probe (diamond). Column chromatography was performed on silica gel by using *n*-pentane/ diethyl ether (15:3) as the eluent.

4.5.2 Materials

Commercially available azoles, trialkoxy(aryl)silanes, and allyltriphenylstannane (97 %, Aldrich) were used as received. Commercial solvents were used without further purification. The following palladium, copper, and fluoride salts were used: $Pd(OAc)_2$ (47.5 % Pd, Acros), $PdCl_2$ (Lancaster), $Pd(PPh_3)_2Cl_2$ (98 %, Lancaster), $Cu(OAc)_2 \cdot H_2O$ (99%, Fisher Scientific), $Cu(OTf)_2$ (98 %, ABCR), $CuBr_2$ (97 %, Fluka), $CuCl_2$ (97 %, Aldrich), AgF (99 %, Aldrich), FeF_3 (99 %, Strem), KF (Merck), $n Bu_4NF \cdot 3H_2O$ (99 %, Acros), CsF (99 %, Acros).

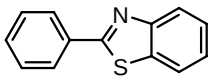
4.5.3 Palladium-Catalyzed Direct Coupling of Azoles with Trialkoxy-(aryl)silanes

***General Procedure A*:** Under air atmosphere, a round-bottom flask was charged with $Pd(OAc)_2$ (2.8 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.10 g, 0.50 mmol), and AgF (64 mg, 0.50 mmol). Then the azole (0.25 mmol) and the trialkoxy(aryl)silane **1** (0.50 mmol) were added

by using microliter syringes. After the addition of DMF (2.5 mL) the reaction mixture was stirred for 5 min at room temperature and then heated at 120 °C for the given time. After cooling to r.t., the reaction mixture was poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. Purification of the crude product by column chromatography (silica gel, eluent: *n*-pentane/Et_2O = 15:3) yielded the 2-aryl-azoles **3**.

2-Phenylbenzothiazole (3a)

Following *General Procedure A*, benzothiazole **2** (29 μL, 0.25 mmol) reacted with **1a** (0.12 mL, 0.50 mmol) for 9 h to give **3a** (49.1 mg, 93 %).



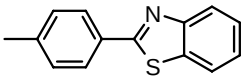
3a

Known compound [CAS Reg. No. 883-93-2]; the NMR spectroscopic data agree with those reported in ref. [S1].^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.40 (m, 1 H), 7.46–7.50 (m, 4 H), 7.88–7.91 (m, 1 H), 8.05–8.11 ppm (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 121.6, 123.2, 125.2, 126.3, 127.6, 129.0, 131.0, 133.6, 135.1, 154.2, 168.1 ppm; mp 113–113.5 °C.

2-(p-Tolyl)benzothiazole (3b)

Following *General Procedure A*, benzothiazole **2** (29 μL, 0.25 mmol) reacted with **1b** (0.11 mL, 0.50 mmol) for 12 h to afford **3b** (48.3 mg, 86 %).

[S1] a) H. Hachiya, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 1737-1740; b) J. Huang, J. Chan, Y. Chen, C. J. Borths, K. D. Baucom, R. D. Larsen, M. M. Faul, *J. Am. Chem. Soc.* **2010**, *132*, 3674-3675.

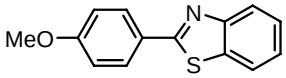


3b

Known compound [CAS Reg. No. 16112-21-3]; the ^{1}H NMR spectroscopic data agree with those reported in ref. [S1]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.41 (s, 3 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.34–7.37 (m, 1 H), 7.45–7.48 (m, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.97 (d, *J* = 8.0 Hz, 2 H), 8.04 ppm (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.5, 121.5, 123.0, 125.0, 126.2, 127.5, 129.7, 131.0, 134.9, 141.4, 154.2, 168.2 ppm; mp 70.5–72 °C.

2-(4-Methoxyphenyl)benzothiazole (3c)

Following *General Procedure A*, benzothiazole **2** (29 μL, 0.25 mmol) reacted with **1c** (0.11 mL, 0.50 mmol) for 20 h to produce **3c** (50.0 mg, 83 %).



3c

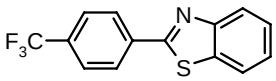
Known compound [CAS Reg. No. 6265-92-5]; the NMR spectroscopic data agree with those reported in ref. [S2]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.87 (s, 3 H), 6.99 (d, *J* = 8.8 Hz, 2 H), 7.31–7.35 (m, 1 H), 7.43–7.47 (m, 1 H), 7.85–7.87 (m, 1 H), 8.00–8.03 ppm (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 55.5, 114.4, 121.5, 122.8, 124.8, 126.2, 126.4, 129.1, 134.9, 154.2, 161.9, 167.8 ppm; mp 119–121 °C (ref. [S3]: mp 119–120 °C).

2-(4-(Trifluoromethyl)phenyl)benzothiazole (3d)

Following *General Procedure A*, benzothiazole **2** (29 μL, 0.25 mmol) reacted with **1d** (0.13 g, 0.50 mmol) for 18 h to afford **3d** (60.6 mg, 87 %).

[S2] *Spectral Database of Organic Compounds* (SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/), National Institute of Advanced Industrial Science and Technology (AIST), Japan, 07.04.2010; SDBS No.: 51357.

[S3] K. Inamoto, C. Hasegawa, K. Hiroya, T. Doi, *Org. Lett.* **2008**, *10*, 5147–5150.

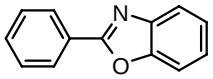


3d

Known compound [CAS Reg. No. 134384-31-9]; the NMR spectroscopic data agree with those reported in ref. [S1]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42 (t, *J* = 8.2 Hz, 1 H), 7.52 (t, *J* = 7.8 Hz, 1 H), 7.74 (d, *J* = 8.4 Hz, 2 H), 7.92 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 7.2 Hz, 1 H), 8.19 ppm (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 121.7, 123.6, 123.8 (q, $^{1}J_{C,F}$ = 272 Hz), 125.8, 126.0 (q, $^{3}J_{C,F}$ = 3.8 Hz), 126.7, 127.8, 132.5 (q, $^{2}J_{C,F}$ = 33 Hz), 135.2, 136.8, 154.1, 166.0 ppm; mp 157–159 °C (ref. [S1]: mp 161–162 °C).

2-Phenylbenzoxazole (3e)

Following *General Procedure A*, benzoxazole (30 mg, 0.25 mmol) reacted with **1a** (0.12 mL, 0.50 mmol) for 12 h to give **3e** (45.3 mg, 93 %).



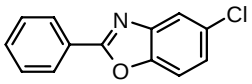
3e

Known compound [CAS Reg. No. 833-50-1]; the NMR spectroscopic data agree with those reported in ref. [S4]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.32–7.36 (m, 2 H), 7.50–7.53 (m, 3 H), 7.56–7.58 (m, 1 H), 7.75–7.78 (m, 1 H), 8.24–8.26 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 110.6, 120.0, 124.6, 125.1, 127.2, 127.6, 128.9, 131.5, 142.1, 150.8, 163.0 ppm; mp 100–102.5 °C.

5-Chloro-2-phenylbenzoxazole (3f)

Following *General Procedure A*, 5-chloro-benzoxazole (40 mg, 0.25 mmol) reacted with **1a** (0.12 mL, 0.50 mmol) for 17 h to furnish **3f** (50.9 mg, 89 %).

[S4] J. J. Lee, J. Kim, Y. M. Jun, B. M. Lee, B. H. Kim, *Tetrahedron* **2009**, *65*, 8821–8831.

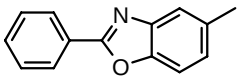


3f

Known compound [CAS Reg. No. 1019-90-5]; the NMR spectroscopic data agree with those reported in ref. [S4]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29–7.33 (m, 1 H), 7.47–7.54 (m, 4 H), 7.73 (s, 1 H), 8.22 ppm (d, *J* = 6.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 111.3, 120.0, 125.4, 126.7, 127.8, 129.0, 130.0, 131.9, 143.3, 149.4, 164.4 ppm; mp 104–104.5 °C.

5-Methyl-2-phenylbenzoxazole (3g)

Following *General Procedure A*, 5-methyl-benzoxazole (34 mg, 0.25 mmol) reacted with **1a** (0.12 mL, 0.50 mmol) for 9 h to furnish **3g** (45.9 mg, 88 %).

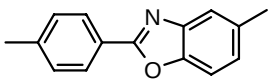


3g

Known compound [CAS Reg. No. 7420-86-2]; the NMR spectroscopic data agree with those reported in ref. [S4]. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.47 (s, 3 H), 7.14–7.15 (m, 1 H), 7.44 (d, *J* = 7.8 Hz, 1 H), 7.49–7.52 (m, 3 H), 7.53–7.54 (m, 1 H), 8.22–8.24 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 21.5, 109.9, 119.9, 126.2, 127.3, 127.5, 128.9, 131.4, 134.4, 142.3, 149.0, 163.1 ppm; mp 101.5–103 °C.

5-Methyl-2-(p-tolyl)benzoxazole (3h)

Following *General Procedure A*, 5-methyl-benzoxazole (34 mg, 0.25 mmol) reacted with **1b** (0.11 mL, 0.50 mmol) for 9 h to furnish **3h** (45.1 mg, 81 %).

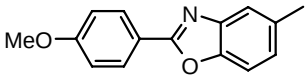


3h

Known compound [CAS Reg. No. 16155-94-5]; the NMR spectroscopic data agree with those reported in ref. [S5]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.42 (s, 3 H), 2.46 (s, 3 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0, 1 H), 7.51–7.52 (m, 1 H), 8.11 ppm (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.5, 21.6, 109.8, 119.7, 124.5, 126.0, 127.5, 129.6, 134.3, 141.9, 142.3, 148.9, 163.4 ppm; mp 136–137.5 °C.

2-(4-Methoxyphenyl)-5-methylbenzoxazole (3i)

Following *General Procedure A*, 5-methyl-benzoxazole (34 mg, 0.25 mmol) reacted with **1c** (0.11 mL, 0.50 mmol) for 9 h to furnish **3i** (50.7 mg, 85 %).

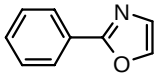


3i

Known compound [CAS Reg. No. 35876-70-1]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.46 (s, 3 H), 3.87 (s, 3 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 7.11 (d, *J* = 9.2 Hz, 1 H), 7.40 (d, *J* = 8.8 Hz, 1 H), 7.50 (s, 1 H), 8.16 ppm (d, *J* = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.5, 55.4, 109.7, 114.3, 119.5, 119.8, 125.7, 129.3, 134.2, 142.4, 148.9, 162.2, 163.2 ppm; mp 104.5–105.5 °C.

2-Phenyloxazole (3j)

Following *General Procedure A*, oxazole (17 µL, 0.25 mmol) reacted with **1a** (0.12 mL, 0.50 mmol) for 8 h to furnish **3j** (30.7 mg, 85 %).



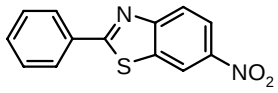
3j

[S5] a) L. Ackermann, S. Barfüsser, J. Pospech, *Org. Lett.* **2010**, *12*, 724–726; b) A. J. Blacker, M. M. Farah, M. I. Hall, S. P. Marsden, O. Saidi, J. M. J. Williams, *Org. Lett.* **2009**, *11*, 2039–2042.

Known compound [CAS Reg. No. 20662-88-8]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.22 (s, 1 H), 7.42–7.46 (m, 3 H), 7.69 (t, *J* = 0.6 Hz, 1 H), 8.02–8.05 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 126.3, 127.5, 128.4, 128.8, 130.3, 138.5, 162.0 ppm.

6-Nitro-2-phenylbenzothiazole (3k)

In analogy to *General Procedure A*, 6-nitro-benzothiazole (45 mg, 0.25 mmol) reacted with **1a** (0.12 mL, 0.50 mmol) in the presence of 10 mol-% $Pd(OAc)_2$ for 48 h in 1,4-dioxane under O_2 (1 atm). The crude product was purified by column chromatography (silica gel, eluent: *n*-pentane/ethyl acetate/triethylamine in a 15:4:1 ratio) to furnish **3k** (37.7 mg, 59 %).

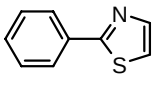


3k

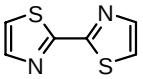
Known compound [CAS Reg. No. 38338-23-7]; the NMR spectroscopic data agree with those reported in ref. [S3]. ^{1}H NMR ($CDCl_3$, 400 MHz): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51–7.55 (m, 3 H), 8.10–8.14 (m, 3 H), 8.36 (dd, *J* = 9.0 Hz, *J* = 2.4 Hz, 1 H), 8.83 ppm (dd, *J* = 2.4 Hz, *J* = 0.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 118.2, 121.9, 123.3, 127.9, 129.3, 132.2, 132.7, 135.3, 144.9, 157.8, 173.8 ppm.; mp 177.5–180 °C

2-Phenylthiazole (3l) and 2,2'-bithiazole

Following *General Procedure A*, thiazole (18 µL, 0.25 mmol) reacted with **1a** (0.12 mL, 0.50 mmol) for 8 h to furnish ***3l*** (20.5 mg, 51 %) and 2,2'-bithiazole (4.6 mg, 22 %).



3l



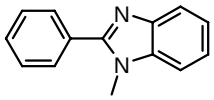
2,2'-bithiazole

3l: Known compound [CAS Reg. No. 1826-11-5]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.31 (d, *J* = 3.2 Hz, 1 H), 7.40–7.45 (m, 3 H), 7.85 (d, *J* = 3.2 Hz, 1 H), 7.94–7.97 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 118.8, 126.6, 128.9, 130.0, 133.6, 143.7, 168.4 ppm.

2,2'-bithiazole: Known compound [CAS Reg. No. 13816-21-2]; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42 (d, *J* = 3.2 Hz, 2 H), 7.88 ppm (d, *J* = 3.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 120.9, 143.9, 161.7 ppm; mp 99–101.5 °C.

1-Methyl-2-phenyl-benzimidazole (3m)

Following *General Procedure A*, 1-methyl-benzimidazole (33 mg, 0.25 mmol) reacted with **1a** (0.12 mL, 0.50 mmol) in the presence of 10 mol-% $Pd(OAc)_2$ for 20 h under O_2 (1 atm). The crude product was purified by column chromatography (silica gel, eluent: *n*-pentane/ethyl acetate/triethylamine in a 15:4:1 ratio) to furnish **3m** (42.1 mg, 81 %).



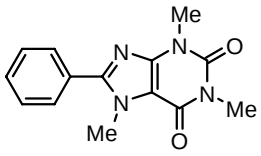
3m

Known compound [CAS Reg. No. 2622-63-1]; the ^{13}C NMR spectroscopic data agree with those reported in ref. [S6]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.86 (s, 3 H), 7.28–7.34 (m, 2 H), 7.38–7.40 (m, 1 H), 7.50–7.53 (m, 3 H), 7.75–7.77 (m, 2 H), 7.82–7.84 ppm (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 31.7, 109.6, 119.8, 122.5, 122.8, 128.2, 128.7, 129.5, 129.8, 136.5, 142.8, 153.7 ppm.

8-Phenyl-caffeine (5) = 3,7-dihydro-1,3,7-trimethyl-8-phenyl-1H-purine-2,6-dione

Following *General Procedure A*, caffeine **4** (49 mg, 0.25 mmol) reacted with **1a** (0.12 mL, 0.50 mmol) for 9 h. The crude product was purified by column chromatography (silica gel, eluent: *n*-pentane/ethyl acetate/triethylamine in a 15:4:1 ratio) to afford **5** (41.8 mg, 62 %).

[S6] *Spectral Database of Organic Compounds* (SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/), National Institute of Advanced Industrial Science and Technology (AIST), Japan, 07.04.2010; SDBS No.: 22471.



5

Known compound [CAS Reg. No. 6439-88-9]; the NMR spectroscopic data agree with those reported in ref. [S7]. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.42 (s, 3 H), 3.62 (s, 3 H), 4.04 (s, 3 H), 7.50–7.52 (m, 3 H), 7.66–7.68 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.0, 29.8, 33.9, 108.5, 128.4, 128.9, 129.2, 130.4, 148.3, 151.7, 152.1, 155.6 ppm; mp 178.6–179.5 °C (ref. [S7b]: mp 180–181 °C).

Details of the crystal structure determination of **5** are reported in Chapter 4.5.5.

4.5.4 Palladium-Catalyzed Direct Coupling of Azoles with Allyltriphenylstannane (8)

General Procedure B: Under air atmosphere, a round-bottom flask was charged with $Pd(OAc)_2$ (2.8 mg, 5 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.10 g, 0.50 mmol), and AgF (64 mg, 0.50 mmol). Then the azole (0.25 mmol) and allyltriphenylstannane **8** (0.50 mmol) were added by using microliter syringes. After the addition of 1,4-dioxane (2.5 mL) the reaction mixture was stirred for 10 min at room temperature and then heated at 120 °C for the given time. After cooling to r.t., the reaction mixture was poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. Purification of the crude product

[S7] a) K. Vollmann, C. E. Müller, *Heterocycles* **2002**, *57*, 871–879; b) L. Ackermann, A. Althammer, S. Fenner, *Angew. Chem.* **2009**, *121*, 207–210; *Angew. Chem. Int. Ed.* **2009**, *48*, 201–204; c) D. Zhao, W. Wang, F. Yang, J. Lan, L. Yang, G. Gao, J. You, *Angew. Chem. Int. Ed.* **2009**, *48*, 3296–3300.

by column chromatography (silica gel, eluent: *n*-pentane/Et_2O = 15:3) yielded the 2-aryl-azoles **3**.

2-Phenylbenzothiazole (3a)

Following *General Procedure B*, benzothiazole **2** (29 μL, 0.25 mmol) reacted with **8** (0.20 g, 0.50 mmol) for 24 h to give **3a** (30.6 mg, 58 %).

2-Phenylbenzoxazole (3e)

Following *General Procedure B*, benzoxazole (30 mg, 0.25 mmol) reacted with **8** (0.20 g, 0.50 mmol) for 18 h to give **3e** (38.5 mg, 79 %).

5-Methyl-2-phenylbenzoxazole (3g)

Following *General Procedure B*, 5-methyl-benzoxazole (34 mg, 0.25 mmol) reacted with **8** (0.20 g, 0.50 mmol) for 24 h to give **3g** (37.0 mg, 71 %).

2-Phenyloxazole (3j)

Following *General Procedure B*, oxazole (17 μL, 0.25 mmol) reacted with **8** (0.20 g, 0.50 mmol) for 24 h to give **3j** (27.4 mg, 76 %).

2-Phenylthiazole (3*l*)

Following *General Procedure B*, thiazole (18 μL, 0.25 mmol) reacted with **8** (0.20 g, 0.50 mmol) for 48 h to give **3*l*** (26.1 mg, 65 %) and 2,2'-bithiazole (6.3 mg, 30 %).

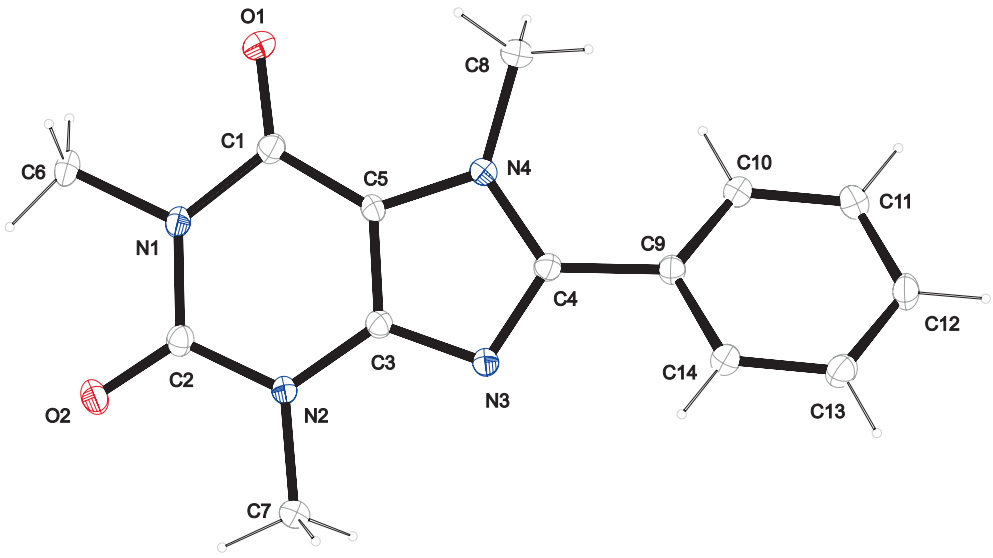
1-Methyl-2-phenyl-benzimidazole (3m)

In analogy to *General Procedure B*, 1-methyl-benzimidazole (33 mg, 0.25 mmol) reacted with **8** (0.20 g, 0.50 mmol) in the presence of 10 mol-% $Pd(OAc)_2$ for 24 h under O_2 (1 atm) to give **3m** (18.0 mg, 35 %).

4.5.5 X-Ray Crystal Structure Analysis of 5

The data collection was performed on a Oxford Diffraction XCalibur diffractometer. The structure was solved by direct methods with SIR97[S8] and refined with SHELXL-97.[S9]

CCDC 771685 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



5

[S8] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115–119.

[S9] G. M. Sheldrick, *Acta Crystallogr. Sect. A: Found. Crystallogr.* **2008**, *64*, 112–122.

Table S1. Crystallographic data for **5**.

	5
net formula	$C_{14}H_{14}N_4O_2$
M_r/g mol^{-1}	270.287
crystal size/mm	0.41 × 0.10 × 0.05
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	triclinic
space group	*P*1bar
a/Å	8.1479(6)
b/Å	8.7335(7)
c/Å	9.4929(9)
α/°	86.740(7)
β/°	66.996(8)
γ/°	87.882(7)
V/Å^3	620.71(9)
Z	2
calc. density/g cm^{-3}	1.4462(2)
μ/mm^{-1}	0.101
absorption correction	'multi-scan'
transmission factor range	0.98714–1.00000
refls. measured	4359
R_{int}	0.0249
mean σ(I)/I	0.0740
θ range	4.22–26.41
observed refls.	1468
x, y (weighting scheme)	0.0431, 0
hydrogen refinement	constr
refls in refinement	2516
parameters	184
restraints	0
$R(F_{obs})$	0.0399
$R_w(F^2)$	0.0923
S	0.859
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.196
min electron density/e Å^{-3}	−0.178

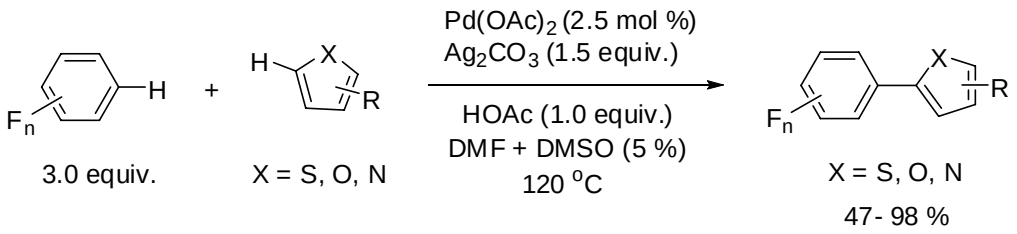
Chapter 5

Palladium-Catalyzed Dehydrogenative Cross Couplings of Azoles

Wei Han, Peter Mayer, Armin R. Ofial, *Angew. Chem. Int. Ed.* **2011**, *50*, 2178-2182.

