C–H Activation

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Beyond Directing Groups: Transition-Metal-Catalyzed C–H Activation of Simple Arenes

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Dedicated to Professor Shinji Murai

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The use of coordinating moieties as directing groups for the functionalization of aromatic C–H bonds has become an established tool to enhance reactivity and induce regioselectivity. Nevertheless, with regard to the synthetic applicability of C–H activation, there is a growing interest in transformations in which the directing group can be fully abandoned, thus allowing the direct functionalization of simple benzene derivatives. However, this approach requires the disclosure of new strategies to achieve reactivity and to control selectivity. In this review, recent advances in the emerging field of non-chelate-assisted C–H activation are discussed, highlighting some of the most intriguing and inspiring examples of induction of reactivity and selectivity.

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1. Introduction

The discovery of new reactivities and transformations that either improve the step and atom economy of existing processes or introduce novel and innovative methods to construct complex molecules is the long-standing goal of synthetic chemists. In this regard, the fast-growing field of C–H activation represents one of the most promising approaches of the last decades.[1] The direct transformation of C–H bonds into C–C or C–heteroatom bonds renders the often circuitous prefunctionalization of starting materials unnecessary and represents a more environmentally friendly and economic strategy than traditional cross-coupling reactions.[2] Even more alluring is the possibility to enable new and original disconnections, which would greatly expand the number of retrosynthetic pathways available to build complex molecular scaffolds.[3]

However, in order for a C–H activation reaction to be of broad synthetic value, one C–H bond in an organic molecule must be selectively activated over all the other C–H bonds present in the molecule. Obviously, this issue can be circumvented by employing molecules with C–H bonds of different reactivity. This strategy has already been applied in the functionalization of various heterocycles that possess at least one position of special reactivity as a result of the presence of one or more heteroatoms.[4,5]

However, in benzene derivatives, the discrepancy in reactivity between the C–H bonds is generally less pronounced and other regioselectivity-controlling elements are required. In these cases, the use of directing groups (DG), such as amides, pyridines, or acetanilides, have become the strategy of choice to allow site-selective functionalization. Over the last few years, a large number of impressive C–C and C–heteroatom bond-forming processes have been realized using this approach, thus leading to a better understanding of C(sp^2)–H activation.

The role of a DG in these reactions is usually twofold. Because of its coordination ability, the DG directs the transition metal into close proximity to the C–H bond to be activated, thus resulting in high levels of regioselectivity and increased reactivity because of the higher effective concentration of the catalyst at the site of interest. However, despite these advantages, the use of DGs has certain limitations. In most cases, functionalization of the arene occurs only at the C–H bond *ortho* to the DG, thus restricting the scope of accessible products.[6] Furthermore, additional synthetic steps are often required to both install the DG into the starting material and to manipulate it after C–H functionalization. Nevertheless, it should be noted that many DGs, especially those derived from carboxylic acids and the carboxylic acids themselves, have been proven to be versatile functionalities for further transformations.[3] Moreover, significant research attention has been focussed on the development of easily modifiable or removable DGs that are applicable to the synthesis of complex molecules and important building blocks.[7,8]

A more appealing strategy for the C–H activation of benzene derivatives would be to avoid using DGs altogether. However, this approach requires the disclosure of new strategies to achieve reactivity and to control selectivity. To date, only a few examples of transition-metal-catalyzed site-selective C–H activation of benzene derivatives without the control of DGs have been disclosed,[9] although recent reports demonstrate a rapidly growing interest in this class of transformation.

In this review, we aim to showcase the state of the art in this field by highlighting different aspects of selectivity control (chemo- and regioselectivity) in the functionalization of simple arenes, which would be valuable for the development of this chemistry (Figure 1). The terms "simple" arenes or benzene derivatives are used in this context to describe aromatic substrates that do not possess functional groups capable of precoordinating the catalyst and governing the site of C–H activation. In the interest of clarity, the C–H activation reactions of these compounds will be referred to as "non-chelate-assisted"[10] rather than "undirected" C–H activation, the latter of which fails to take into account the

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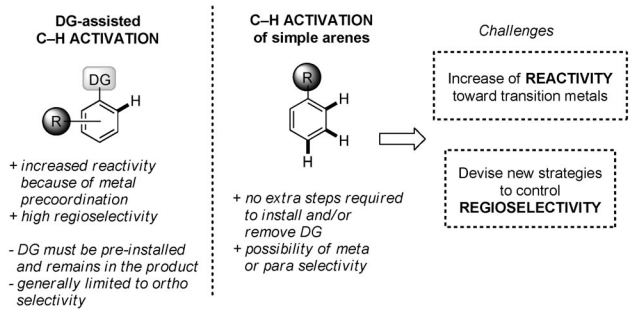

Figure 1. Comparison of "chelate-assisted" and non-chelate-assisted" aryl C–H activation.

electronic and steric directing effects inherent to all substituted arenes.