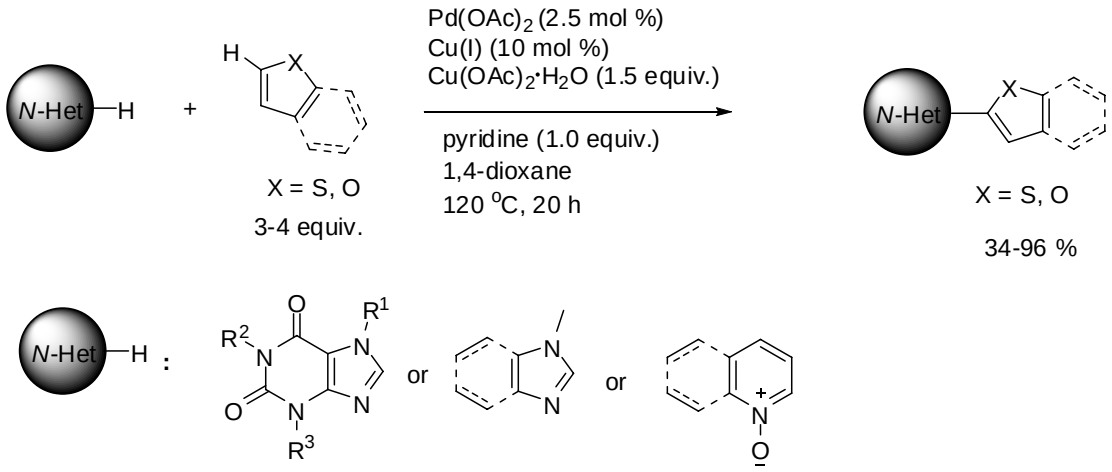
5.1 Introduction

Biaryl compounds play an important role in nature and many functional materials.[1] Classical transition metal-catalyzed methods for the synthesis of biaryls, such as Kumada, Negishi, Stille, Suzuki, or Hiyama-Denmark reactions, require functionalized arenes to enable the selective C–C bond formation between two arenes.[2] Recently, catalytic direct arylations emerged which avoid the introduction of functional groups in at least one of the two coupling partners prior to cross coupling by C–H bond activation.[3] The development of direct selective intermolecular heteroarylations of heteroarenes appears particularly beneficial because prefunctionalizations of heteroarenes are often difficult. From the viewpoint of atom economy, two-fold C–H bond activation is the ideal strategy for interconnecting two heteroarenes, and the groups of Fagnou and DeBoef showed independently that palladium(II) catalysis can be used for oxidative C–H/C–H cross couplings of heteroarenes with carbocyclic arenes.[4] However, the high chemoselectivity in favor of cross-coupling reactions were achieved through the use of the arenes in large excess. A seminal work was recently reported by Zhang and coworkers, who developed $Pd(OAc)_2$-catalyzed oxidative cross coupling of electron-deficient polyfluoroarenes with thiophenes, furans, or *N*-methyl indole in 3:1 ratio by using Ag_2CO_3 in the presence of one equivalent of acetic acid (Scheme 1).[5]

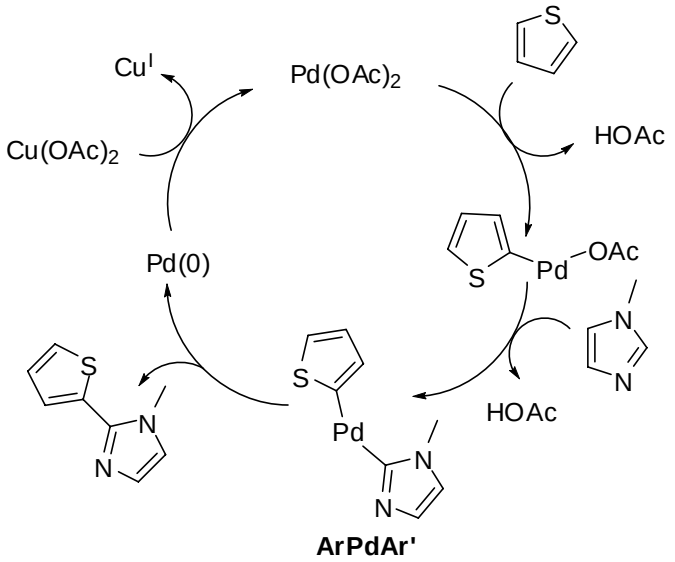


Scheme 1. $Pd(OAc)_2$-catalyzed oxidative cross coupling of electron-deficient polyfluoroarenes with heterocycles.

The metal-catalyzed oxidative cross dehydrogenative reactions of two heteroaryl C-H bonds to form unsymmetrical biheteroaryl molecules remains a formidable challenge.[6] During our research, Hu, You, and coworkers reported on $Pd(OAc)_2$-catalyzed and copper salt activated C–H/C–H cross couplings of xanthines, azoles, and electron-poor pyridine *N*-oxides with thiophenes and furans (3 to 4 equiv.) with high regioselectivity (Scheme 2).[7] Based on DFT calculations, a mechanism was proposed, as depicted in Scheme 3. Initially, thiophene undergoes a regioselective electrophilic C-H substitution (S_EAr) by $Pd(OAc)_2$ to generate an α-thienylpalladium(II) intermediate, which subsequently forms the key heterocoupling intermediate **ArPdAr'** by a concerted metallation-deprotonation (CMD) process, which might be rate-determining for the entire reaction.

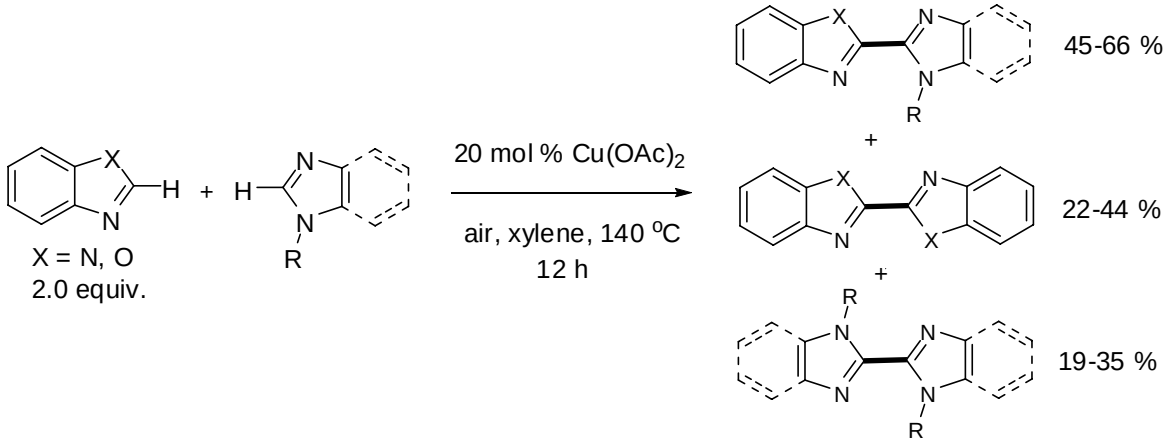


Scheme 2. Pd-catalyzed oxidative C-H/C-H cross-coupling of heteroarenes.



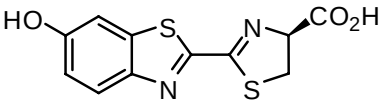
Scheme 3. Plausible catalytic loop for oxidative C–H/C–H cross couplings of heteroarenes.

However, to date, efficient C–H/C–H cross couplings between very similar partners, such as different azoles, remains a challenge because of their tendency to undergo homocoupling.[8] In 2010, Bao and co-workers described $Cu(OAc)_2$-catalyzed oxidative cross couplings of two different azoles under harsh conditions (Scheme 4).[8a] Although the transformation proceeded in high conversion, the selectivity for cross-coupling products are poor. Statistical distributions of products were formed which makes the reactions impractical in organic synthesis. Hence, decarboxylative C–H cross coupling was employed by Zhang and Greaney to link differently substituted azoles in moderate to good yield, but homocoupling was not fully suppressed and remained a limiting issue.[9]

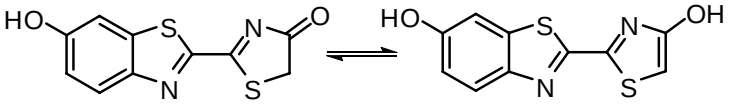


Scheme 4. Cu-catalyzed cross-coupling of two different azoles according to Bao and co-workers.[8a]

Though numerous natural products with important biological activities contain directly linked azoles, the 2,2'-linkage of azoles is a rare motif in nature.[10] The only prominent example is D-luciferin that is used by firefly beetles to generate oxyluciferin in an electronically excited state (Scheme 5). By its return to the ground state oxyluciferin emits light in the range of 530–640 nm (bioluminiscence).[11]



D-luciferin



keto-enol equilibrium of oxyluciferin

Scheme 5. Equilibrium of oxyluciferin.

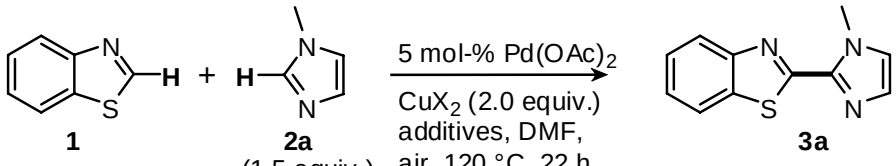
Herein we report a method for the selective C–C coupling between the non-functionalized C-2 positions of azoles by a two-fold C–H bond activation which provides access to a class of widely unexplored unsymmetrical 2,2'-bisheteroaryls.[12]

5.2 Results and Discussion

5.2.1 Scope and Limitations

We chose the reaction between benzothiazole (**1**) and *N*-methyl-imidazole (**2a**) to optimize the conditions for the palladium-catalyzed (5 mol-%) cross coupling reaction (Table 1). In a first series of experiments, the reactions were carried out under an atmosphere of O_2 (1 atm) in *N*,*N*-dimethylformamide (DMF) which gives heterogenous reaction mixtures (Table 1, entries 1–4). Whereas the presence of 2 equivalents of the additive $Cu(OAc)_2 \cdot H_2O$ was not sufficient to afford **3a**, the combination $Cu(OAc)_2 \cdot H_2O$ (2 equiv.)/AgF (2 equiv.) gave rise to the formation of **3a** in an excellent yield of 93%. An X-ray analysis of a single crystal of **3a** proved the 2,2'-bond formation (Figure 1) (see the Experimental Section).[13] Replacing

Table 1. $Pd(OAc)_2$-catalyzed cross coupling of **1** with **2a**.[a]



Entry	CuX_2	Additives	Yield[b] /%
1[c]	$Cu(OAc)_2 \cdot H_2O$	—	trace[d]
2[c]	$Cu(OAc)_2 \cdot H_2O$	AgF (2 equiv.)	93
3[c]	$Cu(OAc)_2 \cdot H_2O$	KF (2 equiv.)	22[d]
4[c]	—	AgF (2 equiv.)	trace[e]
5	$Cu(OAc)_2 \cdot H_2O$	AgF (2 equiv.)	92[f]
6	$Cu(OAc)_2 \cdot H_2O$	$KF/AgNO_3$ (3 + 1.5 equiv.)	91 (63)[g]
7	CuF_2	AgOAc (1.5 equiv.)	87
8[h]	$Cu(OAc)_2 \cdot H_2O$	$KF/AgNO_3$ (3 + 1.5 equiv.)	31[h]
9	—	KF/AgOAc (3 + 1.5 equiv.)	35
10	—	KF/AgOAc (3 + 3 equiv.)	71
11	CuBr	KOAc/AgF (2 + 2 equiv.)	84
12	$CuCl_2$	$KF/AgNO_3$ (3 + 1.5 equiv.)	trace
13	$CuBr_2$	$KF/AgNO_3$ (3 + 1.5 equiv.)	trace
14	$Cu(OTf)_2$	$KF/AgNO_3$ (3 + 1.5 equiv.)	31

[a] A mixture of **1** (0.25 mmol), **2a** (0.38 mmol), $Pd(OAc)_2$ (5 mol-%), CuX_2 (0.50 mmol), and additives in DMF (2.5 mL) was stirred at 120 °C for 22 h under air. [b] Yield of isolated **3a** (homocoupling of either **1** or **2a** gave yields < 5 % if not mentioned otherwise). [c] Under oxygen atmosphere. [d] Homocoupling consumed a part of **2a** by formation of 1,1'-dimethyl-2,2'-biimidazole (21% yield for entry 1; 15 % yield for entry 3). [e] Almost quantitative recovery of the starting materials. [f] The same yield of **3a** was obtained when TEMPO (20 mol-%) was added as radical scavenger. [g] Under an atmosphere of dry nitrogen. [h] Without $Pd(OAc)_2$; **1** was recovered with 63 % yield.

AgF by KF diminished the yield considerably (Table 1, entry 3). The cross coupling failed completely when the reaction was carried out in the presence of AgF but without $Cu(OAc)_2 \cdot H_2O$ (Table 1, entry 4). We were delighted to find that an atmosphere of pure

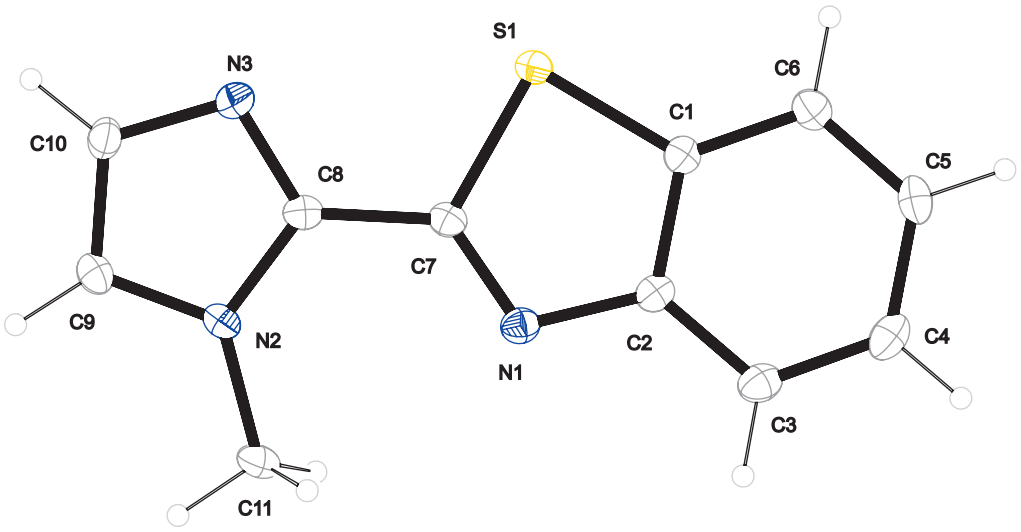


Figure 1. X-ray single crystal structure of **3a**.

oxygen was not necessary to achieve cross coupling, and **3a** was obtained in high yield when **1** and **2a** reacted under normal air atmosphere without exclusion of moisture (92%, Table 1, entry 5). The reliability of this coupling method was confirmed by the successful generation of **3a** on a 1 mmol scale (see the Experimental Section). Combinations of $Cu(OAc)_2 \cdot H_2O/KF/AgNO_3$ or $CuF_2/AgOAc$ were comparably efficient as $Cu(OAc)_2 \cdot H_2O/AgF$ in mediating the formation of **3a** (Table 1, entries 5–7). These results show that the sources of Cu^{2+}, Ag^+, and AcO^- are not crucial for the success of the cross coupling. Different polar aprotic solvents (e.g., DMSO, NMP) could be employed to achieve high yields of **3a**, whereas the use of protic or apolar solvents was less effective.[14]

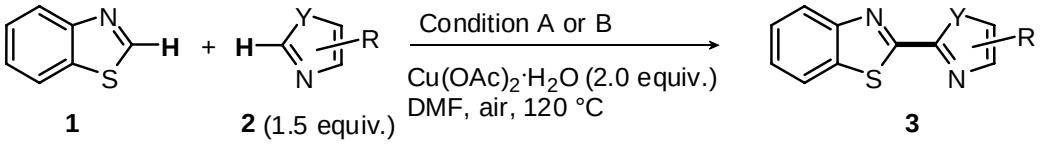
The reaction of **1** with **2a** was significantly attenuated in the absence of the $Pd(OAc)_2$ catalyst (Table 1, entry 8). Whereas the low degree of conversion in the absence of Cu^{2+} could partially be compensated by using 3 equivalents of Ag^+ or providing CuBr (Table 1, entries 9-11),[7,15] combining Cu^{2+} and Ag^+ salts is more economical and gives superior results (Table 1，entries 5–7).

To gain further insight into the fate of the Cu^{2+} and Ag^+ ions during the cross-coupling reaction, the precipitates isolated by filtration at the end of the reactions in entries 5 and 6 of Table 1 were analyzed by powder XRD. The diffraction patterns of both samples were almost identical and showed significant peaks which were assigned to Ag^0 (see Experimental Section Chapter 5.5.7). Hence, Ag^+ ions can be considered as terminal oxidants in these reactions.[16] The role of the Cu^{2+} ions is less clear at present. We assume that, in analogy to the Wacker

process,[17] Cu^{2+} ions catalyze the oxidation of Pd^0 by O_2 when substoichiometric amounts of Ag^+ ions were applied (entries 6 and 7). Moreover, it has been reported that $Pd(OAc)_2$ and $Cu(OAc)_2 \cdot H_2O$ can form polymetallic acetate-bridged clusters in acetic acid.[18,19] It seems possible, therefore, that catalytically active multinuclear Cu-Pd species are generated in situ also under our reaction conditions.[4b,4d,20] To test this hypothesis, we varied the counter ion X in the copper salt CuX_2 in the presence of $KF/AgNO_3$ and catalytic amounts of $Pd(OAc)_2$. The poor results obtained with $CuCl_2$, $CuBr_2$, and $Cu(OTf)_2$ (Table 1, entries 12–14) confirmed the crucial role of acetate ions for achieving high yields of **3a**.

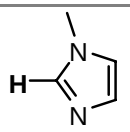
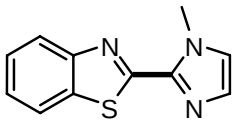
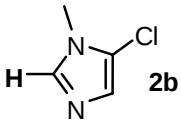
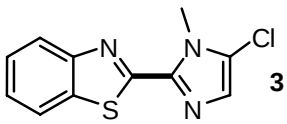
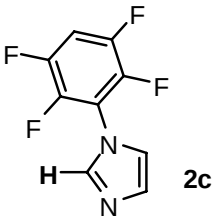
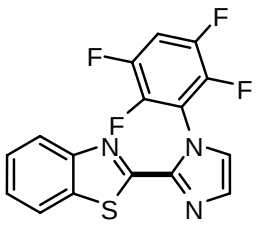
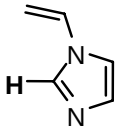
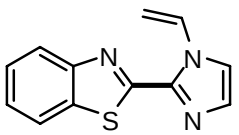
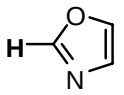
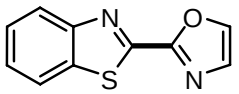
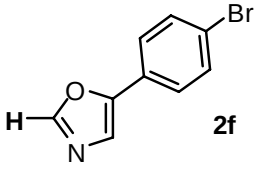
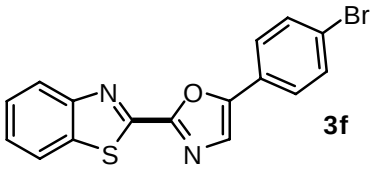
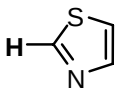
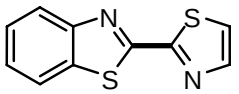
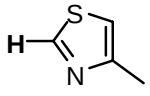
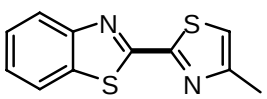
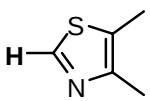
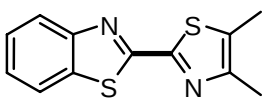
We explored various azoles as coupling partners for benzothiazole (**1**) by employing the two equally efficient additive combinations, that is, $Cu(OAc)_2 \cdot H_2O$ either with $KF/AgNO_3$ or AgF, in the presence of 5 to 10 mol % of $Pd(OAc)_2$ as catalyst (Table 2). The cross coupling of **1** with 5-chloro-1-methyl-imidazole (**2b**) furnished **3b** in excellent yield (Table 2, entry 2). Interestingly, the *N*-(2,3,5,6-tetrafluorophenyl)-substituted imidazole **2c**, which possesses active sites for C–H activation at both rings, reacted with **1** regioselectively at C-2 of the imidazole moiety and gave **3c** (Table 2, entry 3). As the $C(sp^2)$–H bond at the tetrafluorinated phenyl ring in **2c** did not react in the arylation of **1**, subsequent direct functionalizations of **3c** are possible.[5,21] The reaction of **1** with **2d** delivered **3d** carrying an N-vinyl group which could be useful for incorporating the bisheteroaryl unit into functional (co)polymers.

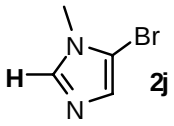
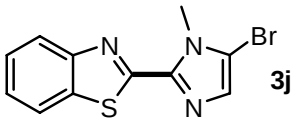
Table 2. $Pd(OAc)_2$-catalyzed C-2 arylation of **1** with azoles **2**.[a]



1 **2** (1.5 equiv.) **3**

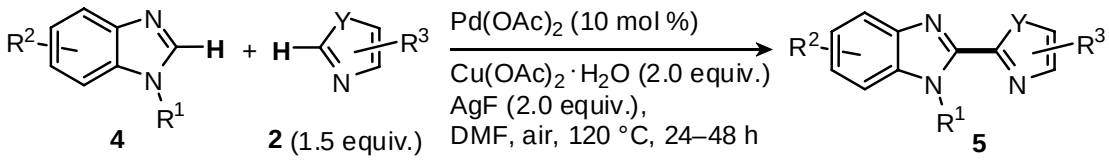
Condition A: $Pd(OAc)_2$ (5 mol %), $KF/AgNO_3$ (3 + 1.5 eqiuv.), 24 h
Condition B: $Pd(OAc)_2$ (10 mol-%), AgF (2.0 equiv.), 48 h

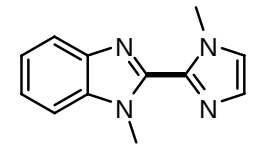
Entry	Azole **2**	Condition	Product **3**	Yield[b] /%
1	 **2a**	A	 **3a**	91
2	 **2b**	B	 **3b**	95
3	 **2c**	B	 **3c**	91
4	 **2d**	A	 **3d**	87
5	 **2e**	B	 **3e**	86
6	 **2f**	B	 **3f**	71
7	 **2g**	A	 **3g**	65
8	 **2h**	A	 **3h**	67
9	 **2i**	A	 **3i**	92

10	 **2j**	B[c]	 **3j**		81

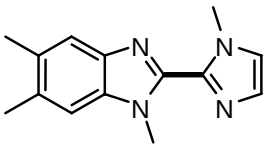
[a] A mixture of **1** (0.25 mmol), **2** (0.38 mmol, 1.5 equiv.), $Pd(OAc)_2$ (5 or 10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (0.50 mmol), and additives ($KF/AgNO_3$ or AgF) in DMF (2.5 mL) was stirred at 120 °C for the given time under air. [b] Isolated yield after column chromatography. [c] The conditions are the same as described for conditions B except that AgOAc was used instead of AgF in DMF (1 mL).

Further reactions of **1** with differently substituted oxazoles and thiazoles (Table 2, entries

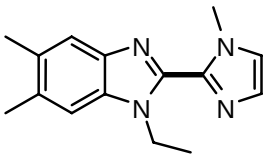




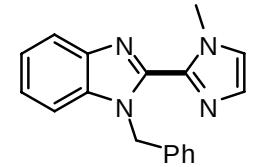
5a, 90%
with 5 mol % $Pd(OAc)_2$



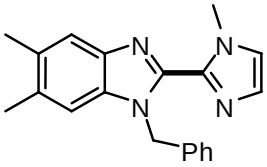
5b, 91%



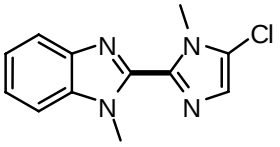
5c, 88%



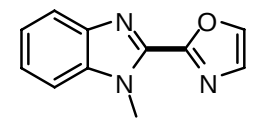
5d, 89%



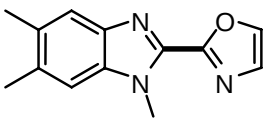
5e, 84%



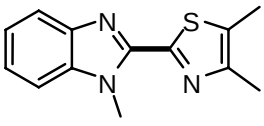
5f, 74%



5g, 61%
with 5 mol % $Pd(OAc)_2$



5h, 71%
under O_2 atmosphere (1 atm)



5i, 86%
with 5 mol % $Pd(OAc)_2$

Scheme 6. Direct C-2 arylation of benzimidazoles **4** with azoles **2** (isolated yields after column chromatography are given).

5–10) show the versatility of this direct oxidative cross coupling methodology. The compatibility of the aryl bromide **2f** and **2j** with the reaction conditions of the cross coupling enables one to extend the bisheteroaryl-aryl scaffold of **3f** and **3j** by classical palladium-catalyzed aryl coupling protocols.

The scope of the catalytic method presented here was then extended to C-2 heteroarylations of a series of benzimidazoles **4** with imidazoles, oxazoles, and thiazoles to furnish the bisheteroaryls **5a**–**i** (Scheme 6).

Through further investigation, the cross couplings of benzazoles could also be achieved with high selectivity (Table 3). The benzothiazole (**1**) reacted smoothly with benzoxazole (**6a**) and 5-methyl-benzoxazole to afford the desired product in 72 % and 80 %, respectively, even in the presence of AgF (40 mol %) and $Cu(OAc)_2 \cdot H_2O$ (40 mol %) (Table 3, entries 1 and 2). The structure of **7b** was confirmed by an X-ray analysis (Figure 2) (see Chapter 5.5.8).

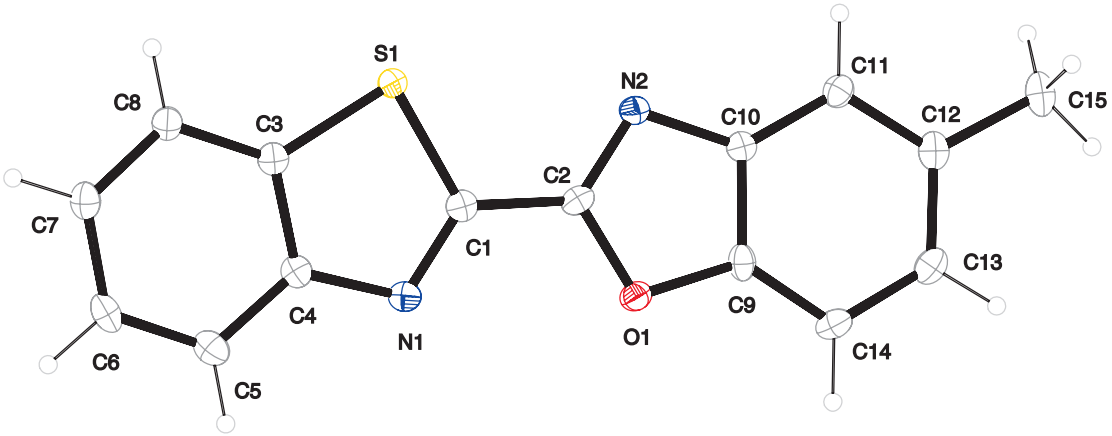
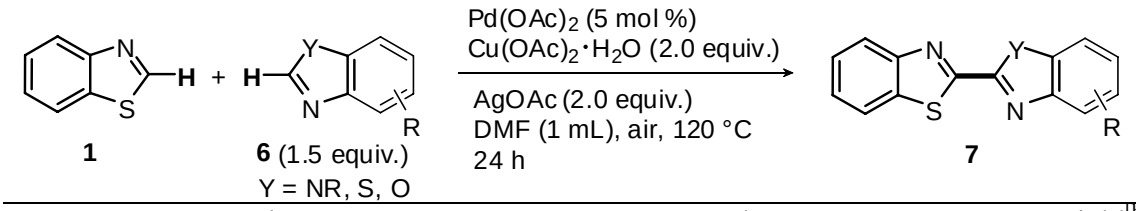


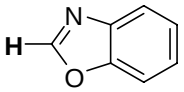
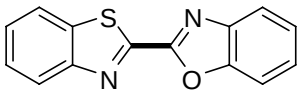
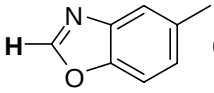
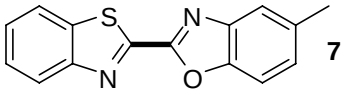
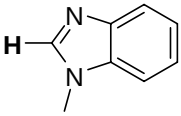
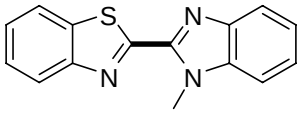
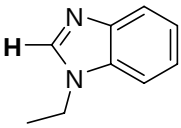
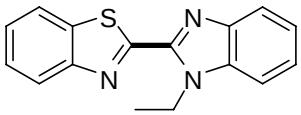
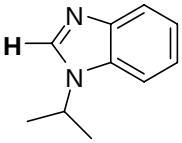
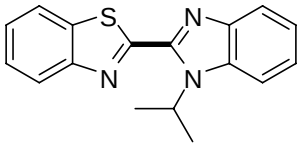
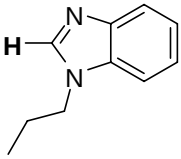
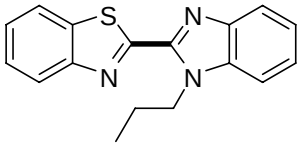
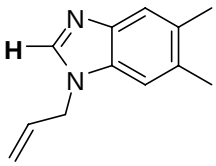
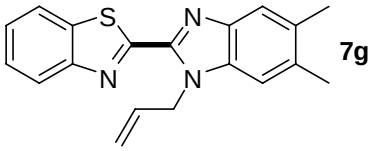
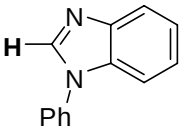
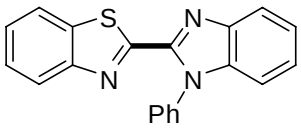
Figure 2. X-ray single crystal structure of **7a**.

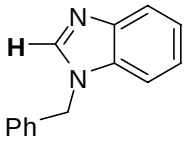
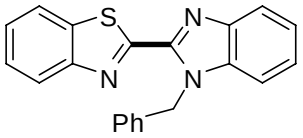
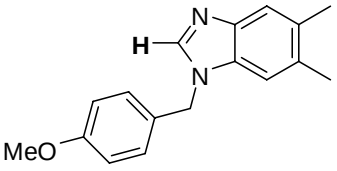
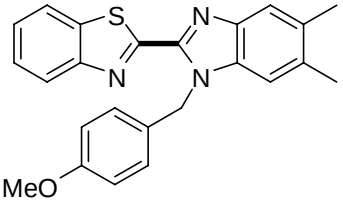
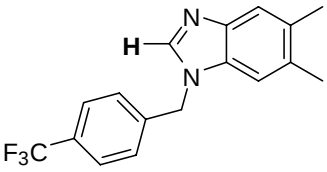
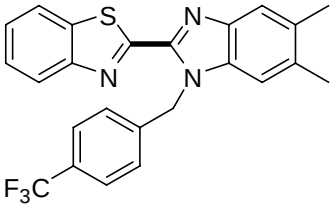
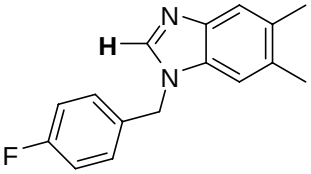
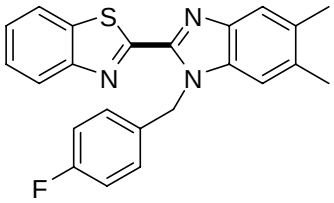
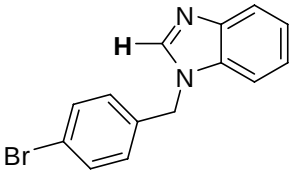
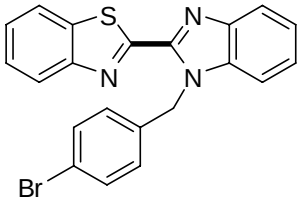
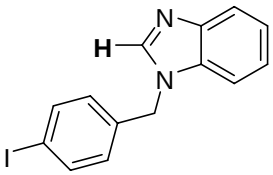
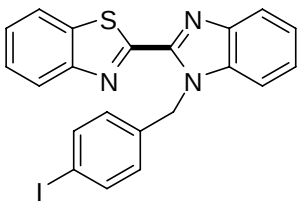
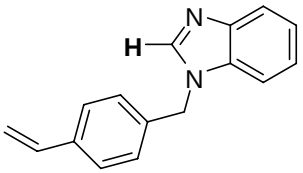
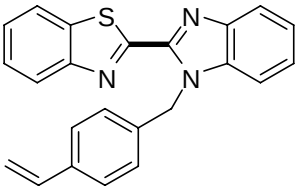
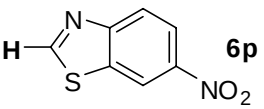
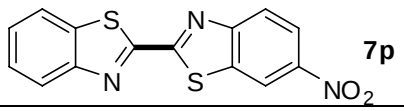
Gratifyingly, the scope of substrates could be extended to various benzimidazoles when AgOAc replaced the expensive and unstable AgF. Under these fluoride-free conditions, *N*-alkylbenzimidazoles were heteroarylated with **1** in good to excellent yields. It is worth noting that under these reaction conditions, the active groups, such as allyl, vinyl, aromatic bromide and even aromatic iodide, remained intact (Table 3, entries 7, 15, 13 and 14), which are capable to undergo further tranformations to construct more complex molecules. As fluorine-containing organic molecules are of considerable interest in pharmaceuticals and liquid crystal materials, we were delighted to find that the fluorinated compounds **6k** and **6l** are good substrates in the catalytic system (Table 3, entries 11 and 12). In contrast, the *N*-

phenylbenzimidazole (**6h**) and 6-nitrobenzothiazole (**6p**) coupled with **1** to give poor results (Table 3, entries 8 and 16).

Table 3. $Pd(OAc)_2$-catalyzed C-2 arylation of **1** with benzazoles **6**.[a]



Entry	Substrate	Product	Yield[b] / %
1[c]	 **6a**	 **7a**	72
2[c]	 **6b**	 **7b**	80
3	 **6c**	 **7c**	75
4	 **6d**	 **7d**	88
5	 **6e**	 **7e**	62
6	 **6f**	 **7f**	83
7	 **6g**	 **7g**	81
8	 **6h**	 **7h**	25

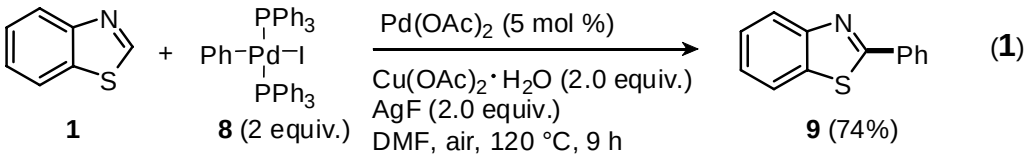
9	 **6i**	 **7i**	81
10	 **6j**	 **7j**	84
11	 **6k**	 **7k**	87
12	 **6l**	 **7l**	74
13	 **6m**	 **7m**	78
14	 **6n**	 **7n**	81
15	 **6o**	 **7o**	89
16	 **6p**	 **7p**	20[d]

[a] Conditions: A mixture of benzothiazole (0.25 mmol), $Pd(OAc)_2$ (5 mol %, 0.0125 mmol), benzoxazole (1.5 equiv., 0.38 mol), DMF (1 mL), AgF (2.0 equiv., 0.50 mmol) and $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv., 0.5 mmol) was stirred under air at 120 °C for 24 h; [b] Yield of the isolated product; [c] Conditions: A mixture of benzothiazole (0.25 mmol), $Pd(OAc)_2$ (5 mol %, 0.0125 mmol), benzoxazole (1.5 equiv., 0.38 mol), DMF (0.5 mL), AgF (40 mol %) and $Cu(OAc)_2 \cdot H_2O$ (40 mol %) was stirred under air at 120 °C for 5 h; [d] Yield based on GC-MS.

5.2.2 Mechanism

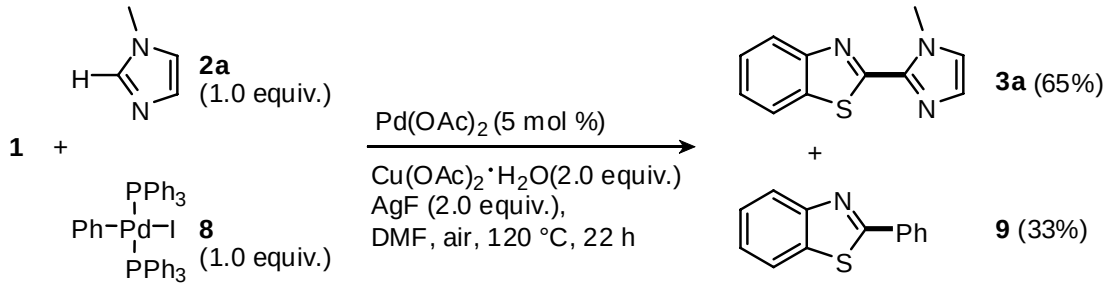
To understand the parameters that determine the selectivity for cross coupling we compared the homocoupling reactions of **1** and **2a**. These azoles behaved differently under the reaction conditions of entry 6 in Table 1. After 9 h, GC-MS analysis showed that less than 10 % of **1** had been converted, while the reaction of **2a** achieved a greater than 90% conversion.

Benzothiazole (**1**) underwent direct arylation with [*trans*-PhPdI(PPh_3)$_2$] (**8**) to form **9** under the reaction conditions of entry 5 in Table 1 (Equation 1).[22]



1 **8** (2 equiv.) **9** (74%) (**1**)

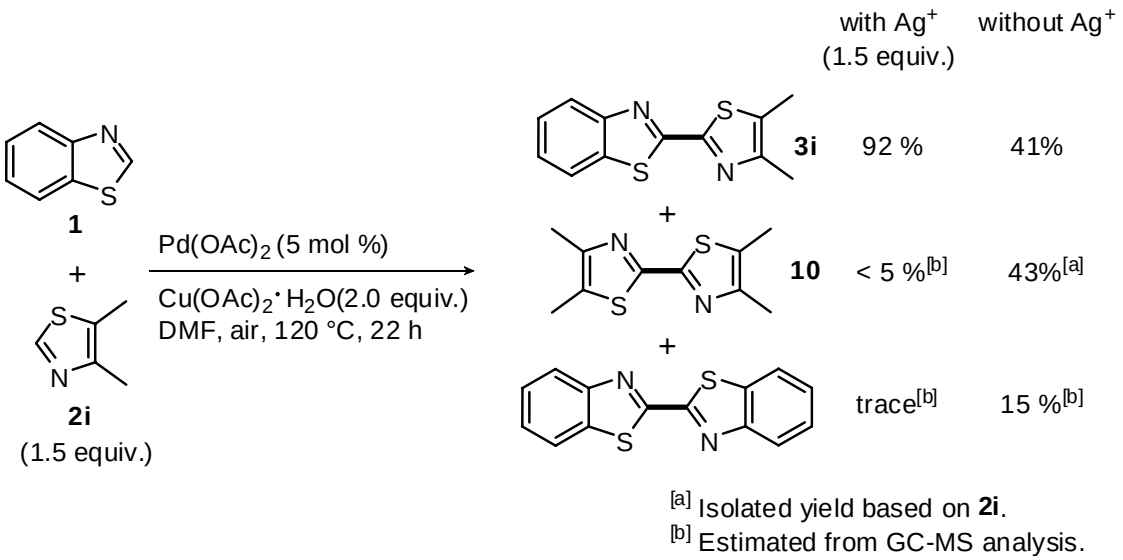
Further, a competition experiment between **1**, **2a**, and **8** gave only two main products (Scheme 7). Whereas only trace amounts of the products from homocoupling of **1**, homocoupling of **2a**, or phenylation of **2a** by **8** were detectable by GC-MS in the crude material, the isolated yields of **3a** (65 %) and **9** (33 %) indicate that the rate of the catalytic heteroarylation of **1** with **2a** is in the same order of magnitude as that of the direct phenylation of **1** with the aryl palladium(II) complex **8**.



Scheme 7. Competition between **2a** and **8** for benzothiazole (**1**).

We investigated the effect of the Ag^+ salt on the ratio of cross- and homocoupling products by studying the reaction of benzothiazole (**1**) with 4,5-dimethylthiazole (**2i**). Scheme 8 shows

that the formation of homocoupling products was suppressed by the presence of Ag^+ ions and that cross-coupling (to **3i**) is favored under these conditions. This pivotal effect of silver(I) is presently not well understood and requires further investigations.



Scheme 8. Reaction of benzothiazole (**1**) with 4,5-dimethylthiazole (**2i**) in the presence (Table 2, entry 9) and the absence of Ag^+ ions.

Palladium-catalyzed cross couplings under oxidative conditions may, in principle, proceed through a Pd^0/Pd^{II} or a Pd^{II}/Pd^{IV} cycle. As diaryliodonium salts are known to oxidize Pd^{II} to Pd^{IV} species,[3s,23] the failure of $[Ph_2I]^+[PF_6]^-$ (2 equiv.) to transfer phenyl to benzothiazole (**1**) or *N*-methyl-imidazole (**2a**) in the presence of $Pd(OAc)_2$ as the catalyst (5 mol-%) suggests that the contribution of an arylpalladium(IV) intermediate to the reaction pathway is unlikely, though we apply oxidative conditions.

Addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 20 mol-%) as a radical trap to the palladium-catalyzed reaction between **1** and **2a** did not affect the yield of **3a** (Table 1, entry 5). This finding indicates that radical species do not play a decisive role in the cross coupling process.[23c, 24]

Despite the presently rather fragmentary information on the mechanism, we propose that the Pd^{II}/Pd^0 catalytic cycle follows a C–H bond cleavage/C–H bond cleavage/C–C coupling sequence. After the first C–H bond activation at the azole HetAr-H to form the intermediate (HetAr)-PdL_n, the presence of Ag^+ facilitates cleavage of the second C–H bond selectively at the other azole HetAr'-H. Thereby the mixed bisheteroaryl-Pd complex (HetAr)-Pd-(HetAr')

is generated as a key intermediate. A change of the mechanism for the Pd–C bond formation may account for the change of substrate selectivity between the first and the second C–H bond cleavage. Reductive elimination from the mixed bisheteroaryl-Pd complex affords the unsymmetrical 2,2'-bisheteroaryls **3** (or **5** or **7**) and a Pd^0 species. Oxidation of Pd^0 by Ag^+ (or Cu^{2+}) and binding of acetate ligands regenerates the initial Pd^{II} species and completes the catalytic cycle. According to our observations (*cf.* Table 1, entries 5 and 12–14), it is likely that Pd-bound acetate plays an important role as proton acceptor during the C–H bond cleavage.

The regioselectivity of the cross couplings is governed by the CH acidity at C-2 of the 1,3-diazoles. However, the corresponding pK_a values[25] do not allow one to predict possible azole combinations for these reactions. Benzothiazole (**1**, pK_a 27.3) underwent cross couplings with oxazole **2e** (pK_a 27.1) as well as with the much less acidic *N*-methyl-imidazole **2a** (pK_a 35.1). *N*-Methyl-benzimidazole (**4**, R^1, R^2 = Me, H: pK_a 32.5) is five orders of magnitude less acidic than **1** but reacted with the same range of azoles as **1** ($27 < pK_a < 35$).

5.3 Conclusion

In summary, we have developed an efficient palladium(II)-catalyzed method for the direct C-2 heteroarylation of benzazoles with (benz)imidazoles, (benz)oxazoles and (benzo)thiazole that is mediated by Cu^{2+}, Ag^+, and acetate ions and robust enough for being carried out under normal air atmosphere. Homocoupling was successfully suppressed such that mixed bisheteroaryls were obtained through selective cleavage of C–H bonds in both substrate molecules without the requirement of prefunctionalized azoles, designed ligands, or huge excess of one azole over the other.

In the solid state,[13] the small twist angles of 9.39(11)° and 7.78(8)° between the least-squares planes of the linked heteroaryl moieties illustrate the planarity of the π-systems of **3a** and **7b**, respectively. As the 2,2'-bisheteroaryls **3** and **5** fluoresce in $CHCl_3$ their rigidity is retained in solution (at room temperature). The biaryls **3** and **5** may, therefore, find application as versatile ligands, building blocks in organic synthesis, pharmaceuticals, and functional materials. Further investigations will concentrate on elucidating the mechanism of the reaction and extending this catalytic method to other cross coupling reactions.

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www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336–033; e-mail: deposit@ccdc.cam.ac.uk].

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5.5 Experimental Section

5.5.1 General

^{1}H (400 MHz) and ^{13}C NMR spectra (100 MHz) of solutions in $CDCl_3$ were recorded on a Varian Inova 400 NMR spectrometer. Chemical shifts were expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals (δ_H 7.24 and δ_C 77.0 ppm). Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. HRMS was performed on a Finnigan MAT 95Q. Infrared spectra of neat substances were recorded on a Perkin-Elmer Spectrum BX II FT-IR spectrometer equipped with an ATR probe (diamond). Melting points were determined on a Büchi B-540.

5.5.2 Materials

Commercially available azoles were used as received: Benzothiazole (95 %, Fluka), 1-methyl-imidazole (99 %, Fluka), 5-chloro-1-methyl-imidazole (98 %, ABCR), 1-(2,3,5,6-tetrafluorophenyl)-imidazole (99 %, Aldrich), 1-vinyl-imidazole (99 %, ABCR), oxazole (98 %, ABCR), 5-(4-bromophenyl)-oxazole (Apollo), thiazole (99 %, ABCR), 4-methyl-thiazole (99 %, ABCR), 4,5-dimethyl-thiazole (99 %, ABCR). Literature procedures were used to synthesize 1-benzyl-benzimidazole, 1-benzyl-5,6-dimethyl-benzimidazole, 1-ethyl-5,6-dimethyl-benzimidazole, and 1,5,6-trimethyl-benzimidazole by N-alkylations of benzimidazole or 5,6-dimethylbenzimidazole with methyl iodide, ethyl iodide or benzyl bromide, respectively.[S1] Commercial solvents were used without further purification.
The following palladium, copper and fluoride salts were used: $Pd(OAc)_2$ (47.5 % Pd, Acros), $Cu(OAc)_2 \cdot H_2O$ (99%, Fisher Scientific), $Cu(OTf)_2$ (98 %, ABCR), $CuBr_2$ (97 %, Fluka), $CuCl_2$ (97 %, Aldrich), CuF_2 (99.5 %, abcr), CuBr (98 %, Fluka), $AgNO_3$ (Rectapur), AgOAc (99 %, Fluka), AgF (99 %, Aldrich), KF (Merck).

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Diphenyliodonium hexafluorophosphate (98 %, ABCR) and TEMPO (98 %, Acros) were purchased.

5.5.3 Products from Palladium-Catalyzed C–C Couplings of Azoles

General Procedure A: Under air atmosphere, a 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (2.8 mg, 5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (0.10 g, 0.50 mmol), KF (44 mg, 0.75 mmol), and $AgNO_3$ (65 mg, 0.38 mmol). The benzazole (0.25 mmol) and five-membered ring azole (0.38 mmol) were added by using syringes. After the addition of DMF (2.5 mL) the reaction mixture was stirred for 10 min at room temperature and then heated at 120 °C in an oil bath for the indicated time. After completion of the reaction (TLC control), the mixture was cooled to room temperature, poured into a saturated aqueous NaCl solution (20 mL), and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (eluent mixture: *n*-pentane/ethyl acetate/triethylamine).

General Procedure B: Under air atmosphere, a 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (5.6 mg, 10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (0.10 g, 0.50 mmol), and AgF (64 mg, 0.50 mmol). The benzazole (0.25 mmol) and five-membered ring azole (0.38 mmol) were added by using syringes. After the addition of DMF (2.5 mL) the reaction mixture was stirred for 10 min at room temperature and then heated at 120 °C in an oil bath for the indicated time. After completion of the reaction (TLC control), the mixture was cooled to room temperature, poured into a saturated aqueous NaCl solution (20 mL), and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (eluent mixture: *n*-pentane/ethyl acetate/triethylamine).

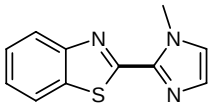
General Procedure for C : Under air atmosphere, a 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (5.6 mg, 5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (0.10 g, 0.50 mmol), and AgOAc (86 mg, 0.50 mmol). The benzothiazole (0.25 mmol) and benzazole (0.38 mmol) were added by using syringes. After the addition of DMF (1.0 mL) the reaction mixture was stirred for 10 min at

room temperature and then heated at 120 °C in an oil bath for the indicated time. After completion of the reaction (TLC control), the mixture was cooled to room temperature, poured into a saturated aqueous NaCl solution (20 mL), and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (eluent mixture: *n*-pentane/ethyl acetate).

2-(1-Methyl-1H-imidazol-2-yl)benzothiazole (3a)

*Synthesis of **3a** (1 mmol scale)*: Under air atmosphere, a round-bottom flask was charged with $Pd(OAc)_2$ (11.3 mg, 5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (404 mg, 2.00 mmol), and AgF (256 mg, 2.00 mmol). Then **1** (116 µL, 1.00 mmol) and **2a** (120 µL, 1.50 mmol) were added by using syringes. After the addition of DMF (2.5 mL) the mixture was stirred for 10 min at room temperature and then heated at 120 °C for 22 h. After cooling to r.t., the reaction mixture was poured into a saturated aqueous NaCl solution (40 mL) and extracted with EtOAc (3 × 40 mL). The organic phases were combined, and the volatile components were removed in a rotary evaporator. Purification of the crude product by column chromatography (silica gel, eluent: *n*-pentane/EtOAc/NEt_3) yielded **3a**[12] as a colorless solid (196 mg, 91 %).