In general, only homogeneous processes in which a distinct aryl–metal intermediate has been proposed will be discussed here, excluding those that are thought to occur through radical mechanisms.[11] Taking into consideration that chemo- and regioselectivity in intramolecular reactions are already determined by conformational restrictions that result from the connection of the arene to its coupling partner, the focus will be on intermolecular reactions, and mostly on cross-coupling reactions that address biaryl formations. Besides aryl–C bond-forming reactions, selected examples of aryl–heteroatom bond formations will be presented, because they exhibit intriguing ways of functionalizing simple arenes and might therefore also be of great industrial interest.

2. C–C Bond Formation

2.1. Biaryl Formation

The biaryl moiety is an important structural motif in biologically active compounds, natural products, and materials. Its construction through a direct cross-coupling of two arenes is therefore an attractive process that offers superior sustainability and environmental compatibility to conventional transition-metal-catalyzed cross-couplings between aryl halides or triflates and organometallic reagents.

In general, C–H arylation reactions can be divided into two classes: 1) the coupling of a simple arene with either an aryl halide (Ar–X + Ar–H) or an organometallic species (Ar–H + Ar–M), also called direct arylation,[12] and 2) dehydrogenative couplings (Ar–H + Ar–H) in which both reaction partners contain C–H bonds (Scheme 1).

2.1.1. Non-Oxidative Direct Arylation (Ar–X + Ar–H)

The direct arylation of aromatic C–H bonds with aryl halides is arguably the most intensively studied C–H activation approach to build the biaryl motif.[13] In these processes, simple benzene derivatives are employed in place of organometallic reagents, which are often difficult to access and handle. Moreover, because of their high reactivity, most organometallic reagents show only a limited functional-group tolerance. In contrast, the comparative stability and wide-

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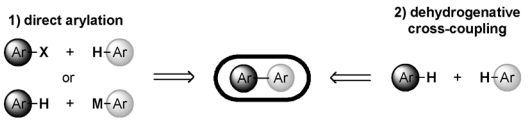


Scheme 1. C–H activation pathways to build the biaryl motif.

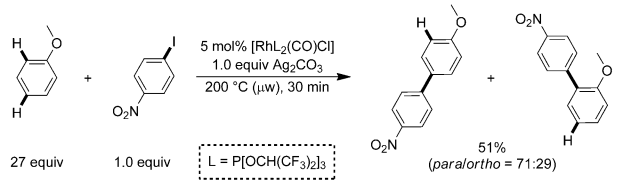
spread commercial availability of aryl halides renders direct arylation an attractive method to access biaryl systems.

Apart from regioselectivity issues, a major challenge of the direct arylation of simple benzene derivatives is to identify a set of conditions that promote C–H activation of the comparatively unreactive arene partner while avoiding homocoupling of the more reactive aryl halide. This generally requires careful optimization of the catalyst, ligand, solvent, and other reaction parameters.

Among the four global mechanistic pathways that are invoked for transition-metal-catalyzed C–H activation[1,14] – a) oxidative addition, b) σ-bond metathesis, c) electrophilic metalation, and d) concerted metalation–deprotonation (CMD) – the latter two mechanisms (c and d) are commonly thought to predominate in these transformations.

In the last years, several approaches toward the direct arylation of benzene and its derivatives using palladium[15] and other transition metals[16] as catalysts have been disclosed.