Following *General Procedure A*, **1** (29 µL, 0.25 mmol) and **2a** (30 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and $KF/AgNO_3$ (3 + 1.5 equiv.) for 22 h to afford **3a** (48.9 mg, 91 %).



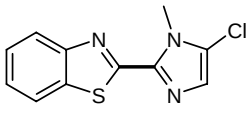
3a

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (s, 3 H), 7.04 (s, 1 H), 7.17 (s, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.46 (t, *J* = 7.8 Hz, 1 H), 7.90 (d, *J* = 7.6 Hz, 1 H), 8.00 ppm (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.6, 121.6, 123.3, 125.0, 125.4, 126.1, 129.8, 134.7, 140.6, 154.1, 159.6 ppm; HRMS (EI) calcd for $C_{11}H_9N_3S$ *m/z* 215.0517, found *m/z* 215.0512; IR: ν = 3127, 3109, 1596, 1549, 1500, 1467, 1439, 1398, 1314, 1290, 1228, 1083, 983, 913, 854, 768, 755, 724, 713, 706 cm^{-1}; mp 134–136 °C (from EtOAc).

Details of the crystal structure determination of **3a** are reported in Chapter 5.5.8.

2-(5-Chloro-1-methyl-1H-imidazol-2-yl)benzothiazole (3b)

Following *General Procedure B*, **1** (29 µL, 0.25 mmol) and **2b** (36 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 48 h to afford **3b** (59.1 mg, 95 %).

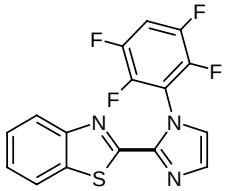


3b

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (s, 3 H), 7.12 (s, 1 H), 7.37–7.41 (m, 1 H), 7.45–7.49 (m, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 8.01 ppm (d, *J* = 9.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.8, 121.6, 122.5, 123.4, 125.7, 126.3, 126.7, 134.6, 140.1, 153.8, 159.3 ppm; HRMS (EI) calcd for $C_{11}H_8{}^{35}ClN_3S$ *m/z* 249.0127, found *m/z* 249.0121; IR: ν = 3056, 1548, 1481, 1467, 1434, 1398, 1312, 1219, 998, 914, 805, 752, 721, 708, 675, 625 cm^{-1}; mp 128–129.5 °C (from EtOAc).

2-(1-(2,3,5,6-Tetrafluorophenyl)-1H-imidazol-2-yl)benzothiazole (3c)

Following *General Procedure B*, **1** (29 µL, 0.25 mmol) and **2c** (82 mg, 0.38 mmol) were combined with $Pd(OAc)_2$ (10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 48 h to afford **3c** (79.2 mg, 91 %).



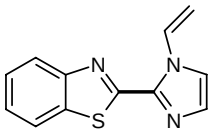
3c

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (br s, 1 H), 7.28 (tt, $^3J_{H,F}$ = 9.7 Hz, $^4J_{H,F}$ = 7.1 Hz, 1 H), 7.36–7.39 (m, 2 H), 7.43 (br s, 1 H), 7.66–7.69 (m, 1 H), 7.88–7.90 ppm (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 106.7 (dt, $^2J_{C,F}$ = 22.6 Hz), 118.8 (s), 121.6 (d), 123.6 (d), 124.3 (d), 125.9 (d), 126.2 (d), 131.3 (d), 135.0 (s), 141.1 (s), 143.2 (m with $^1J_{C,F}$ = ca. 260 Hz), 145.8 (m with $^1J_{C,F}$ = ca. 260 Hz), 153.6 (s), 157.0 ppm (s), signal multiplicities were assigned on the basis of additional HSQC and HMBC experiments, however, the low signal intensities in the ^{13}C NMR spectrum prevented a detailed analysis of the ^{13}C,^{19}F couplings; ^{19}F NMR

(376.3 MHz, $CDCl_3$): δ –145.6 (B part of an AA'BB'X system with J_{AB} = 22.0 Hz, $J_{A'B}$ = –11.4 Hz, $J_{BB'}$ = 1.3 Hz, $^4J_{F,H}$ = 7.1 Hz), –138.3 ppm (A part of an AA'BB'X system with J_{AB} = 22.0 Hz, $J_{AB'}$ = –11.4 Hz, $J_{AA'}$ = 4.0 Hz, $^3J_{F,H}$ = 9.7 Hz), NMR spectral synthesis[S2] was employed to calculate the coupling constants *J* observed in the ^{19}F NMR spectrum; HRMS (ESI+) calcd for $C_{16}H_8F_4N_3S$ [M + H^+] *m/z* 350.0370, found *m/z* 350.0370; IR: ν = 3162, 3138, 3017, 2361, 2339, 1711, 1646, 1625, 1599, 1556, 1510, 1495, 1436, 1408, 1313, 1207, 1193, 1182, 1079, 975, 939, 910, 882, 859, 828, 766, 750, 742, 712, 698, 688 cm^{-1}; mp 177–178 °C (from EtOAc).

2-(1-Vinyl-1H-imidazol-2-yl)benzothiazole (3d)

Following *General Procedure A*, **1** (29 µL, 0.25 mmol) and **2d** (35 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and $KF/AgNO_3$ (3 + 1.5 equiv.) for 24 h to afford **3d** (49.3 mg, 87 %).



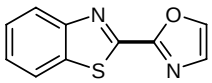
3d

^1H NMR (400 MHz, $CDCl_3$): δ 5.09 (dd, *J* = 8.8 Hz, *J* = 1.5 Hz, 1 H), 5.39 (dd, *J* = 15.8 Hz, *J* = 1.5 Hz, 1 H), 7.29 (br s, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.54 (br s, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 8.54 ppm (dd, *J* = 15.8 Hz, *J* = 8.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 103.4 (t), 119.3 (2 C), 121.6 (d), 123.6 (d), 125.8 (d), 126.3 (d), 130.8 (d), 131.2 (d), 139.6, 154.1, 158.8 ppm, signal multiplicities were assigned on the basis of additional HSQC and HMBC experiments, however, fast relaxation of ^{13}C prevented a detailed analysis for some of the resonances; HRMS (EI) calcd for $C_{12}H_9N_3S$ *m/z* 227.0517, found *m/z* 227.0495; IR: ν = 1639, 1594, 1546, 1489, 1438, 1306, 1275, 1243, 1185, 1085, 966, 910, 879, 862, 761, 748, 719, 695 cm^{-1}; mp 116.5–117.5 °C (from EtOAc).

[S2] D. S. Stephenson, G. Binsch, *J. Magn. Reson.* **1980**, *37*, 395–407.

2-(Benzothiazol-2-yl)oxazole (3e)

Following *General Procedure B*, **1** (29 µL, 0.25 mmol) and **2e** (26 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 48 h to afford **3e** (43.3 mg, 86 %).[S3]

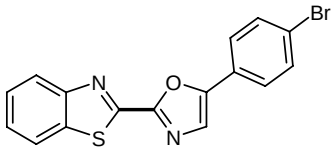


3e

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 1 H), 7.45–7.49 (m, 1 H), 7.52–7.56 (m, 1 H), 7.86 (s, 1 H), 7.95 (d, *J* = 7.6 Hz, 1 H), 8.17 ppm (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.8 (d), 124.4 (d), 126.7 (d), 126.9 (d), 129.4 (d), 135.3 (s), 140.6 (d), 153.5 (s), 154.2 (s), 156.6 ppm (s), signal multiplicities were assigned on the basis of an additional HSQC experiment; HRMS (EI) calcd for $C_{10}H_6N_2OS$ *m/z* 202.0201, found *m/z* 202.0193; IR: ν = 3158, 3134, 3052, 1567, 1550, 1492, 1462, 1454, 1430, 1375, 1315, 1143, 1108, 1078, 1002, 926, 910, 784, 760, 723, 699 cm^{-1}; mp 144.5–146 °C (from EtOAc).

2-(Benzothiazol-2-yl)-5-(4-bromophenyl)oxazole (3f)

Following *General Procedure B*, **1** (29 µL, 0.25 mmol) and **2f** (84 mg, 0.38 mmol) were combined with $Pd(OAc)_2$ (10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 48 h to afford **3f** (63.1 mg, 71 %).



3f

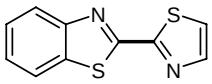
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.50 (m, 1 H), 7.54–7.61 (m, 4 H), 7.67–7.71 (m, 2 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 8.20 ppm (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.8 (d), 123.5 (s), 124.4 (d), 124.6 (d), 125.9 (s), 126.4 (d), 126.7 (d), 127.0 (d), 132.3 (d),

[S3] C2-substitution of oxazole has been derived by comparison with experimental ^{13}C NMR data for 2-phenyl-oxazole [20662-88-8], 4-phenyl-oxazole [20662-89-9], and 5-phenyl-oxazole [1006-68-4] available from databases (e.g. SciFinder).

135.3 (s), 152.7 (s), 153.7 (s), 154.1 (s), 156.0 ppm (s), signal multiplicities were assigned on the basis of additional HSQC and HMBC experiments; HRMS (EI) calcd for $C_{16}H_9{}^{79}BrN_2OS$ *m/z* 355.9619, found *m/z* 355.9632; IR: ν = 3116, 3053, 2962, 1609, 1481, 1456, 1426, 1313, 1261, 1137, 1074, 1054, 1027, 1008, 950, 928, 858, 822, 752, 726, 719, 698 cm^{-1}; mp 172–173 °C (from EtOAc).

2-(Thiazol-2-yl)benzothiazole (3g)[S4]

Following *General Procedure A*, **1** (29 µL, 0.25 mmol) and **2g** (27 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and $KF/AgNO_3$ (3 + 1.5 equiv.) for 24 h to afford **3g** (35.3 mg, 65 %).



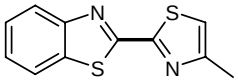
3g

Yellow solid, known compound [CAS Reg. No. 63565-78-6]. ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (t, *J* = 8.0 Hz, 1 H), 7.49–7.53 (m, 2 H), 7.92–7.97 (m, 2 H), 8.08 ppm (d, *J* = 8.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.9 (d), 122.2 (d), 123.7 (d), 126.2 (d), 126.7 (d), 135.3 (s), 144.3 (d), 153.5 (s), 161.3 (s), 161.7 ppm (s), signal multiplicities were assigned on the basis of an additional HSQC experiment; HRMS (EI) calcd for $C_{10}H_6N_2S_2$ *m/z* 217.9972, found *m/z* 217.9950; IR: ν = 1592, 1553, 1529, 1466, 1452, 1432, 1394, 1323, 1310, 1049, 1014, 919, 877, 841, 760, 731, 703 cm^{-1}; mp 139–140 °C (from EtOAc; lit.[S4b]: mp 139–142 °C).

2-(4-Methylthiazol-2-yl)benzothiazole (3h)

Following *General Procedure A*, **1** (29 µL, 0.25 mmol) and **2h** (35 µL, 0.39 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and $KF/AgNO_3$ (3 + 1.5 equiv.) for 24 h to afford **3h** (38.8 mg, 67 %).

[S4] a) A. Dondoni, T. Dall'Occo, G. Galliani, A. Mastellari, A. Medici, *Tetrahedron Lett.* **1984**, *25*, 3637–3640; b) N. Suzuki, M. Sato, H. Yokoyama, H. Morikawa, T. Goto, *Agric. Biol. Chem.* **1977**, *41*, 217–218.

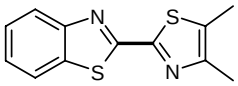


3h

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.54 (s, 3 H), 7.08 (s, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 8.07 ppm (d, *J* = 8.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 117.1, 121.9, 123.6, 126.0, 126.6, 135.3, 153.5, 154.8, 160.7, 161.5 ppm; HRMS (EI) calcd for $C_{11}H_8N_2S_2$ *m/z* 232.0129, found *m/z* 232.0132; IR: ν = 3100, 3054, 2922, 1556, 1498, 1476, 1440, 1418, 1377, 1318, 1160, 975, 906, 858, 829, 766, 739, 729, 672 cm^{-1}; mp 137–138.5 °C (from EtOAc).

2-(4,5-Dimethylthiazol-2-yl)benzothiazole (3i)

Following *General Procedure A*, **1** (29 µL, 0.25 mmol) and **2i** (41 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and $KF/AgNO_3$ (3 + 1.5 equiv.) for 24 h to afford **3i** (56.5 mg, 92 %).

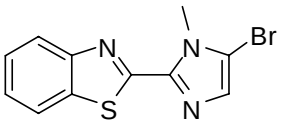


3i

Yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3 H), 2.44 (s, 3 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.90 (d, *J* = 7.2 Hz, 1 H), 8.04 ppm (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 14.9, 121.8, 123.4, 125.8, 126.5, 131.0, 135.2, 150.6, 153.6, 156.4, 161.8 ppm; HRMS (EI) calcd for $C_{12}H_{10}N_2S_2$ *m/z* 246.0285, found *m/z* 246.0275; IR: ν = 3050, 2913, 2855, 1553, 1536, 1509, 1437, 1415, 1388, 1371, 1314, 1278, 1241, 1111, 1011, 919, 828, 764, 759, 731, 724, 686 cm^{-1}; mp 194–195 °C (from EtOAc).

2-(5-Bromo-1-methyl-1H-imidazol-2-yl)benzothiazole (3j)

Following *General Procedure C*, **1** (29 µL, 0.25 mmol) and **2j** (60.5 mg, 0.380 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) in DMF (1 mL) for 24 h to afford **3i** (59.2 mg, 81 %).

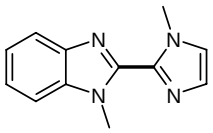


3j

Yellow solid, ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.22 (s, 3 H), 7.19 (s, 1 H), 7.38-7.41 (m, 1 H), 7.46-7.48 (m, 1 H), 7.89 (d, *J* = 7.8 Hz, 1 H), 8.01 ppm (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 34.1, 109.2, 121.6, 123.4, 125.7, 126.3, 130.1, 134.7, 141.2, 153.8, 158.9 ppm; HRMS (EI) calcd for $C_{11}H_9BrN_3S^+$ [M + H^+] *m/z* 293.9701, found *m/z* 293.9694; IR: ν = 3053, 2926, 1542, 1466, 1435, 1394, 1314, 1271, 1222, 996, 912, 814, 763, 733, 673, 626 cm^{-1}; mp 152–154 °C (from EtOAc).

1-Methyl-2-(1-methyl-1H-imidazol-2-yl)-1H-benzimidazole (5a)

Analogous to *General Procedure B*, 1-methyl-benzimidazole (33 mg, 0.25 mmol) and **2a** (30 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 24 h to afford **5a** (47.5 mg, 90 %).



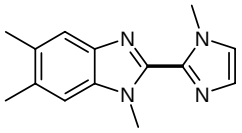
5a

Known compound [CAS Reg. No. 188799-42-0]. The NMR spectroscopic data agree with those described in lit. [S5]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (s, 3 H), 4.19 (s, 3 H), 7.04 (s, 1 H), 7.19 (s, 1 H), 7.24–7.32 (m, 2 H), 7.39–7.41 (m, 1 H), 7.77–7.79 ppm (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.1, 35.7, 109.7, 119.8, 122.4, 123.2, 123.8, 128.6, 135.9, 138.2, 142.5, 143.7 ppm.

1,5,6-Trimethyl-2-(1-methyl-1H-imidazol-2-yl)-1H-benzimidazole (5b)

Following to *General Procedure B*, 1,5,6-trimethyl-benzimidazole (41 mg, 0.25 mmol) and **2a** (30 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 45 h to afford **5b** (54.6 mg, 91 %).

[S5] J. R. Ames, M. A. Houghtaling, D. L. Terrian, T. P. Mitchell, *Can. J. Chem.* **1997**, *75*, 28–36.

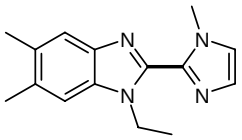


5b

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3 H), 2.41 (s, 3 H), 4.13 (s, 3 H), 4.14 (s, 3 H), 7.03 (br s, 1 H), 7.17 (s, 1 H), 7.18 (br s, 1 H), 7.54 ppm (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3, 20.6, 32.1, 35.7, 109.9, 119.8, 123.5, 128.4, 131.4, 132.5, 134.5, 138.5, 141.1, 142.9 ppm; HRMS (EI) calcd for $C_{14}H_{16}N_4$ *m/z* 240.1375, found *m/z* 240.1365; IR: ν = 3112, 2963, 2859, 1560, 1504, 1487, 1455, 1436, 1426, 1396, 1354, 1324, 1281, 1150, 1066, 1031, 1003, 919, 877, 8834, 820, 746, 728, 660 cm^{-1}; mp 144–146 °C (from EtOAc).

1-Ethyl-5,6-dimethyl-2-(1-methyl-1H-imidazol-2-yl)-1H-benzimidazole (5c)

Following to *General Procedure B*, 1-ethyl-5,6-dimethyl-benzimidazole (44 mg, 0.25 mmol) and **2a** (30 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 48 h to afford **5c** (55.8 mg, 88 %).

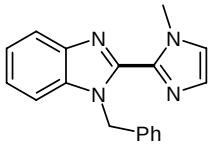


5c

Viscous liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (t, *J* = 7.2 Hz, 3 H), 2.38 (s, 3 H), 2.41 (s, 3 H), 4.12 (s, 3 H), 4.72 (q, *J* = 7.2 Hz, 2 H), 7.03 (br s, 1 H), 7.18 (br s, 1 H), 7.19 (s, 1 H), 7.55 ppm (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 20.3, 20.7, 35.7, 40.0, 110.1, 119.9, 123.5, 128.5, 131.2, 132.4, 133.4, 138.3, 141.3, 142.3 ppm; HRMS (EI) calcd for $C_{15}H_{18}N_4$ *m/z* 254.1531, found *m/z* 254.1528; IR: ν = 3113, 3023, 2979, 2966, 2929, 2868, 1539, 1507, 1480, 1448, 1399, 1375, 1344, 1322, 1281, 1188, 1155, 1087, 1042, 998, 960, 920, 867, 838, 784, 748, 732, 678 cm^{-1}.

1-Benzyl-2-(1-methyl-1H-imidazol-2-yl)-1H-benzimidazole (5d)

Following to *General Procedure B*, 1-benzyl-benzimidazole (53 mg, 0.25 mmol) and **2a** (30 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 48 h to afford **5d** (64.1 mg, 89 %).

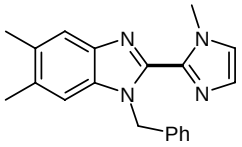


5d

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (s, 3 H), 6.07 (s, 2 H), 7.03 (s, 1 H), 7.12–7.14 (m, 2 H), 7.17–7.23 (m, 4 H), 7.24–7.31 (m, 3 H), 7.80 ppm (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.7 (q), 48.5 (t), 110.7 (d), 119.9 (d), 122.6 (d), 123.4 (d), 123.8 (d), 126.9 (d), 127.4 (d), 128.59 (d), 128.64 (d), 135.3 (s), 137.1 (s), 138.0 (s), 142.7 (s), 143.5 ppm (s), signal multiplicities were assigned on the basis of additional HSQC and HMBC experiments; HRMS (EI) calcd for $C_{18}H_{16}N_4$ *m/z* 288.1375, found *m/z* 288.1360; IR: ν = 3029, 2956, 2362, 1604, 1557, 1495, 1452, 1432, 1398, 1347, 1283, 1164, 1150, 983, 920, 749, 730, 689 cm^{-1}; mp 126.5–128 °C (from EtOAc).

1-Benzyl-5,6-dimethyl-2-(1-methyl-1H-imidazol-2-yl)-1H-benzimidazole (5e)

Following to *General Procedure B*, 1-benzyl-5,6-dimethyl-benzimidazole (60 mg, 0.25 mmol) and **2a** (30 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 48 h to afford **5e** (66.2 mg, 84 %).

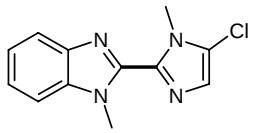


5e

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3 H), 2.35 (s, 3 H), 4.08 (s, 3 H), 6.00 (s, 2 H), 7.00–7.10 (m, 4 H), 7.14–7.22 (m, 4 H), 7.56 ppm (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (q), 20.7 (q), 35.6 (q), 48.4 (t), 110.7 (d), 119.9 (d), 123.7 (d), 126.8 (d), 127.3 (d), 128.5 (d), 128.6 (d), 131.6 (s), 132.7 (s), ca. 134.0 (s), 137.4 (s), 141.4 (s), 142.8 ppm (s), signal multiplicities were assigned on the basis of additional HSQC and HMBC experiments; HRMS (EI) calcd for $C_{20}H_{20}N_4$ *m/z* 316.1688, found *m/z* 316.1685; IR: ν = 3107, 3023, 2965, 1606, 1556, 1523, 1476, 1496, 1397, 1369, 1346, 1321, 1284, 1167, 1154, 1121, 997, 974, 918, 877, 837, 762, 728, 696, 675 cm^{-1}; mp 186–188 °C (from EtOAc).

2-(5-Chloro-1-methyl-1H-imidazol-2-yl)-1-methyl-1H-benzimidazole (5f)

Following to *General Procedure B*, 1-benzyl-benzimidazole (33 mg, 0.25 mmol) and **2b** (36 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 30 h to afford **5f** (45.5 mg, 74 %).

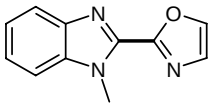


5f

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (s, 3 H), 4.16 (s, 3 H), 7.14 (s, 1 H), 7.29–7.33 (m, 2 H), 7.42 (d, *J* = 7.2 Hz, 1 H), 7.80 ppm (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.1, 33.0, 109.8, 119.9, 121.5, 122.7, 123.5, 125.6, 135.9, 137.6, 142.2, 143.1 ppm; HRMS (EI) calcd for $C_{12}H_{11}{}^{35}ClN_4$ *m/z* 246.0672, found *m/z* 246.0671; IR: ν = 3106, 3065, 3039, 2960, 1557, 1490, 1474, 1455, 1436, 1391, 1321, 1285, 1242, 1153, 1109, 1064, 1006, 932, 900, 832, 809, 728, 695, 672 cm^{-1}; mp 143–144.5 °C (from EtOAc).

2-(1-Methyl-1H-benzimidazol-2-yl)oxazole (5g)

Analogous to *General Procedure B*, 1-methyl-benzimidazole (33 mg, 0.25 mmol) and **2e** (26 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 24 h to afford **5g** (30.3 mg, 61 %).[S3]

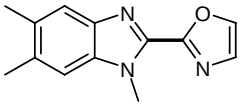


5g

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (s, 3 H), 7.32–7.46 (m, 4 H), 7.88–7.90 ppm (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.0 (q), 110.0 (d), 120.9 (d), 123.2 (d), 124.4 (d), 128.5 (d), 136.4 (s), 139.7 (d), 140.4 (s), 142.5 (s), 154.2 ppm (s), signal multiplicities were assigned on the basis of an additional HSQC experiment; HRMS (EI) calcd for $C_{11}H_9N_3O$ *m/z* 199.0746, found *m/z* 199.0739; IR: ν = 3113, 2960, 1600, 1514, 1484, 1448, 1327, 1230, 1113, 1082, 936, 915, 791, 734, 673 cm^{-1}; mp 87–90 °C (from EtOAc).

2-(1,5,6-Trimethyl-1H-benzimidazol-2-yl)oxazole (5h)

Analogous to *General Procedure B*, 1,5,6-trimethyl-benzimidazole (41 mg, 0.25 mmol) and **2e** (26 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (10 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) under an atmosphere of O_2 (1 atm) for 30 h to afford **5h** (40.2 mg, 71 %).[S3]

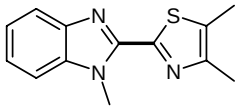


5h

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3 H), 2.40 (s, 3 H), 4.21 (s, 3 H), 7.18 (s, 1 H), 7.32 (s, 1 H), 7.58 (s, 1 H), 7.81 ppm (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3 (q), 20.8 (q), 31.9 (q), 110.0 (d), 120.6 (d), 128.4 (d), 132.4 (s), 134.0 (s), 135.0 (s), 139.4 (d), 139.6 (s), 141.2 (s), 154.4 ppm (s), signal multiplicities were assigned on the basis of an additional HSQC experiment; HRMS (EI) calcd for $C_{13}H_{13}N_3O$ *m/z* 227.1059, found *m/z* 227.1057; IR: ν = 3135, 3109, 2964, 2943, 2919, 2851, 1599, 1524, 1514, 1485, 1451, 1424, 1407, 1387, 1377, 1322, 1229, 1113, 1076, 998, 914, 870, 832, 794, 738, 670 cm^{-1}; mp 177–180 °C (from EtOAc).

4,5-Dimethyl-2-(1-methyl-1H-benzimidazol-2-yl)thiazole (5i)

Analogous to *General Procedure B*, 1-methyl-benzimidazole (33 mg, 0.25 mmol) and **2i** (41 µL, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgF (2 equiv.) for 24 h to afford **5i** (52.2 mg, 86 %).

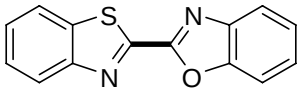


5i

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3 H), 2.42 (s, 3 H), 4.27 (s, 3 H), 7.25–7.33 (m, 2 H), 7.38–7.40 (m, 1 H), 7.77–7.79 ppm (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.4, 15.0, 32.0, 109.7, 120.0, 122.8, 123.5, 129.5, 137.0, 142.7, 145.8, 149.9, 154.7 ppm; HRMS (EI) calcd for $C_{13}H_{13}N_3S$ *m/z* 243.0830, found *m/z* 243.0824; IR: ν = 3049, 2921, 1544, 1523, 1472, 1448, 1406, 1330, 1248, 1200, 1007, 899, 798, 735, 706 cm^{-1}; mp 131–132 °C.

2-(Benzothiazol-2-yl)benzo[d]oxazole (7a)

Analogous to *General Procedure B*, **1** (29 µL, 0.25 mmol) and **6a** (45 mg, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (21 mg, 40 mol %), and AgF (13 mg, 40 mol %) in DMF (0.5 mL) for 5 h to afford **7a** (45.3 mg, 72 %).



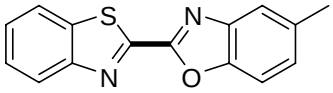
7a

Known compound[S6].

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 (m, 2 H), 7.50–7.53 (m, 1 H), 7.57–7.59 (m, 1 H), 7.69 (d, J = 7.8 Hz, 1 H), 7.86 (d, J = 8.4 Hz, 1 H), 8.00 (d, J = 7.8 Hz, 1 H), 8.25 ppm (d, J = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 111.4, 121.0, 121.9, 124.8, 125.5, 127.08, 127.12, 127.15, 135.8, 141.4, 151.0, 153.6, 154.5, 157.0 ppm; HRMS (ESI+) calcd for $C_{14}H_9N_2OS^+$ [M + H^+] *m/z* 253.0430, found *m/z* 253.0428; IR: ν = 3062, 1565, 1471, 1450, 1430, 1315, 1246, 1074, 1019, 1008, 998, 932, 896, 762, 747, 730, 702 cm^{-1}; mp 189–191 °C (lit. [S6]: mp 197-200 °C).

2-(Benzothiazol-2-yl)-5-methylbenzooxazole (7b)

Analogous to *General Procedure B*, **1** (29 µL, 0.25 mmol) and **6b** (50 mg, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (21 mg, 40 mol %), and AgF (13 mg, 40 mol %) in DMF (0.5 mL) for 5 h to afford **7b** (53.2 mg, 80 %).



7b

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.50 (s, 3 H), 7.26–7.28 (m, 1 H), 7.59 (m, 3 H), 7.626–7.631 (m, 1 H), 7.98–8.00 (m, 1 H), 8.23–8.24 ppm (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.6, 110.8, 120.7, 121.9, 124.7, 127.0, 127.1, 128.4, 135.5, 135.8, 141.6, 149.3, 153.7, 154.6, 157.1 ppm; HRMS (ESI+) calcd for $C_{15}H_{11}N_2OS^+$ [M + H^+] *m/z* 267.0592, found *m/z*

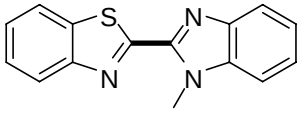
[S6] F. Derridj, J. Roger, F. Geneste, S. Djebbar, H. Doucet, *J. Organomet. Chem.* **2009**, *694*, 455-465.

267.0588; IR: ν = 3057, 2919, 1565, 1468, 1454, 1429, 1315, 1262, 1191, 1076, 1019, 1010, 933, 870, 810, 762, 731, 720, 700 cm^{-1}; mp 194.5–196.5 °C.

Details of the crystal structure determination of **7b** are reported in Chapter 5.5.8.

2-(1-Methyl-1H-benzimidazol-2-yl)benzothiazole (7c)

Following to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6c** (50.1 mg, 0.380 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **5i** (49.5 mg, 75 %).

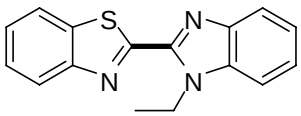


7c

^1H NMR (600 MHz, $CDCl_3$): δ 4.43 (s, 3 H), 7.33–7.36 (m, 1 H), 7.38–7.40 (m, 1 H), 7.44–7.47 (m, 2 H), 7.51–7.54 (m, 1 H), 7.88 (d, *J* = 7.8 Hz, 1 H), 7.96–7.98 (m, 1 H), 8.10–8.12 ppm (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 32.4, 110.1, 120.4, 121.8, 123.4, 123.9, 124.6, 126.2, 126.5, 135.4, 137.1, 142.4, 145.1, 154.0, 159.4 ppm; HRMS (ESI+) calcd for $C_{15}H_{12}N_3S^+$ [M + H^+] *m/z* 266.0746, found *m/z* 266.0748; IR: ν = 3054, 2946, 1548, 1468, 1449, 1417, 1332, 1316, 1157, 993, 898, 791, 768, 740, 729, 688 cm^{-1}; mp 217-218.5 °C.

2-(1-Ethyl-1H-benzimidazol-2-yl)benzothiazole (7d)

Following to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6d** (56.3 mg, 0.380 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **7d** (61.3 mg, 88 %).



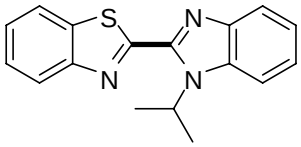
7d

^1H NMR (600 MHz, $CDCl_3$): δ 1.55 (t, *J* = 7.2 Hz, 3 H), 5.01 (q, *J* = 7.2 Hz, 2 H), 7.40 (m, 2 H), 7.44–7.53 (m, 3 H), 7.90 (d, *J* = 7.8 Hz, 1 H), 7.98 (d, *J* = 7.8 Hz, 1 H), 8.10 ppm (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.2, 40.4, 110.2, 120.5, 121.8, 123.4, 123.9, 124.5, 126.2, 126.4, 135.4, 136.0, 142.4, 144.4, 154.1, 159.0 ppm; HRMS (ESI+) calcd for $C_{16}H_{14}N_3S^+$ [M + H^+] *m/z* 280.0903, found *m/z* 280.0900; IR: ν = 3054, 2976, 2934, 1546,

1467, 1438, 1429, 1408, 1331, 1180, 1157, 1006, 954, 901, 768, 744, 730, 682 cm^{-1}; mp 158.5-161.5 °C.

2-(1-Isopropyl-1H-benzimidazol-2-yl)benzothiazole (7e)

Following to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6e** (61 mg, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **7e** (45.4 mg, 62 %).

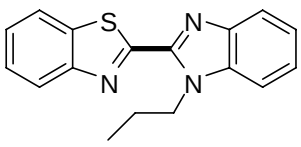


7e

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.76 (d, *J* = 7.2 Hz, 6 H), 6.65 (sept, *J* = 7.2 Hz, 1 H), 7.32–7.34 (m, 1 H), 7.46 (t, *J* = 7.5 Hz, 1 H), 7.52 (t, *J* = 7.2 Hz, 1 H), 7.71 (t, *J* = 4.5 Hz, 1 H), 7.91 (t, *J* = 4.5 Hz, 1 H), 7.97 (d, *J* = 7.8 Hz, 1 H), 8.11 ppm (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.4, 48.9, 113.2, 120.8, 121.7, 123.1, 123.9, 124.0, 126.2, 126.4, 134.9, 135.6, 142.9, 144.1, 153.9, 159.6 ppm; HRMS (ESI+) calcd for $C_{16}H_{14}N_3S^+$ [M + H^+] *m/z* 294.1059, found *m/z* 294.1057; IR: ν = 3062, 2967, 2934, 1538, 1484, 1438, 1428, 1391, 1333, 1312, 1255, 1178, 1157, 1103, 990, 902, 794, 770, 742, 732 cm^{-1}; mp 168-172 °C.

2-(1-Propyl-1H-benzimidazol-2-yl)benzothiazole (7f)

Following to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6f** (61 mg, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **7f** (60.7 mg, 83 %).



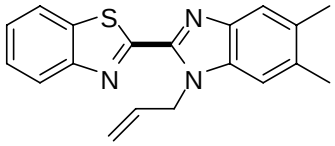
7f

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.2 Hz, 3 H), 1.99 (sext, *J* = 7.2 Hz, 2 H), 4.91 (t, *J* = 7.5 Hz, 2 H), 7.31–7.38 (m, 2 H), 7.43–7.48 (m, 2 H), 7.50–7.53 (m, 1 H), 7.89 (d, *J* = 7.8 Hz, 1 H), 7.97 (d, *J* = 7.8 Hz, 1 H), 8.09 ppm (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.3, 23.4, 46.7, 110.4, 120.5, 121.7, 123.3, 123.9, 124.4, 126.1, 126.4, 135.4, 136.5, 142.5, 144.7, 154.1, 159.4 ppm; HRMS (ESI+) calcd for $C_{16}H_{14}N_3S^+$ [M + H^+] *m/z*

294.1059, found *m/z* 294.1057; IR: ν = 3059, 2964, 2930, 2877, 1540, 1484, 1449, 1439, 1427, 1420, 1330, 1314, 1173, 1006, 912, 808, 760, 739, 729, 683 cm^{-1}; mp 88.2-91 °C.

2-(1-Allyl-5,6-dimethyl-1H-benzimidazol-2-yl)benzothiazole (7g)

Analogous to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6g** (71 mg, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **7g** (64.5 mg, 81 %).

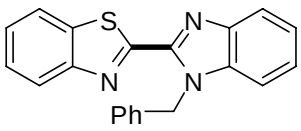


7g

^1H NMR (600 MHz, $CDCl_3$): δ 2.38 (s, 3 H), 2.40 (s, 3 H), 5.12 (d, *J* = 16.8 Hz, 1 H), 5.19 (d, *J* = 10.2 Hz, 1 H), 5.60–5.62 (m, 2 H), 6.05–6.12 (m, 1 H), 7.20 (s, 1 H), 7.42–7.45 (m, 1 H), 7.49–7.52 (m, 1 H), 7.66 (s, 1 H), 7.95 (d, *J* = 7.8 Hz, 1 H), 8.06–8.07 ppm (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.4, 20.9, 47.5, 110.6, 117.4, 120.1, 121.7, 123.8, 123.9, 126.1, 126.4, 132.6, 133.1, 134.6, 134.8, 135.4, 143.4, 154.0, 159.2 ppm; HRMS (ESI+) calcd for $C_{19}H_{18}N_3S^+$ [M + H^+] *m/z* 320.1216, found *m/z* 320.1214; IR: ν = 3059, 3021, 2918, 2854, 1542, 1478, 1446, 1419, 1370, 1359, 1316, 1159, 1024, 992, 926, 878, 838, 761, 730, 696 cm^{-1}; mp 197-198.5 °C.

2-(1-Benzyl-1H-benzimidazol-2-yl)benzothiazole (7i)

Analogous to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6i** (79 mg, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **7i** (68.9 mg, 81 %).



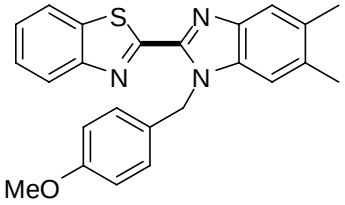
7i

^1H NMR (600 MHz, $CDCl_3$): δ 6.29 (s, 2 H), 7.21–7.23 (m, 1 H), 7.24–7.28 (m, 4 H), 7.29–7.34 (m, 2 H), 7.38–7.39 (m, 1 H), 7.42–7.45 (m, 1 H), 7.48–7.50 (m, 1 H), 7.89–7.90 (m, 1 H), 7.96 (d, *J* = 7.8 Hz, 1 H), 8.05 ppm (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 48.6, 110.9, 120.6, 121.7, 123.5, 123.9, 124.7, 126.2, 126.4, 127.1, 127.6, 128.7, 135.4,

136.69, 136.73, 142.8, 144.9, 154.0, 159.5 ppm; HRMS (ESI+) calcd for $C_{21}H_{16}N_3S^+$ [M + H^+] *m/z* 342.1059, found *m/z* 342.1060; IR: ν = 3026, 2980, 2926, 1544, 1495, 1448, 1429, 1333, 1312, 1164, 1078, 1040, 959, 763, 748, 727, 708, 695 cm^{-1}; mp 192-193.5 °C.

2-(1-(4-Methoxybenzyl)-5,6-dimethyl-1H-benzimidazol-2-yl)benzothiazole (7j)

Analogous to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6j** (104 mg, 0.380 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **7j** (83.7 mg, 84 %).

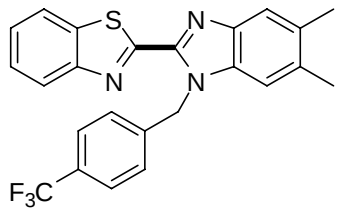


7j

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.35 (s, 3 H), 2.36 (s, 3 H), 3.71 (s, 3 H), 6.16 (s, 2 H), 6.77–6.79 (m, 2 H), 7.18 (s, 1 H), 7.21–7.23 (m, 2 H), 7.42–7.45 (m, 1 H), 7.48–7.51 (m, 1 H), 7.68 (s, 1 H), 7.96 (d, *J* = 7.8 Hz, 1 H), 8.05 ppm (d, *J* = 8.4 Hz, 1 H); HRMS (ESI+) calcd for $C_{24}H_{22}N_3OS^+$ [M + H^+] *m/z* 400.1478, found *m/z* 400.1479; IR: ν = 3020, 2983, 2970, 2937, 2909, 2855, 2835, 1610, 1548, 1544, 1513, 1450, 1427, 1384, 1366, 1330, 1302, 1251, 1240, 1186, 1178, 1102, 1026, 1010, 950, 850, 808, 756, 729, 704 cm^{-1}; mp 208-209 °C.

2-(5,6-Dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-benzimidazol-2-yl)benzothiazole (7k)

Analogous to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6k** (119 mg, 0.380 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **7k** (94.9 mg, 87 %).



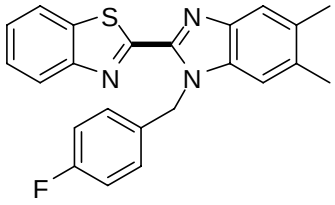
7k

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.36 (s, 3 H), 2.38 (s, 3 H), 6.28 (s, 2 H), 7.09 (s, 1 H), 7.33 (d, *J* = 7.8 Hz, 2 H), 7.42–7.44 (m, 1 H), 7.46–7.49 (m, 1 H), 7.52 (d, *J* = 7.8 Hz, 2 H), 7.68

(s, 1 H), 7.95 (d, J = 7.2 Hz, 1 H), 7.99 ppm (d, J = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.4, 20.9, 48.2, 110.4, 116.1, 121.2, 121.7, 123.8, 123.9 (CF_3, J = 271 Hz), 124.8, 125.7 (CF_3, J = 3.9 Hz), 126.3, 126.5, 127.1, 128.8, 129.8 (CF_3, J = 32.3 Hz), 131.9, 135.0 (CF_3, J = 15.5 Hz), 135.4, 140.8, 153.8, 160.2 ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): δ = -62.63 ppm; HRMS (ESI+) calcd for $C_{24}H_{19}F_3N_3S^+$ [M + H^+] *m/z* 438.1246, found *m/z* 438.1244; IR: ν = 3060, 2976, 2927, 2859, 1620, 1446, 1417, 1387, 1374, 1326, 1163, 1116, 1066, 1018, 963, 941, 872, 840, 756, 728, 683, 632, 607 cm^{-1}; mp 235.9-236.2 °C.

2-(1-(4-Fluorobenzyl)-5,6-dimethyl-1H-benzimidazol-2-yl)benzothiazole (7l)

Analogous to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6l** (97 mg, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **7l** (71.5 mg, 74 %).

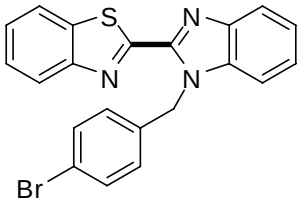


7l

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.37 (s, 3 H), 2.38 (s, 3 H), 6.18 (s, 2 H), 6.95 (t, J = 8.7 Hz, 2 H), 7.14 (s, 1 H), 7.25–7.27 (m, 2 H), 7.43–7.45 (m, 1 H), 7.48–7.51 (m, 1 H), 7.67 (s, 1 H), 7.96 (d, J = 7.8 Hz, 1 H), 8.03 ppm (d, J = 8.4, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.4, 20.9, 47.9, 110.6, 115.6 (F, J = 21.5 Hz), 120.3, 121.7, 123.0 (F, J = 307 Hz), 123.7, 126.1, 126.4, 126.7 (F, J = 31.2 Hz), 128.8 (F, J = 8.1 Hz), 132.6, 133.1, 134.7, 135.1, 135.3, 153.9 161.3, 163.0 ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): δ = -114.67 ppm; HRMS (ESI+) calcd for $C_{23}H_{19}FN_3S^+$ [M + H^+] *m/z* 388.1278, found *m/z* 388.1274; IR: ν = 3065, 2968, 2923, 1603, 1545, 1509, 1451, 1425, 1414, 1382, 1369, 1315, 1220, 1154, 1010, 955, 818, 758, 730, 706, 696, 683 cm^{-1}; mp 221.8-223.5 °C.

2-(1-(4-Bromobenzyl)-1H-benzimidazol-2-yl)benzothiazole (7m)

Analogous to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6m** (107 mg, 0.380 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **7m** (81.7 mg, 78 %).

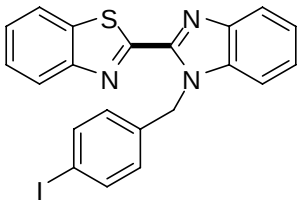


7m

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.22 (s, 2 H), 7.15 (d, *J* = 8.4 Hz, 2 H), 7.32–7.39 (m, 5 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.91 (d, *J* = 7.2 Hz, 1 H), 7.97 (d, *J* = 7.8 Hz, 1 H), 8.03 ppm (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 48.1, 110.7, 120.6, 121.7, 121.8, 123.8, 123.9, 125.0, 126.4, 126.6, 128.8, 131.9, 135.5, 135.6, 136.4, 142.4, 144.6, 153.8, 160.0 ppm; HRMS (ESI+) calcd for $C_{21}H_{15}BrN_3S^+$ [M + H^+] *m/z* 420.0165, found *m/z* 420.0162; IR: ν = 3056, 2948, 1487, 1447, 1427, 1448, 1316, 1152, 1070, 1028, 1012, 943, 84, 803, 790, 754, 738, 727, 688 cm^{-1}.

2-(1-(4-Iodobenzyl)-1H-benzimidazol-2-yl)benzothiazole (7n)

Analogous to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6n** (129 mg, 0.380 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **7n** (94.5 mg, 81 %).

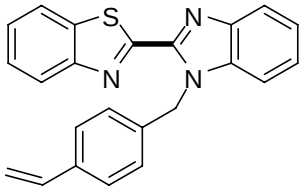


7n

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.22 (s, 2 H), 7.01 (d, *J* = 8.4 Hz, 2 H), 7.32–7.37 (m, 3 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.49-7.52 (m, 1 H), 7.59 (d, *J* = 7.8 Hz, 2 H), 7.92 (d, *J* = 7.8 Hz, 1 H), 7.97 (d, *J* = 7.8 Hz, 1 H), 8.03 ppm (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 48.2, 93.2, 110.7, 120.6, 121.8, 123.9, 124.0, 125.1, 126.4, 126.6, 129.0, 135.5, 136.2, 136.3, 137.8, 142.2, 144.5, 153.8, 158.8 ppm; HRMS (ESI+) calcd for $C_{21}H_{15}IN_3S^+$ [M + H^+] *m/z* 468.0026, found *m/z* 468.0023; IR: ν = 3058, 1482, 1459, 1444, 1418, 1406, 1317, 1251, 1160, 1007, 967, 931, 803, 753, 744, 725, 700 cm^{-1}; mp 228.5-231 °C.

2-(1-(4-Vinylbenzyl)-1H-benzimidazol-2-yl)benzothiazole (7o)

Analogous to *General Procedure C*, **1** (29 µL, 0.25 mmol) and **6o** (90 mg, 0.38 mmol) were combined with $Pd(OAc)_2$ (5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (2 equiv.), and AgOAc (2 equiv.) for 24 h to afford **7o** (81.6 mg, 89 %).



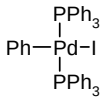
7o

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.18 (d, *J* = 10.8 Hz, 1 H), 5.65 (d, *J* = 17.4 Hz, 1 H), 6.27 (s, 2 H), 6.62 (dd, *J* = 17.4 Hz, *J* = 10.8 Hz, 1 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 7.31–7.35 (m, 2 H), 7.38–7.40 (m, 1 H), 7.43–7.46 (m, 1 H), 7.48–7.51 (m, 1 H), 7.91 (d, *J* = 8.4 Hz, 1 H), 7.97 (d, *J* = 7.8 Hz, 1 H), 8.04–8.05 ppm (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 48.5, 110.9, 114.1, 120.5, 121.7, 123.7, 124.0, 124.9, 126.3, 126.48, 126.54, 127.3, 135.5, 136.1, 136.2, 136.6, 137.1, 142.5, 144.7, 153.9, 159.1 ppm; HRMS (ESI+) calcd for $C_{23}H_{18}N_3S^+$ [M + H^+] *m/z* 368.1216, found *m/z* 368.1213; IR: ν = 3060, 2980, 2917, 2360, 2341, 1543, 1513, 1447, 1423, 1406, 1331, 1315, 1250, 1158, 965, 944, 911, 894, 826, 745, 760, 731, 700 cm^{-1}; mp 163.5-164.7 °C.

5.5.4 Reactions of Benzothiazole with *trans*-[PhPdI(PPh_3)$_2$] (8)

***trans*-[PhPdI(PPh_3)$_2$] (8)**[S7]

Under an atmosphere of dry N_2, a solution of [(Ph_3P)$_4$Pd] (1.16 g, 1.00 mmol) in toluene (15 mL) was prepared. After the addition of iodobenzene (124 µL, 1.09 mmol), the mixture was stirred at room temperature for 20 h. The product was isolated in air. The solvent was removed under vacuum to give a colorless solid. Recrystallization from CH_2Cl_2/*n*-pentane yielded **8** (726 mg, 87 %).



8

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.20 (t, *J* = 7.4 Hz, 2 H), 6.31 (t, *J* = 7.2 Hz, 1 H), 6.57–6.60 (m, 2 H), 7.20–7.24 (m, 12 H), 7.30 (t, *J* = 7.4 Hz, 6 H), 7.46–7.51 ppm (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.8, 127.7 (virtual t, *J* = 5.1 Hz), 129.6, 132.2 (virtual t, *J* = 23.0 Hz), 134.9 (virtual t, *J* = 6.2 Hz), 136.0 ppm (virtual t, *J* = 5.0 Hz), 159.1 (virtual t, *J* = 2.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.9 ppm.

Reactions between Benzothiazole 1 and the Palladium Complex 8

a) *Under Optimized Reaction Conditions*: Under air atmosphere, a 25 mL Schlenk flask was charged with *trans*-[PhPdI(PPh_3)$_2$] (**8**, 0.21 g, 0.25 mmol), $Pd(OAc)_2$ (1.4 mg, 5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (51 mg, 0.25 mmol) and AgF (32 mg, 0.25 mmol). Benzothiazole **1** (14.5 µL, 0.125 mmol) and DMF (2.5 mL) were added by using syringes. The reaction mixture was stirred for 10 min at room temperature and then heated at 120 °C in an oil bath for 9 h. After the completion of the reaction, the mixture was poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was

[S7] a) Y. Hu, J. Liu, Z. Lü, X. Luo, H. Zhang, Y. Lan, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 3153–3158; b) V. V. Grushin, *Organometallics* **2000**, *19*, 1888–1900.

purified by column chromatography on silica gel to give 2-phenyl-benzothiazole (**9**, 19.5 mg, 74 %).

9: Known compound [CAS 883-93-2]. The NMR spectroscopic data agree with those reported in lit. [S8].^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.40 (m, 1 H), 7.46–7.50 (m, 4 H), 7.88–7.91 (m, 1 H), 8.05–8.11 ppm (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.6, 123.2, 125.2, 126.3, 127.6, 129.0, 131.0, 133.6, 135.1, 154.2, 168.1 ppm; mp 113–113.5 °C.

b) *Without Additive*: Under air atmosphere, a 25 mL Schlenk flask was charged with *trans*-[$(PPh_3)_2$PhPdI] (**8**, 0.21 g, 0.25 mmol). Then benzothiazole **1** (14.5 μL, 0.125 mmol) and DMF (2.5 mL) were added by using syringes. The reaction mixture was stirred for 10 min at room temperature and then heated at 120 °C in an oil bath for 9 h. After the completion of the reaction, the mixture was poured into a saturated aqueous NaCl solution (5 mL) and extracted with ethyl acetate (5 mL). Only trace amounts of **9** were detected in the organic phase by GC-MS analysis.

c) *Competition Experiment (Scheme 7)*: Under air atmosphere, a 25 mL Schlenk flask was charged with *trans*-[$(PPh_3)_2$PhPdI] **8** (0.21 g, 0.25 mmol), $Pd(OAc)_2$ (5 mol-%, 2.8 mg), $Cu(OAc)_2 \cdot H_2O$ (0.50 mmol, 0.10 g) and AgF (64 mg, 0.50 mmol). Then benzothiazole **1** (29 μL, 0.25 mmol) and 1-methyl-imidazole **2a** (20 μL, 0.25 mmol) were added, followed by DMF (2.5 mL) with syringe. The reaction mixture was stirred for 10 min at room temperature and then heated at 120 °C in an oil bath for 22 h. After the completion of the reaction, the mixture was poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel to give **3a** (34.9 mg, 65 %) and **9** (17.4 mg, 33 %).

[S8] H. Hachiya, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 1737–1740.

5.5.5 Reaction of Benzothiazole 1 with 4,5-Dimethylthiazole 2i without AgF (*Scheme 8*)

Under air atmosphere, a 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (2.8 mg, 5 mol-%,) and $Cu(OAc)_2 \cdot H_2O$ (0.10 g, 0.50 mmol). Benzothiazole **1** (29 µL, 0.25 mmol), 4,5-dimethylthiazole **2i** (41 µL, 0.38 mmol), and DMF (2.5 mL) were added by using syringes. The reaction mixture was stirred for 10 min at room temperature and then heated at 120 °C in an oil bath for 22 h. After completion of the reaction, the mixture was cooled to room temperature and poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was analyzed by GC-MS (the presence of a species with *m*/*z* 268 was assigned to 2,2'-bibenzothiazole, ca. 15 %). Further purification by column chromatography on silica gel afforded **3i** (25.2 mg, 41 %, calculated on the basis of **1**) and 4,4',5,5'-tetramethyl-2,2'-bithiazole (**10**, 18.4 mg, 43 %, calculated on the basis of **2i**).

10: Known compound [CAS Reg. No. 3944-30-7]. The NMR spectroscopic data agree with those described in lit. [S9]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 6 H), 2.37 ppm (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 14.8, 128.1, 149.5, 157.1 ppm.

5.5.6 Palladium-Catalyzed Reactions of Azoles with $[Ph_2I]^+[PF_6]^-$

Reaction of Benzothiazole (1) with $[Ph_2I]^+[PF_6]^-$:

Under air atmosphere, a 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (2.8 mg, 5 mol-%) and $[Ph_2I]^+[PF_6]^-$ (0.22 g, 0.52 mmol). Benzothiazole **1** (29 µL, 0.25 mmol) was added by using a syringe. After the addition of DMF (2.5 mL) the reaction mixture was stirred for 10 min at room temperature and then heated at 120 °C in an oil bath for 22 h. Then, the mixture was cooled to room temperature and poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate. GC-MS analysis of the crude product did not show signals that could be assigned to a phenylated benzothiazole.

[S9] Y. Li, J. Jin, W. Qian, W. Bao, *Org. Biomol. Chem.* **2010**, *8*, 326–330.

Reaction of 1-Methyl-imidazole (2a) with $[Ph_2I]^+[PF_6]^-$:

Under air atmosphere, a 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (2.8 mg, 5 mol-%) and $[Ph_2I]^+[PF_6]^-$ (0.22 g, 0.52 mmol). Imidazole **2a** (20 µL, 0.25 mmol) was added by using a syringe. After the addition of DMF (2.5 mL) the reaction mixture was stirred for 10 min at room temperature and then heated at 120 °C in an oil bath for 22 h. Then, the mixture was cooled to room temperature and poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate. GC-MS analysis of the crude product did not show signals that could be assigned to a phenylated imidazole.

5.5.7 Powder X-Ray Diffraction Analysis (XRD Analysis)

XRD analyses were carried out on a Huber G670 with Guinier imaging plate detector (Cu-K_1 radiation, λ = 154.051 pm, Ge(111) monochromator).

(*a*) The reaction was carried out under the conditions of Table 1, entry 5. Under air atmosphere, a 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (2.8 mg, 5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (0.10 g, 0.50 mmol), and AgF (64 mg, 0.50 mmol). Then benzothiazole **1** (29 µL, 0.25 mmol) and 1-methyl-imidazole **2a** (30 µL, 0.38 mmol) were added by using syringes. After the addition of DMF (2.5 mL) the reaction mixture was stirred for 10 min at room temperature and then heated at 120 °C in an oil bath for 22 h. After completion of the reaction (TLC control), the mixture was cooled to room temperature. The solid components of the slurry were isolated by filtration, washed with diethyl ether (2 ×), dried in the vacuum, and analyzed by XRD (blue line in Figure S1).

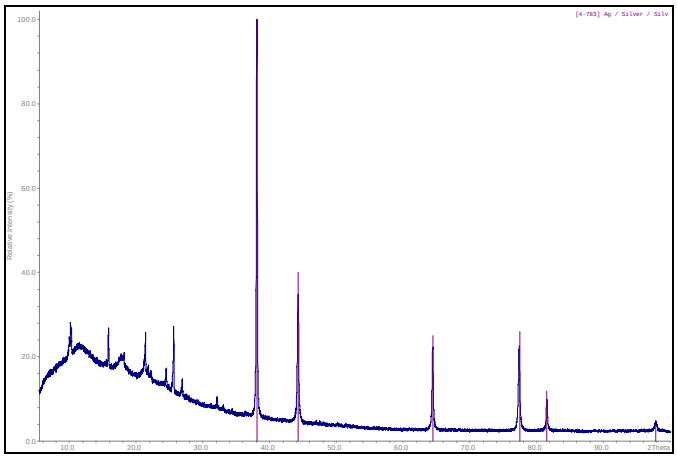


Figure S1. XRD of the solid components of the reaction mixture of **1** and **2a** after completion of the reaction (using AgF). Violet lines were assigned to Ag^0.

(*b*) The reaction was carried out under the conditions of Table 1, entry 6. Under air atmosphere, a 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (2.8 mg, 5 mol-%), $Cu(OAc)_2 \cdot H_2O$ (0.10 g, 0.50 mmol), KF (44 mg, 0.75 mmol), and $AgNO_3$ (65 mg, 0.38 mmol). Then benzothiazole **1** (29 µL, 0.25 mmol) and 1-methyl-imidazole **2a** (30 µL, 0.38 mmol) were added by using syringes. After the addition of DMF (2.5 mL) the reaction mixture was stirred for 10 min at room temperature and then heated at 120 °C in an oil bath for 22 h. After completion of the reaction (TLC control), the mixture was cooled to room temperature The solid components of the reaction mixture were isolated by filtration, washed with diethyl ether (2 ×), dried in the vacuum, and analyzed by XRD (blue line in Figure S2).

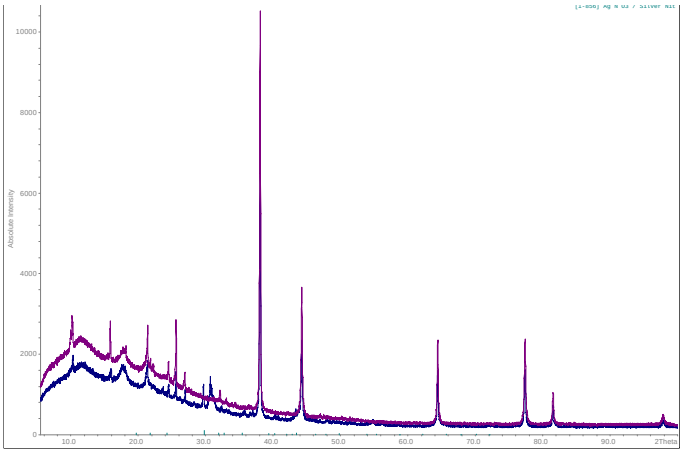


Figure S2. XRD of the solid components of the reaction mixture of **1** and **2a** with $KF/AgNO_3$ (upper line, in violet color) after completion of the reaction and compared to the sample

obtained from the reaction with AgF (lower line, in blue color; for the assignment of the diffraction pattern, see above).

5.5.8 X-Ray Crystal Structure Analysis

X-Ray Crystal Structure Analysis of 3a

The data collection was performed on a Oxford Diffraction XCalibur diffractometer. The structure was solved by direct methods with SIR97[S10] and refined with SHELXL-97.[S11] The shown thermal ellipsoids are drawn at the 50% probability level (Figure S3).

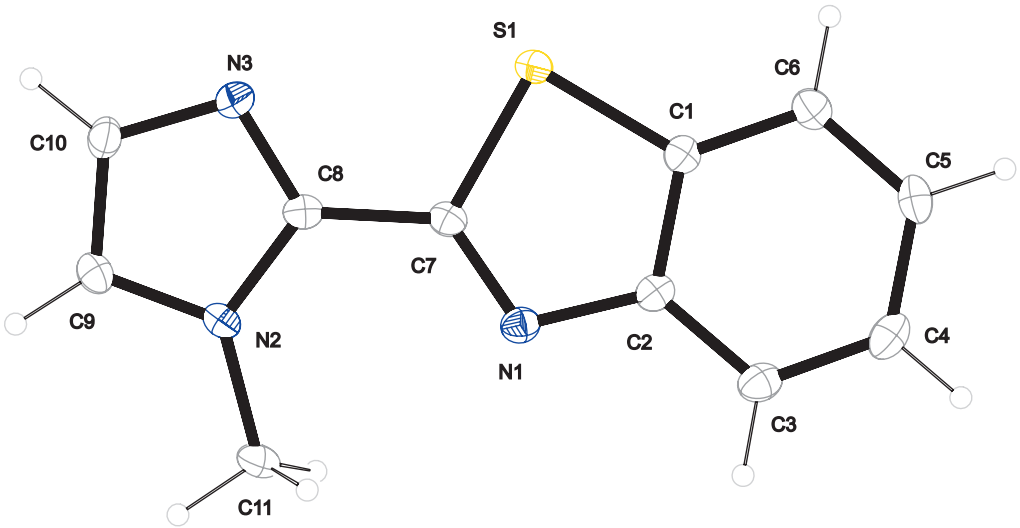


Figure S3. X-ray single crystal structure of **3a**.

CCDC 785105 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[S10]A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115–119.

[S11]G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112–122.

3a. Crystallographic data.

	3a
net formula	$C_{11}H_9N_3S$
M_r/g mol^{-1}	215.275
crystal size/mm	0.28 × 0.11 × 0.06
T/K	173(2)
radiation	MoKα
diffractometer	'Oxford XCalibur'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	4.5770(2)
b/Å	11.8447(5)
c/Å	18.1620(9)
α/°	90
β/°	90
γ/°	90
V/Å^3	984.62(8)
Z	4
calc. density/g cm^{-3}	1.45225(12)
μ/mm^{-1}	0.294
absorption correction	'multi-scan'
transmission factor range	0.80245–1.00000
refls. measured	3871
R_{int}	0.0277
mean σ(I)/I	0.0723
θ range	4.49–26.31
observed refls.	1414
x, y (weighting scheme)	0.0286, 0
hydrogen refinement	constr
Flack parameter	−0.04(10)
refls in refinement	1923
parameters	137
restraints	0
$R(F_{obs})$	0.0346
$R_w(F^2)$	0.0650
S	0.852
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.240
min electron density/e Å^{-3}	−0.257

X-Ray Crystal Structure Analysis of 7b

The data collection was performed on a Oxford Diffraction XCalibur diffractometer. The structure was solved by direct methods with SIR97[S9] and refined with SHELXL-97.[S10] The shown thermal ellipsoids are drawn at the 50% probability level (Figure S4).

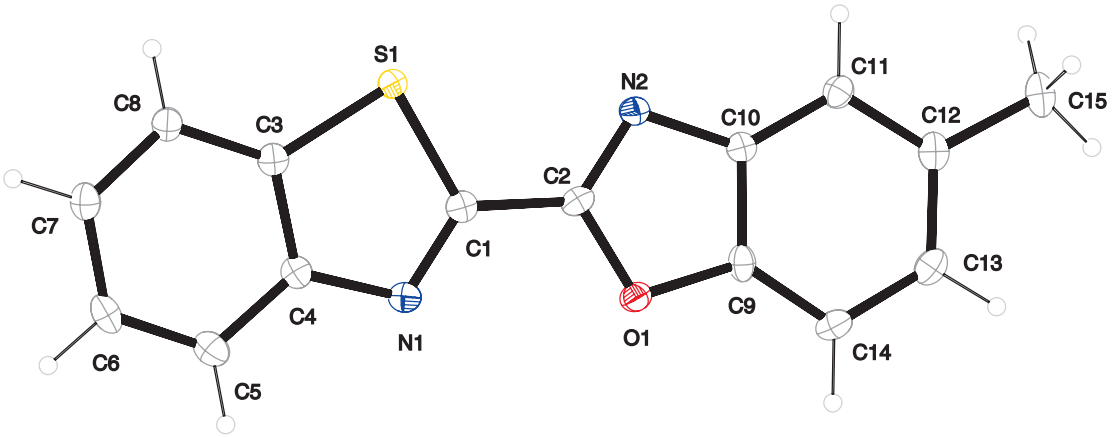


Figure S4. X-ray single crystal structure of **7b**.

7b. Crystallographic data.

	7b
net formula	$C_{15}H_{10}N_2OS$
M_r/g mol^{-1}	266.319
crystal size/mm	0.58 × 0.07 × 0.03
T/K	173(2)
radiation	MoKα
diffractometer	'KappaCCD'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	6.02530(10)
b/Å	8.8223(2)
c/Å	23.0442(6)
α/°	90
β/°	90
γ/°	90
V/Å^3	1224.96(5)
Z	4
calc. density/g cm^{-3}	1.44409(6)
μ/mm^{-1}	0.255
absorption correction	none
refls. measured	7977
R_{int}	0.0419
mean σ(I)/I	0.0314
θ range	3.50–25.38
observed refls.	2134
x, y (weighting scheme)	0.0449, 0.6855
hydrogen refinement	constr
Flack parameter	0.28(10)
refls in refinement	2241
parameters	173
restraints	0
$R(F_{obs})$	0.0378
$R_w(F^2)$	0.0985
S	1.102
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.612
min electron density/e Å^{-3}	−0.190

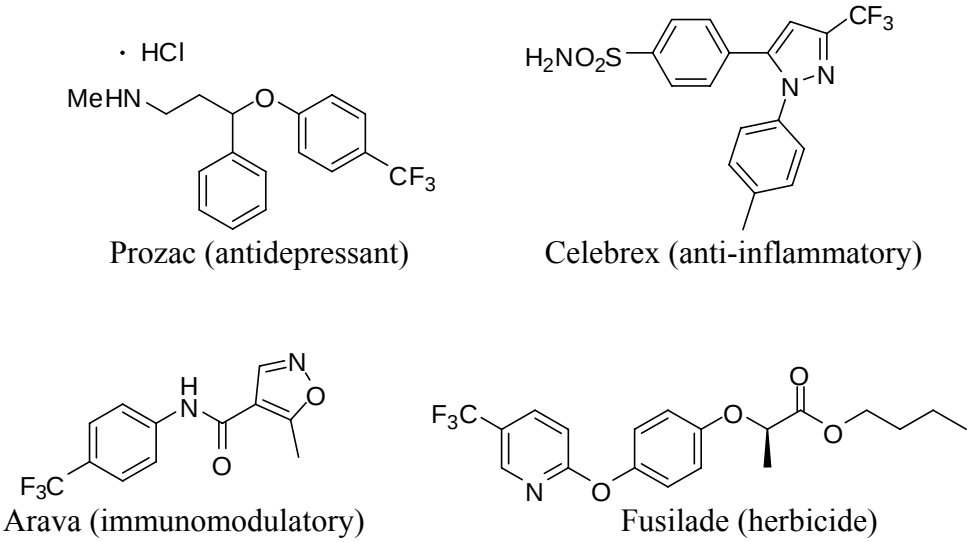
909 Friedel pairs have been measured.

Chapter 6

Palladium-Catalyzed Direct Trifluoromethylation of Azoles via sp^2 C-H Activation

6.1 Introduction

The introduction of a CF_3 group into a molecule can modulate its physical, chemical, and biological properties in many ways, including alteration of the shape and size[1] of the reference substance, its acidity,[2] its dipole moments and polarizability,[3] its lipophilicity and transport behavior,[4] and its chemical and metabolic stability.[5] All this makes the CF_3 unit featured in many important pharmaceuticals and herbicides, such as the antidepressant fluoxetine (Prozac), the anti-inflammatory drug celecoxib (Celebrex), Arava and the herbicide Fusilade (Scheme 1).[6] So, the development of methods for the introduction of trifluoromethyl groups at aromatic rings has been of increasing interest.[7]

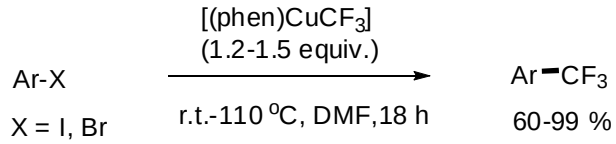


Scheme 1. Trifluoromethylated aromatic pharmaceuticals and herbicides.

Traditional methods for introducing a trifluoromethyl group include the Swarts reaction[8] and the treatment of benzoic acid derivatives with SF_4.[9] Both options usually require harsh

conditions that limit the functional group tolerance. Alternatively, copper-mediated trifluoromethylations of aryliodides or activated aryl bromides with CF_3 sources, such as trifluoromethylsilanes, trifluoroacetate salts, methyl fluorosulfonyldifluoroacetate and trifluoromethyl sulfonium triflate, have been developed.[10, 15] Recently, Qing and coworkers reported a stoichiometric copper-mediated oxidative trifluoromethylation of arylboronic acids at 45 ^oC.[11] Concurrently, Buchwald et al. reported a more benign and economic system for the copper-mediated oxidative cross-coupling of aryl boronic acids and Me_3SiCF_3 at room temperature.[12]

Notably, all of the above-mentioned methods must use stoichiometric amounts of copper. The seminal example of copper-catalyzed aromatic trifluoromethylation of aryl iodides was reported by Amii et al. using a CuI/1,10-phenanthroline complex as the catalyst and Me_3SiCF_3 as the CF_3 source.[13] Subsequently, Gooßen and coworkers introduced potassium (trifluoromethyl)trimethoxyborate as an air-stable CF_3 reagent that reacts with aryl iodides employing a CuI/1,10-phenanthroline catalytic system.[14] They proposed that the reactions proceeded via an intermediate phenanthroline-ligated copper(I) complex [(phen)$CuCF_3$], but this key intermediate had not been generated previously and was not isolated or detected spectroscopically in the catalytic system. Very recently, the Hartwig group prepared and isolated this complex [(phen)$CuCF_3$].[15] Moreover, [(phen)$CuCF_3$] was found to react well with activated or unactivated aryl iodides as well as with aryl bromides under mild conditions, even at room temperature (Scheme 2).



Scheme 2. Copper-mediated trifluoromethylation with isolated [(phen)$CuCF_3$].

Palladium is a versatile metal in organic synthesis, particularly in cross-coupling reactions with carbon-carbon bond formation. The Ar-CF_3 coupling reaction is one special type of C-C couplings. Generally, the challenging step of the catalytic cycle in the Ar-CF_3 coupling reaction is the reductive elimination of [$L_nPd(Ar)CF_3$] due to the inert nature and strength of Pd-CF_3 bond.[16]

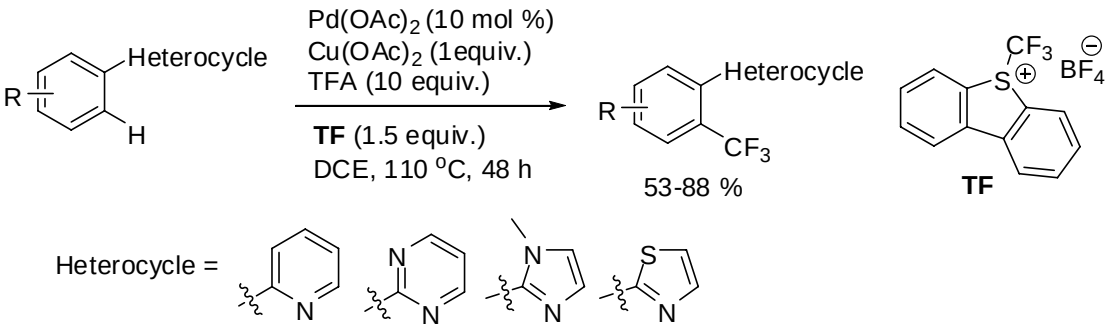
In this respect, breakthroughs have been achieved by Grushin[17] and Sanford,[18] who demonstrated the feasibility of reductive eliminations of CF_3 groups from well-defined Pd^{II} and Pd^{IV} complexes. Although a catalytic version of aromatic trifluoromethylation was

achieved by the Ishikawa group, the scope of the substrates is quite limited. Very recently, a landmark of Pd-catalyzed aromatic trifluoromethylation was reported by Buchwald et al.[20] This methodology allowed for trifluoromethylation of unactivated aryl chlorides bearing electron-rich or electron-poor substituents (see Chapter 1.4).

Especially noteworthy, all of the transition-metal mediated processes described above must employ prefunctionalized substrates, such as aryl halides or arylboronic acids.

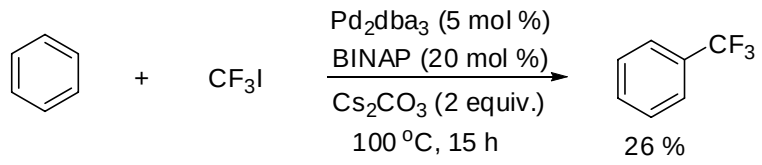
In recent years, transition-metal-catalyzed functionalization of C-H bond have attracted considerable interest in view of the importance of green and sustainable chemistry.[21] Compared to the above mentioned examples, direct trifluoromethylation reactions through cleavage of C-H bonds[21] represent an environmentally and economically more attractive strategy which avoids the preparation of functional groups and thus, makes synthetic schemes shorter and more efficient.

However, metal-catalyzed aryl C–H trifluoromethylation protocols remain rare. In 2010, Yu and co-workers first demonstrated the direct trifluoromethylation of arenes with a dibenzothiophenium reagent (Scheme 3).[22] This transformation enabled arenes bearing pyrimidine, imidazole, or thiazole as directing groups to be efficiently trifluoromethylated with high regioselectivity. However, the reaction strictly requires the presence of a heterocyclic directing group in the substrate.



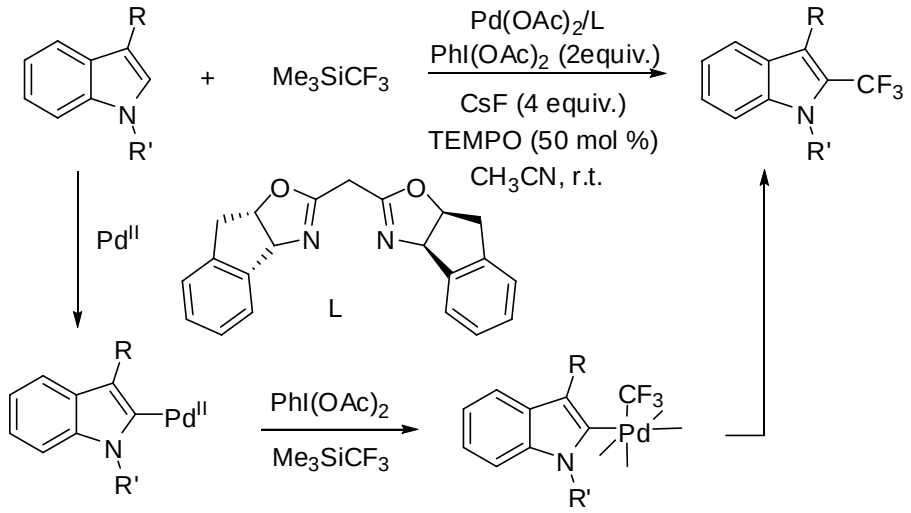
Scheme 3. Pd(II)-catalyzed *ortho*-trifluoromethylation of arenes via sp^2 C-H activation.

Subsequently, without the aid of a directing group palladium-catalyzed reactions between perfluoroalkyl iodides and simple arenes were described by the group of Sanford. Although this protocol can be performed under milder conditions, most of substrates are limited to electron-rich arenes and it is inefficient to trifluoromethylate arenes with CF_3I (Scheme 4).[23]



Scheme 4. Palladium-catalyzed trifuoromethylation of benzene with CF_3I.

Almost at the same time, Liu and co-workers reported a new palladium-catalyzed oxidative trifluoromethylation of indoles with Me_3SiCF_3 at room temperature (Scheme 5).[24] This transformation afforded trifluoromethylated indoles in 33-75 % with high regioselectivities. A possible mechanism was proposed in which the first step of the reaction is electrophilic palladation of indole generating an $(Ar)Pd^{II}$ intermediate, followed by being oxidized into a $(Ar)Pd^{IV}$-CF_3 intermediate in the presence of $PhI(OAc)_2/Me_3SiCF_3$. This species finally undergoes reductive elimination to give the aryl C-CF_3 bond.



Scheme 5. Pd^{II}-catalyzed trifluoromethylation of indoles with Me_3SiCF_3 at room temperature.

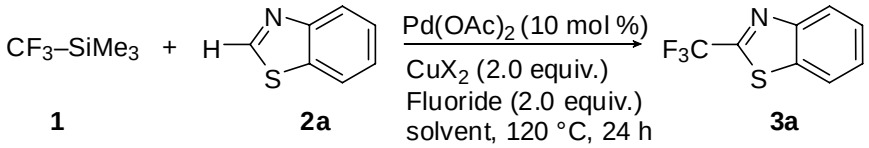
2-(Trifluoromethyl)benzimidazoles are of wide interest due to their diverse biological activity acting as antiviral, antifungal, antibacterial, anticancer and antiparasitic drugs.[25] Herein, we develop a new method for the palladium(II)-catalyzed trifluoromethylation of C-2 positions in azoles with Me_3SiCF_3 (named Ruppert's Reagent)[26] via sp^2 C-H activation without any directing group.

6.2 Results and Discussion

6.2.1 Reaction Optimization

Recently, our group has successfully reported a triple metal system $Pd(OAc)_2$/ $Cu(OAc)_2 \cdot H_2O$/AgF for direct Hiyama-type reactions, i.e., azoles with triethoxy(aryl)silanes via sp^2 C-H activation.[27] Initially, we chose the reaction of benzothiazole (**2a)** and Me_3SiCF_3 as a model reaction with the triple metal system to identify and optimize the critical reaction parameters (Table 1). When the reaction was performed under the same conditions as described for the direct Hiyama reaction,[27] product **3a** was obtained in 35 % yield with high regioselectivity for C-2 (Table 1, entry 1). Considering the fact that the Me_3SiCF_3 is sensitive to moisture, we conducted the same reaction under dry nitrogen atmosphere and consequently, the yield increased slightly to 39 % (Table 1, entry 2). Gratifyingly, a good yield was obtained (61 %) when the reaction was proceeded under oxygen atmosphere (Table 1, entry 3). This result implies that oxygen is helpful for the reaction. The yield was further improved to 68 % by using anhydrous $Cu(OAc)_2$ instead of $Cu(OAc)_2 \cdot H_2O$ (Table 1, entry 4). Compared to the AgF, the combination of $AgNO_3$ and KF gave **3a** in a lower yield (Table 1, entry 5). Among the different solvents screened, DMF/DMSO (v/v 4:1) is the most suitable for the transformation (Table 1, entries 6-14). A ligand is useful to address the challenging reductive elimination of CF_3-PdAr.[16] Hence, we tested several ligands, such as pyridine, 1,10-phenanthroline and 2,2'-bipyridine in the semi-optimized system to afford **3a** in 73 %, 59 % and 83 % yields, respectively (Table 1, entries 15-17). Other copper sources ($Cu(OTf)_2$, CuF_2) were inefficient for the reaction (Table 1, entries 15-17).

Table 1. Optimization of the palladium-catalyzed direct C–H trifluoromethylation of **2a** with Me_3SiCF_3 (**1**).[a]



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

Entry	Fluoride	CuX_2	Solvent	Yield[b] [%]
1[c]	AgF	$Cu(OAc)_2 \cdot H_2O$	DMF	35
2[d]	AgF	$Cu(OAc)_2 \cdot H_2O$	DMF	39
3	AgF	$Cu(OAc)_2 \cdot H_2O$	DMF	61
4	AgF	$Cu(OAc)_2$	DMF	68
5	$AgNO_3$ (2.0) and KF (3.0)	$Cu(OAc)_2$	DMF	59
6	AgF	$Cu(OAc)_2$	toluene	38
7	AgF	$Cu(OAc)_2$	dioxane	trace
8	AgF	$Cu(OAc)_2$	CH_3CN	31
9	AgF	$Cu(OAc)_2$	DMF/DMSO (20 mol %)	69
10	AgF	$Cu(OAc)_2$	DMF/DMSO (v/v 9:1)	71
11	AgF	$Cu(OAc)_2$	DMF/DMSO (v/v 4:1)	76
12	AgF	$Cu(OAc)_2$	DMSO	70
13	AgF	$Cu(OAc)_2$	DMF/$PhCF_3$ (v/v 4:1)	58
14	AgF	$Cu(OAc)_2$	DMF/NMP (v/v 4:1)	46
15[e]	AgF	$Cu(OAc)_2$	DMF/DMSO (v/v 4:1)	73
16[f]	AgF	$Cu(OAc)_2$	DMF/DMSO (v/v 4:1)	59
17[g]	AgF	$Cu(OAc)_2$	DMF/DMSO (v/v 4:1)	83

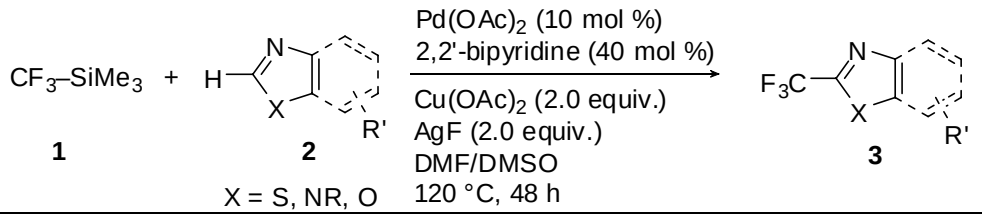
18[g]	AgF	$Cu(OTf)_2$	DMF/DMSO (v/v 4:1)	33
19[g]	AgF	CuF_2	DMF/DMSO (v/v 4:1)	trace

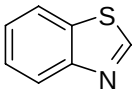
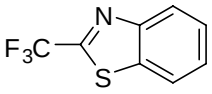
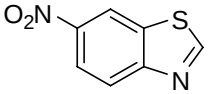
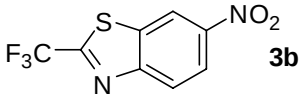
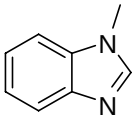
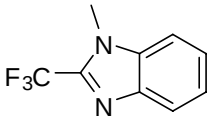
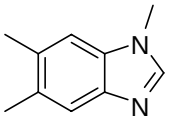
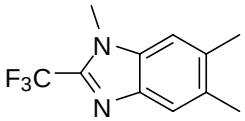
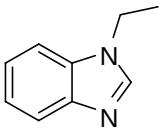
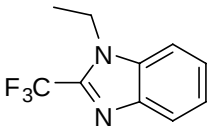
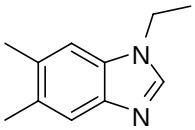
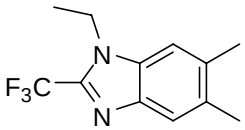
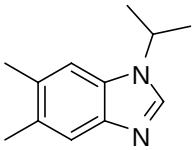
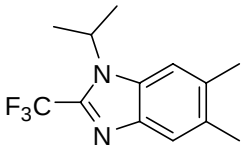
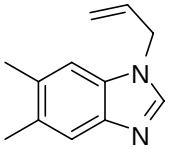
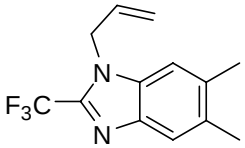
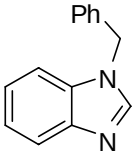
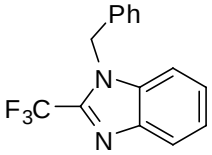
[a] A mixture of Me_3SiCF_3 (0.75 mmol), benzothiazole (0.25 mmol), $Pd(OAc)_2$ (10 mol-%), CuX_2 (0.50 mmol), and fluoride (0.50 mmol) in solvent (1.0 mL) was stirred at 120 °C for 24 h in oxygen. [b] Yield of isolated **3a**. [c] Air atmosphere. [d] Nitrogen atmosphere. [e] Pyridine (1.0 equiv.). [f] 1,10-Phenanthroline (40 mo %). [g] 2,2'-Bipyridine (40 mol %).

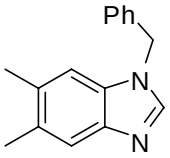
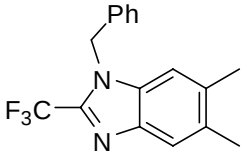
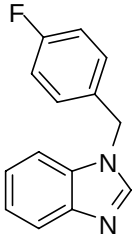
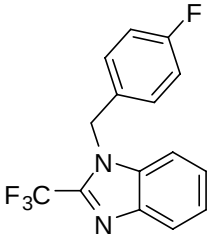
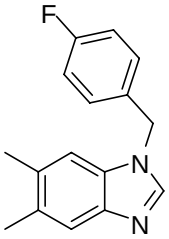
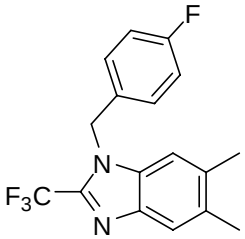
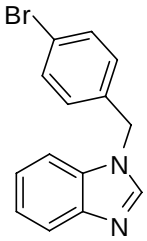
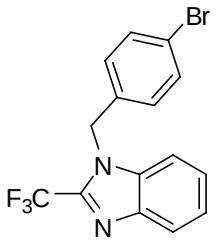
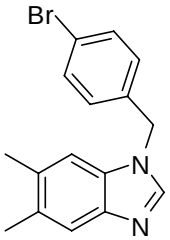
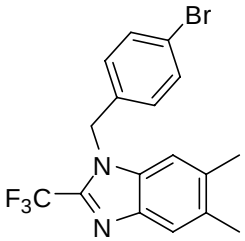
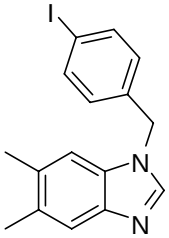
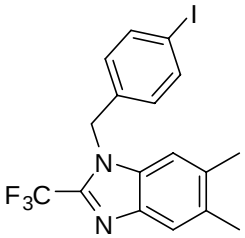
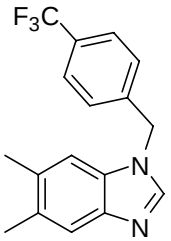
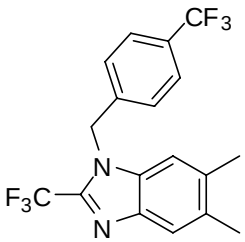
6.2.2 Substrate scope

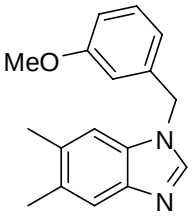
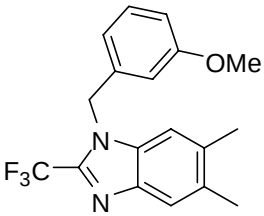
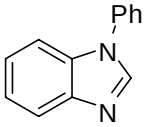
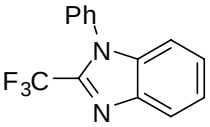
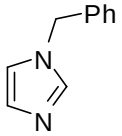
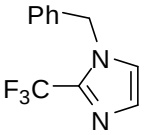
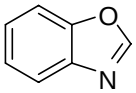
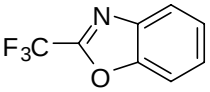
With the optimal conditions in hand [$Pd(OAc)_2$ (5 mol%)/2,2'-bipyridine (40 mol %) as the catalyst, AgF (2.0 equiv.) as the fluoride, $Cu(OAc)_2$ (2.0 equiv.) as oxidant, and DMF/DMSO (4:1) as the solvent at 120 ^oC for 24 h in oxygen atmosphere], we explored the scope of azoles (Table 2). Benzothiazole and 6-nitrobenzothiazole were smoothly trifluoromethylated by Me_3SiCF_3 (**1**) to the corresponding products **3a** and **3b** in 83 % and 56 % yield, respectively (Table 2, entries 1 and 2). Further reactions of **1** with various N-alkylbenzimidazoles (Table 2, entries 3–17) show the versatility of this direct oxidative trifluoromethylation methodology. Among them, the benzimidazoles bearing NMe and NEt gave good results (Table 2, entries 3–6), while the benzimidazole having N*i*Pr was observed to deliver **3g** in quite low yield (18 %) (Table 2, entry 7). Active groups, such as allyl, fluoride, bromide or iodide were tolerated by the catalytic system and led to 59-71 % yields (Table 2, entries 8, 11-15). Especially noteworthy, the C-I bond on the aromatic ring remained intact, which could not be obtained by previously reported copper- and palladium-mediated trifluoromethylation systems.[10m,15,20] In contrast, 1-phenyl-1H-benzimidazole (**2r**), 1-benzyl-1H-imidazole (**2s**), and benzoxazole (**2t**) were substrates of low activity in the catalytic system (Table 2, entries 18–20).

Table 2 $Pd(OAc)_2$-catalyzed oxidative trifluoromethylations of azoles.[a]



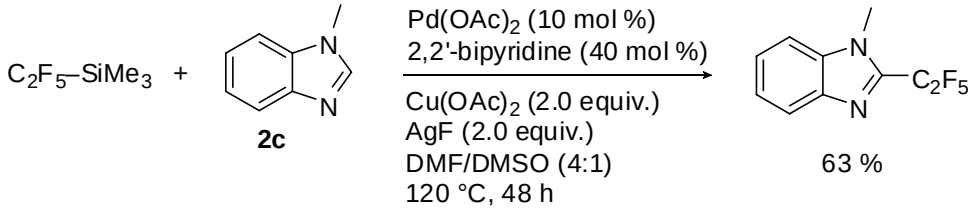
Entry	substrate	product	Yield[b] (%)
1[c]	 **2a**	 **3a**	83
2	 **2b**	 **3b**	56
3	 **2c**	 **3c**	66
4	 **2d**	 **3d**	81
5	 **2e**	 **3e**	67
6	 **2f**	 **3f**	72
7[d]	 **2g**	 **3g**	18
8	 **2h**	 **3h**	61
9	 **2i**	 **3i**	60

10		**2j**		**3j**	67
11		**2k**		**3k**	60
12		**2l**		**3l**	71
13		**2m**		**3m**	63
14		**2n**		**3n**	65
15		**2o**		**3o**	59
16		**2p**		**3p**	62

17		**2q**		**3q**	66
18[d]		**2r**		**3r**	30
19[d]		**2s**		**3s**	20
20[d]		**2t**		**3t**	trace

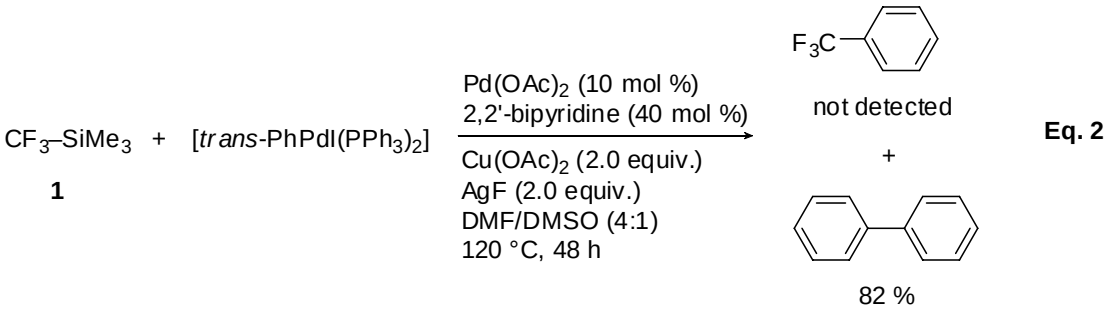
[a] *Conditions*: A mixture of **1** (1.5 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (10 mol-%), 2,2'-bipyridine (40 mol %), $Cu(OAc)_2$ (1.0 mmol), and AgF (1.0 mmol) in DMF/DMSO (4:1) (1.0 mL) was stirred at 120 °C for 48 h in oxygen. [b] Yield of isolated **3**. [c] 24 h. [d] Yields were estimated from GC-MS.

Gratifyingly, this protocol can be extended to pentafluoroethylation of 1-methyl-1H-benzimidazole (**2c**). Similar to the trifluoromethylation mentioned above, the pentafluoroethylation of **2c** with $Me_3SiCF_2CF_3$ generated 1-methyl-2-(pentafluoroethyl)-1H-benzimidazole in 63 % yield under the same conditions (Eq. 1).



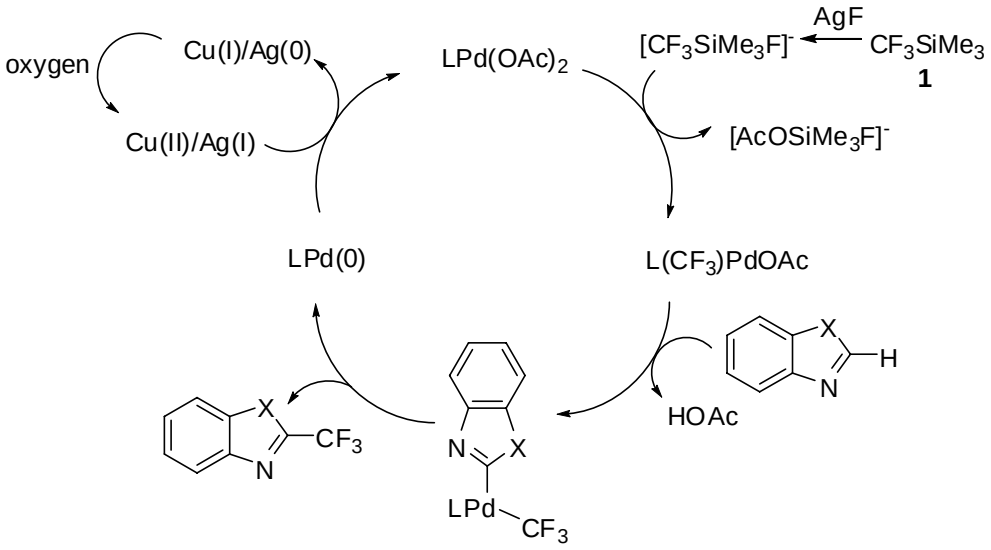
Eq. 1

Recently, Yu and coworkers proposed that the process of trifluoromethylation of arenes is initiated by C-H activation to generate $ArPd^{II}L_n$ species.[22] Hence, we prepared the related species [*trans*-$PhPdI(PPh_3)_2$] which reacted with Me_3SiCF_3 (**1**) under the normal conditions [Eq. 2] to give biphenyl in 82 % yield. The formation of trifluoromethylbenzene was not observed. We, therefore, conclude that the $ArPd^{II}L_n$ species should not be involved in the catalytic cycle.



Eq. 2

It is reasonable to assume, therefore, that the catalytic cycle starts with a fluoride ion-assisted transmetalation of the silicon compound **1** with $Pd(OAc)_2$ to form an $[CF_3Pd^{II}OAc]$ species, as illustrated in Scheme 6. Subsequent C–H bond cleavage at the azole generates a mixed trifluoromethyl heteroaryl palladium complex which undergoes reductive elimination to afford the 2-trifluoromethylated azoles and releases Pd^0. To complete the catalytic cycle, the Pd^0 complex is reoxidized by Ag^+/Cu^{2+} ions. However, the possibility that the reported intermediate $[LCuCF_3]$ involves in the reaction can not be ruled out.[10m,13,14,15]



Scheme 6. A plausible mechanism for Pd^{II}-catalyzed trifluoromethylation of azoles.

6.3 Conclusion

In summary, a novel and facile methodology has been developed for the direct trifluoromethylation of arenes with Me_3SiCF_3 in the absence of the assistance of a directing group for the preparation of 2-CF_3 substituted azoles in moderate to excellent yields. The utility of this process is underscored by the synthesis of druglike and/or pharmaceutically relevant molecules from easily available starting materials. Detailed mechanistic investigations and expanded application of the methodology should be investigated in future work.

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6.5 Experimental Section

6.5.1 General

^1H (400 MHz or 600 MHz) and ^{13}C NMR spectra (100 MHz or 150 MHz) of solutions in $CDCl_3$ were recorded on a Varian Inova 400 NMR spectrometer. Chemical shifts were expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals (δ_H 7.24 and δ_C 77.0 ppm). Abbreviations for signal couplings are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. HRMS was performed on a Finnigan MAT 95Q mass spectrometer. Infrared spectra of neat substances were recorded on a Perkin-Elmer Spectrum BX II FT-IR spectrometer equipped with an ATR probe (diamond). Melting points were determined on a BÜCHI B-540.

6.5.2 Materials

Commercially available azoles and Me_3SiCF_3 were used as received. Literature procedures were used to synthesize 1-benzyl-benzimidazole, 1-benzyl-5,6-dimethyl-benzimidazole, 1-ethyl-5,6-dimethyl-benzimidazole, 1-isopropyl-5,6-dimethyl-1H-benzoimidazole,1-allyl-5,6-dimethyl-1H-benzoimidazole, 1-(4-fluorobenzyl)-1H-benzoimidazole, 1-(4-fluorobenzyl)-5,6-dimethyl-1H-benzoimidazole,1-(4-bromobenzyl)-1H-benzoimidazole,1-(4-bromobenzyl)-5,6-dimethyl-1H-benzoimidazole, 1-(4-iodobenzyl)-5,6-dimethyl-1H-benzoimidazole, 5,6-dimethyl-1-(4-(trifluoromethyl)benzyl)-1H-benzoimidazole, 1-(3-methoxybenzyl)-5,6-dimethyl-1H-benzoimidazole, 1-benzyl-1H-imidazole and 1,5,6-trimethyl-benzimidazole by *N*-alkylations of benzimidazole, 1H-imidazole or 5,6-dimethylbenzimidazole with methyl iodide, ethyl iodide isopropyl iodide, 3-bromoprop-1-ene, 1-(chloromethyl)-4-fluorobenzene, 1-bromo-4-(bromomethyl)benzene, 1-(bromomethyl)-4-iodobenzene, 1-(bromomethyl)-4-(trifluoromethyl)benzene, 1-(chloromethyl)-3-methoxybenzene or benzyl bromide, respectively.[S1] Commercial solvents were used without further purification.

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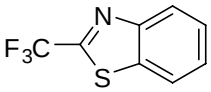
The following palladium, copper and fluoride salts were used: $Pd(OAc)_2$ (47.5 % Pd, Acros), $Cu(OAc)_2 \cdot H_2O$ (99%, Fisher Scientific), $Cu(OTf)_2$ (98 %, ABCR), $CuBr_2$ (97 %, Fluka), $CuCl_2$ (97 %, Aldrich), CuF_2 (99.5 %, ABCR), $AgNO_3$ (RECTAPUR), AgOAc (99 %, Fluka), AgF (99 %, Aldrich), KF (Merck).

6.5.3 General Procedure for Palladium-Catalyzed Direct Trifluoromethylation of Azoles

Under oxygen atmosphere, a 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (11.2 mg, 10 mol %), $Cu(OAc)_2$ (202 mg, 1.00 mmol), AgF (128 mg, 1.00 mmol) and 2,2'-bipyridine (31.2 mg, 40 mol %). The azole (0.50 mmol) and Me_3SiCF_3 (222 µL, 1.50 mmol) were added, followed by DMF (0.8 mL) and DMSO (0.2 mL) with syringe. The reaction mixture was stirred for 5 min at room temperature and then heated at 120 °C in an oil bath for the indicated time. After completion of the reaction, the mixture was cooled to room temperature and poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (eluent mixture: *n*-pentane/diethyl ether).

2-(Trifluoromethyl)benzothiazole (3a)

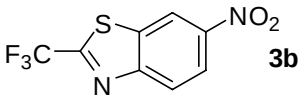


3a

Following *General procedure*, **2a** (58 µL, 0.50 mmol) reacted with **1** (222 µL, 1.50 mmol) for 24 h to furnish **3a** (84 mg, 83 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.53-7.63 (m, 2 H), 7.98 (d, J = 8.8 Hz, 1 H), 8.19 ppm (d, J = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 119.8 (q, $^1J_{C,F}$ = 271 Hz, CF_3), 122.0, 125.0, 127.4, 127.5, 135.0, 152.1, 156.0 ppm (q, $^2J_{C,F}$ = 40.2 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.72 ppm.

6-Nitro-2-(trifluoromethyl)benzothiazole (3b)

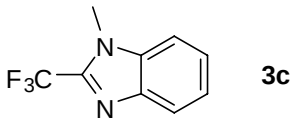


3b

Following *General procedure*, **2b** (92.2 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3b** (69 mg, 56 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.33 (d, *J* = 9.2 Hz, 1 H), 8.48 (dd, *J* = 9.0 Hz, *J* = 2.4 Hz, 1 H), 8.94 ppm (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 118.8, 119.2 (q, $^1J_{C,F}$ = 269 Hz, CF_3), 122.7, 125.7, 135.4, 146.6, 155.4, 161.2 ppm (q, $^2J_{C,F}$ = 42.4 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -62.19 ppm; HRMS (EI) calcd for $C_8H_3F_3N_2O_2S$ *m/z* 247.9867, found *m/z* 247.9857; IR: ν = 1603, 1571, 1515, 1464, 1345, 1295, 1155, 1047, 1014, 901, 844, 746, 720 cm^{-1}.

1-Methyl-2-(trifluoromethyl)-1H-benzoimidazole (3c)

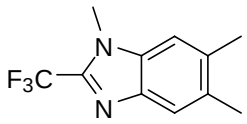


3c

Following *General procedure*, **2c** (66.8 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3c** (66 mg, 66 %).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 3.93 (s, 3 H), 7.35-7.38 (m, 1 H), 7.43 (s, 1 H), 7.44 (s, 1 H), 7.86 ppm (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 30.8, 110.0, 119.1 (q, $^1J_{C,F}$ = 269 Hz, CF_3), 121.6, 123.7, 125.3, 136.0, 140.8 (q, $^2J_{C,F}$ = 39.1 Hz), 140.9 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -62.56 ppm; HRMS (EI) calcd for $C_9H_7F_3N_2$ *m/z* 200.0561, found *m/z* 200.0548; IR: ν = 2963, 1589, 1518, 1485, 1405, 1335, 1259, 1232, 1180, 1086, 1014, 902, 794, 745, 726 cm^{-1}.

1,5,6-Trimethyl-2-(trifluoromethyl)-1H-benzoimidazole (3d)

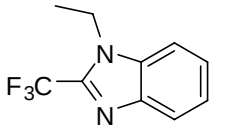


3d

Following *General procedure*, **2d** (82.4 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3d** (92 mg, 81 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.37 (s, 3 H), 2.41 (s, 3 H), 3.87 (s, 3 H), 7.17 (s, 1 H), 7.59 ppm (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.3, 20.8, 30.7, 109.9, 119.2 (q, $^1J_{C,F}$ = 267 Hz, CF_3), 121.2, 132.9, 134.7, 135.0, 139.6, 139.7 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -62.39 ppm; HRMS (EI) calcd for $C_{11}H_{11}F_3N_2$ *m/z* 228.0874, found *m/z* 228.0867; IR: ν = 2960, 2976, 2921, 1578, 1521, 1464, 1414, 1386, 1342, 1324, 1274, 1235, 1172, 1120, 1088, 1022, 884, 844, 823, 748 cm^{-1}; mp 107.5-109 °C.

1-Ethyl-2-(trifluoromethyl)-1H-benzoimidazole (3e)

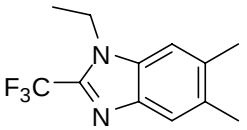


3e

Following *General procedure*, **2e** (74.5 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3e** (71 mg, 67 %).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.47 (t, *J* = 7.2 Hz, 3 H), 4.90-4.93 (m, 2 H), 7.34-7.41 (m, 2 H), 7.51 (d, *J* = 7.8 Hz, 1 H), 7.88 ppm (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 15.4, 40.5, 110.3, 120.4, 122.6 (q, $^1J_{C,F}$ = 272 Hz, CF_3), 123.0, 124.1, 125.2, 135.0, 135.1, 141.9 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -62.33 ppm; HRMS (EI) calcd for $C_{10}H_9F_3N_2$ *m/z* 214.0718, found *m/z* 214.0716; IR: ν = 3018, 2964, 2919, 2850, 1482, 1461, 1450, 1406, 1396, 1260, 1017, 950, 780, 766, 734, 698 cm^{-1}; mp 171.5-174 °C.

1-Ethyl-5,6-dimethyl-2-(trifluoromethyl)-1H-benzoimidazole (3f)

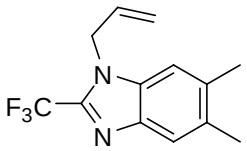


3f

Following *General procedure*, **2f** (88.2 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3f** (87 mg, 72 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.45 (t, *J* = 7.2 Hz, 3 H), 2.36 (s, 3 H), 2.40 (s, 3 H), 4.31 (m, 2 H), 7.19 (s, 1 H), 7.60 ppm (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.1, 20.3, 20.7, 39.8, 109.2, 119.3 (q, $J_{C,F}$ = 269 Hz, CF_3), 121.3, 132.7, 133.6, 134.9, 136.0, 139.8 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -62.15 ppm; HRMS (EI) calcd for $C_{12}H_{13}F_3N_2$ *m/z* 242.1031, found *m/z* 242.1034; IR: ν = 2972, 2932, 1578, 1517, 1491, 1464, 1456, 1437, 1382, 1364, 1353, 1285, 1269, 1210, 1173, 1137, 1102, 1070, 1027, 1002, 960, 883, 842, 748, 720, 672 cm^{-1}; mp 99-100 °C.

1-Allyl-5,6-dimethyl-2-(trifluoromethyl)-1H-benzoimidazole (3h)

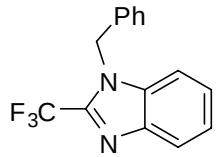


3h

Following *General procedure*, **2h** (96.2 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3h** (77 mg, 61 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.36 (s, 3 H), 2.39 (s, 3 H), 4.86 (d, *J* = 5.2 Hz, 2 H), 5.07 (d, *J* = 16.8 Hz, 1 H), 5.23 (d, *J* = 10.4 Hz, 1 H), 5.88-5.98 (m, 1 H), 7.14 (s, 1 H), 7.60 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.3, 20.8, 47.0 (q, $^4J_{C,F}$ = 1.9 Hz), 110.6, 119.2 (q, $^1J_{C,F}$ = 270 Hz, CF_3), 118.2, 121.2, 131.1, 133.0, 133.9, 135.1, 139.5 (q, $^2J_{C,F}$ = 38.2 Hz), 139.7 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.77 ppm; HRMS (EI) calcd for $C_{13}H_{13}F_3N_2$ *m/z* 254.1031, found *m/z* 254.1024 ; IR: ν = 2977, 2953, 2926, 1578, 1520, 1474, 1451, 1418, 1381, 1340, 1274, 1173, 1116, 1070, 925, 883, 840, 748 cm^{-1}; mp 83.5-84.5 °C.

1-Benzyl-2-(trifluoromethyl)-1H-benzoimidazole (3i)

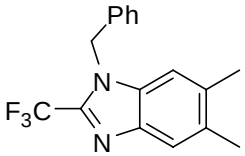


3i

Following *General procedure*, **2i** (106 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3i** (82 mg, 60 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.53 (s, 2 H), 7.08-7.10 (m, 2 H), 7.25-7.37 (m, 6 H), 7.88-7.90 ppm (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 48.3 (q, $^4J_{C,F}$ = 2.0 Hz), 111.1, 119.1 (q, $^1J_{C,F}$ = 270 Hz, CF_3), 121.7, 123.8, 125.5, 126.3, 128.2, 129.0, 134.9, 135.6, 140.7, 141.2 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.60 ppm; HRMS (EI) calcd for $C_{15}H_{11}F_3N_2$ *m/z* 276.0874, found *m/z* 276.0865; IR: ν = 3061, 2919, 1590, 1521, 1497, 14781453, 1429, 1282, 1269, 1173, 1123, 1094, 747, 732, 720, 690 cm^{-1}; mp 70-71.5 ^oC.

1-Benzyl-5,6-dimethyl-2-(trifluoromethyl)-1H-benzoimidazole (3j)

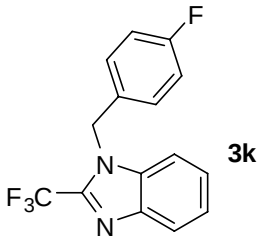


3j

Following *General procedure*, **2j** (120 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3j** (124 mg, 67 %).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.31 (s, 3 H), 2.35 (s, 3 H), 5.47 (s, 2 H), 7.02 (s, 1 H), 7.06 (d, *J* = 7.2 Hz, 2 H), 7.26-7.31 (m, 3 H), 7.63 ppm (s, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 20.3, 20.8, 48.3, 110.8, 119.2 (q, $^1J_{C,F}$ = 273 Hz, CF_3), 121.3, 126.1, 128.1, 129.0, 133.2, 134.2, 135.2, 135.3, 139.7, 140.0 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.43 ppm; HRMS (EI) calcd for $C_{18}H_{14}F_6N_2$ *m/z* 372.1061, found *m/z* 372.1051; IR: ν = 3028, 2977, 2956, 2920, 1579, 1518, 1497, 1477, 1450, 1436, 1382, 1365, 1273, 1262, 1172, 1122, 1069, 972, 884, 840, 746, 719, 699 cm^{-1}; mp 125.2-128 ^oC.

1-(4-Fluorobenzyl)-2-(trifluoromethyl)-1H-benzoimidazole (3k)

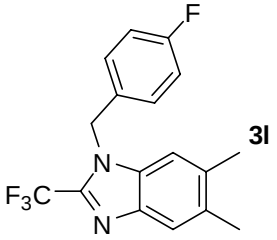


3k

Following *General procedure*, **2k** (117 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3k** (88 mg, 60 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.49 (s, 2 H), 6.97-7.03 (m, 2 H), 7.06-7.10 (m, 2 H), 7.25-7.28 (m, 1 H), 7.33-7.38 (m, 2 H), 7.88-7.92 ppm (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 47.8 (q, $^4J_{C,F}$ = 1.9 Hz), 110.9, 115.5 (d, $^2J_{C,F}$ = 21.7 Hz), 119.1 (q, $^1J_{C,F}$ = 270 Hz, CF_3), 121.8, 123.9, 125.7, 128.2 (d, $^3J_{C,F}$ = 8.2 Hz), 130.6 (d, $^4J_{C,F}$ = 3.3 Hz), 135.4, 140.8 (q, $^2J_{C,F}$ = 38.1 Hz), 141.2, 162.5 ppm (d, $^1J_{C,F}$ = 246 Hz, CF); ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.58, -113.50 ppm; HRMS (EI) calcd for $C_{15}H_{10}F_4N_2$ *m/z* 294.0780, found *m/z* 294.0777 ; IR: ν = 3058, 2931, 1607, 1592, 1512, 1468, 1450, 1418, 1268, 1227, 1189, 1118, 1092, 1015, 988, 831, 742, 696 cm^{-1};

1-(4-Fluorobenzyl)-5,6-dimethyl-2-(trifluoromethyl)-1H-benzoimidazole (3l)

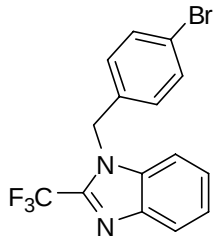


3l

Following *General procedure*, **2l** (138 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3l** (114 mg, 71 %).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.32 (s, 3 H), 2.35 (s, 3 H), 5.43 (s, 2 H), 6.97-7.01 (m, 3 H), 7.04-7.06 (m, 2 H), 7.63 ppm (s, 1 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 20.3, 20.8, 47.6, 110.7, 116.0 (d, $^2J_{C,F}$ = 21.6 Hz), 119.2 (q, $^1J_{C,F}$ = 272 Hz, CF_3), 121.4, 127.9 (d, $^3J_{C,F}$ = 8.3 Hz), 130.9 (d, $^4J_{C,F}$ = 3.3 Hz), 133.3, 134.2, 135.5, 139.7, 162.4 (d, $^1J_{C,F}$ = 246 Hz, CF) ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.44, -113.81 ppm; HRMS (EI) calcd for $C_{17}H_{14}F_4N_2$ *m/z* 322.1093, found *m/z* 322.1083; IR: ν = 2965, 2921, 1608, 1580, 1511, 1481, 1451, 1440, 1418, 1384, 1366, 1273, 1260, 1230, 1171, 1120, 1071, 932, 884, 840, 818, 750, 722, 685, 629 cm^{-1}; mp 132.8-134 ^oC.

1-(4-Bromobenzyl)-2-(trifluoromethyl)-1H-benzoimidazole (3m)

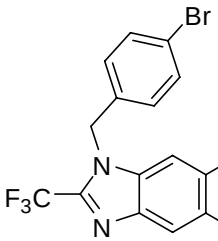


3m

Following *General procedure*, **2m** (146 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3m** (111 mg, 63 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.47 (s, 2 H), 6.95 (d, *J* = 8.0 Hz, 2 H), 7.33-7.09 (m, 2 H), 7.43 (d, *J* = 8.4 Hz, 2 H), 7.89-7.91 ppm (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 47.8 (q, $^4J_{C,F}$ = 1.9 Hz), 110.8, 119.1 (q, $^1J_{C,F}$ = 270 Hz, CF_3), 121.9, 122.3, 124.0, 125.7, 127.9, 132.2, 133.9, 135.4, 140.6, 141.2 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.60 ppm; HRMS (EI) calcd for $C_{15}H_{10}BrN_2F_3$ *m/z* 353.9973, found *m/z* 353.9968; IR: ν = 3059, 2928, 2856, 1592, 1524, 1490, 1467, 1450, 1426, 1408, 1278, 1190, 1118, 1093, 1011, 989, 827, 802, 744, 734 cm^{-1}.

1-(4-Bromobenzyl)-5,6-dimethyl-2-(trifluoromethyl)-1H-benzoimidazole (3n)



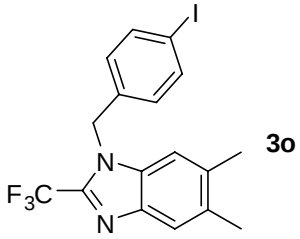
3n

Following *General procedure*, **2n** (162 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3n** (124 mg, 65 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.32 (s, 3 H), 2.35 (s, 3 H), 5.41 (s, 2 H), 6.92 (d, *J* = 8.4 Hz, 2 H), 6.98 (s, 1 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.62 ppm (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.3, 20.8, 47.6 (q, $^4J_{C,F}$ = 2.0 Hz), 110.6, 119.2 (q, $^1J_{C,F}$ = 270 Hz, CF_3), 121.4, 122.1, 127.8, 132.1, 133.3, 134.0, 134.2, 135.5, 139.8, 139.9 ppm (q, $^2J_{C,F}$ = 38.6 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.47 ppm; HRMS (EI) calcd for $C_{17}H_{14}BrF_3N_2$ *m/z* 382.0292, found *m/z* 382.0287 ; IR: ν = 3086, 2979, 2920, 2851, 1602, 1580, 1521, 1474, 1433, 1407,

1381, 1352, 1336, 1283, 1264, 1185, 1168, 1121, 1072, 1010, 986, 884, 841, 795, 736, 722, 608 cm^{-1}; mp 137-139 °C.

1-(4-Iodobenzyl)-5,6-dimethyl-2-(trifluoromethyl)-1H-benzoimidazole (3o)

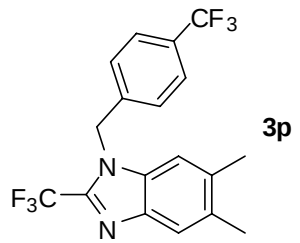


3o

Following *General procedure*, **2o** (188 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3o** (126 mg, 59 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.32 (s, 3 H), 2.35 (s, 3 H), 5.4 (s, 2 H), 6.79 (d, *J* = 8.4 Hz, 2 H), 6.98 (s, 1 H), 7.61 (s, 1 H), 7.63 ppm (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.3, 20.8, 47.7, 93.6, 110.6, 119.2 (q, $^1J_{C,F}$ = 268 Hz, CF_3), 121.4, 128.0, 133.4, 134.0, 134.9, 135.6,138.1, 139.7, 139.8 ppm (q, $^2J_{C,F}$ = 36.6 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.43 ppm; HRMS (EI) calcd for $C_{17}H_{14}F_3IN_2$ *m/z* 430.0154, found *m/z* 430.0149 ; IR: ν = 2978, 2947, 1580, 1521, 1475, 1434, 1401, 1383, 1351, 1283, 1263, 1186, 1169, 1123, 1074, 1008, 986, 884, 840, 791, 749, 713, 624 cm^{-1}; mp 152.5-154 °C.

5,6-Dimethyl-2-(trifluoromethyl)-1-(4-(trifluoromethyl)benzyl)-1H-benzoimidazole (3p)



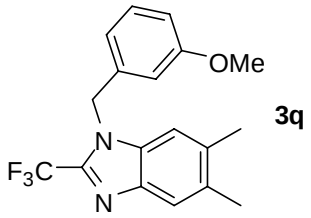
3p

Following *General procedure*, **2p** (157 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3p** (115 mg, 62 %).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.32 (s, 3 H), 2.36 (s, 3 H), 5.52 (s, 2 H), 6.98 (s, 1 H), 7.15 (d, *J* = 7.8 Hz, 2 H), 7.56 (d, *J* = 7.8 Hz, 2 H), 7.65 (s, 1 H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 20.3, 20.8, 47.7, 110.4, 119.1 (q, $^1J_{C,F}$ = 270 Hz, CF_3), 123.8 (q, $^1J_{C,F}$ = 271 Hz, CF_3), 126.0 (q, $^3J_{C,F}$ = 3.8 Hz), 126.3, 128.1, 130.5 (q, $^2J_{C,F}$ = 32.6 Hz), 133.5, 134.0, 135.7, 139.2, 139.77, 139.8 ppm (q, $^2J_{C,F}$ = 38.9 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.51, -

62.76 ppm; HRMS (EI) calcd for $C_{18}H_{14}F_6N_2$ *m/z* 372.1061, found *m/z* 372.1055; IR: ν = 2957, 2926, 1582, 1517, 1474, 1450, 1438, 1418, 1386, 1363, 1325, 1280, 1169, 1108, 1068, 1017, 988, 944, 880, 841, 813, 749, 724 cm^{-1}; mp 114.5-117 °C.

1-(3-Methoxybenzyl)-5,6-dimethyl-2-(trifluoromethyl)-1H-benzo[d]imidazole (3q)



3q

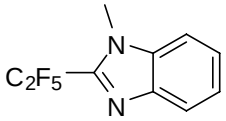
Following *General procedure*, **2q** (157 mg, 0.500 mmol) reacted with **1** (222 μL, 1.50 mmol) for 48 h to furnish **3q** (110 mg, 66 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.31 (s, 3 H),2.35 (s, 3 H), 3.71 (s, 3 H), 5.43 (s, 2 H), 6.59 (s, 1 H), 6.64 (d, *J* = 9.2 Hz, 1 H), 6.80 (dd, *J* = 10.8 Hz, *J* = 2.4 Hz, 1 H), 7.02 (s, 1 H), 7.21 (t, *J* = 7.8 Hz, 1 H), 7.62 ppm (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.3, 20.8, 48.1 (q, $^4J_{C,F}$ = 1.9 Hz), 55.2, 110.8, 112.1, 113.1, 118.4, 119.2 (q, $^1J_{C,F}$ = 272 Hz, CF_3), 121.2, 130.0, 133.2, 134.2, 135.3, 136.7, 139.7, 139.8 (q, $^2J_{C,F}$ = 37.9 Hz), 160.0 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.38 ppm; HRMS (EI) calcd for $C_{18}H_{17}F_3N_2O$ *m/z* 334.1293, found *m/z* 334.1287; IR: ν = 3053, 3002, 2954, 2920, 2853, 2830, 1612, 1587, 1518, 1475, 1457, 1434, 1424, 1386, 1356, 1278, 1174, 1140, 1118, 1072, 1058, 984, 888, 867, 839, 770, 712, 686 cm^{-1}; mp 117.5-118 °C.

6.5.4 Procedure for the Palladium-Catalyzed Direct Pentafluoroethylation of 1-Methyl-1H-benzimidazole (2c)

Under oxygen atmosphere, a 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (11.2 mg, 10 mol-%), $Cu(OAc)_2$ (202 mg,1.00 mmol), AgF (128 mg, 1.00 mmol) and 2,2'-bipyridine (31.2 mg, 40 mol %). The **2c** (66.8 mg, 0.500 mmol) and $Me_3SiCF_2CF_3$ (270 μL, 1.50 mmol) were added, followed by DMF (0.8 mL) and DMSO (0.2 mL) with syringe. The reaction mixture was stirred for 5 min at room temperature and then heated at 120 °C in an oil bath for the indicated time. After completion of the reaction, the mixture was cooled to room temperature

and poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (eluent mixture: *n*-pentane/diethyl ether) to furnish 1-methyl-2-(pentafluoroethyl)-1H-benzimidazole (78.5 mg, 63 %).



^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.96 (s, 3 H), 7.35-7.40 (m, 1 H), 7.44 (d, *J* = 3.6 Hz, 2 H), 7.89 ppm (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 31.2, 110, 110.1 ($^1J_{C,F}$ = 253 Hz, $^2J_{C,F}$ = 39 Hz, CF_2), 118.4 ($^1J_{C,F}$ = 286 Hz, $^2J_{C,F}$ = 36 Hz, CF_3), 121.7, 123.6, 125.4, 136.3, 139.6, 141.5 ppm; ^{19}F NMR ($CDCl_3$, 376 MHz): δ = -110.55, -82.36 ppm.

6.5.5 Procedure for the Reaction between Complex *trans*-[$(PPh_3)_2$PhPdI] and Trifluoromethyltrimethylsilane

Under oxygen atmosphere, a 25 mL Schlenk flask was charged with *trans*-[$(PPh_3)_2$PhPdI] (210 mg, 0.250 mmol), $Pd(OAc)_2$ (5.6 mg, 10 mol %), $Cu(OAc)_2$ (101 mg, 0.500 mmol), AgF (64 mg, 0.50 mmol) and 2,2'-bipyridine (15.6 mg, 40 mol %). The Me_3SiCF_3 (0.75 mmol, 111 μL) was added, followed by DMF (0.4 mL) and DMSO (0.1 mL) with syringe. The reaction mixture was stirred for 5 min at room temperature and then was heated at 120 ^{o}C in an oil bath for 48 h. After the reaction was completed, the reaction mixture was cooled to room temperature and poured into a saturated aqueous NaCl solution (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel to afford the product biphenyl in 82 % (31.5 mg) yield.

Curriculum Vitae

Personal information

Name:	HAN, WEI
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Education

Ph.D. in Organic Chemistry:	(2008-present): Department Chemie und Biochemie Ludwig-Maximilians-Universität München, Germany
Thesis Supervisor:	Prof. Dr. Herbert Mayr
Thesis Title:	Iron and palladium catalyzed C-H functionalization
Master of Engineering:	(2005-2008) School of Chemical Engineering Dalian University of Technology, China
Thesis Supervisor:	Assoc. Prof. Dr. Chun Liu
Thesis Title:	Ligand-free palladium nanoparticles-catalyzed C-C coupling reactions
Bachelor of Engineering:	(2001-2005) School of Chemical Engineering and Pharmacy, Wuhan Insititute of Chemical Technology, China
Thesis Supervisor:	Assoc. Prof. Dr. Dezhong Yu
Thesis Title:	Synthesis and characterization of zinc (II) porphyrin

Fellowship

Ph.D fellowship by the China Scholarship Council (2008-present)