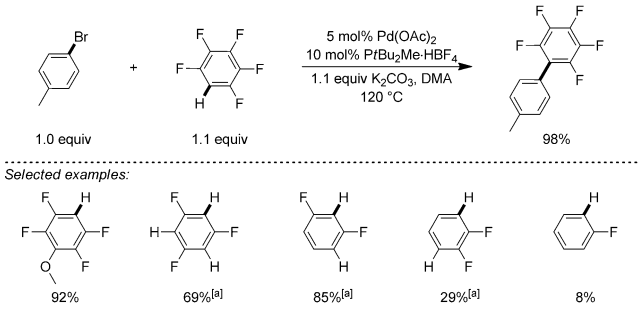
In 2006, while initially studying the direct arylation of various electron-rich five-membered heteroarenes, Itami and co-workers realized a rhodium-catalyzed coupling of *para*-nitrophenyl iodide with anisole and 1,3-dimethoxybenzene.[17] Anisole was arylated with an astonishing *para*/*ortho* selectivity of 79:29 at 200 °C under microwave conditions (Scheme 2).



Scheme 2. Direct arylation of anisole developed by Itami and co-workers.[17]

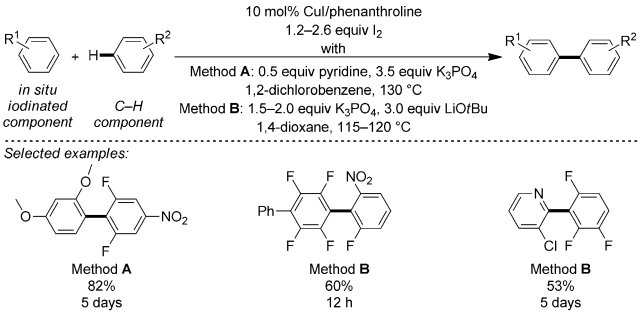
The key to success was the design of a rhodium(I) complex that bears two bulky, π-accepting phosphite ligands and that was proposed to promote C–H activation through an electrophilic metalation pathway.

Based on previous studies on intramolecular direct arylations, Fagnou and co-workers found generally applicable conditions ($Pd(OAc)_2$, the electron-rich phosphine ligand $PtBu_2Me{\cdot}HBF_4$, and K_2CO_3 as base) for the intermolecular direct coupling of electron-rich 1,3-benzodioxole.[18] Furthermore, they reported that electron-poor polyfluorinated arenes could also efficiently undergo a direct coupling with aryl halides with the same catalytic system.[19,20] Intriguingly, an almost equimolar ratio of both reaction partners (1:1.1 molar ratio) was sufficient to achieve satisfying results with some substrates. The observed inversion of classical reactivity was ascribed to a concerted metalation–deprotonation (CMD) mechanism in which the carbonate base, coordinated to the palladium–aryl intermediate, promotes the C–H activation step on the polyfluorinated arene via a six-membered transition state. Thus, reactivity and regioselectivity were found to correlate well with the acidity of the functionalized fluoroarene (Scheme 3). However, for substrates with more than one C–H bond available for reaction, di- and triarylated products were also obtained.[19a]



Scheme 3. Cross-coupling of 4-bromotoluene with polyfluoroarenes (1.0–1.3 equiv) reported by Fagnou and co-workers.[19a] [a] For simplicity, the amounts of bi- and triarylated products are not indicated.

Following the idea that selective C–H activation on electron-deficient arenes can be controlled by the C–H bond acidity, Daugulis and co-workers accomplished a selective copper(I)-catalyzed direct arylation of electron-deficient arenes ($pK_a < 35$) with aryl iodides.[21] In this case, C–H activation follows a deprotonation–metalation mechanism in which the arene is first selectively deprotonated by a sufficiently strong base (K_3PO_4 or Li*O*t*Bu*) at its most acidic position, and subsequently transmetalated onto the copper(I)–phenanthroline catalyst.[21c] Recently, this copper-catalyzed arylation was combined with an in situ iodination protocol in a one-pot reaction, which constitutes a very general approach to cross-couple electron-poor (hetero)arenes with various electron-rich heterocycles and benzene derivatives. With this methodology, good selectivities for the cross-coupled over homo-coupled products as well as excellent regioselectivies could be obtained (Scheme 4).[21a]

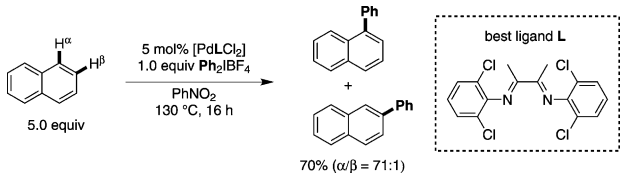


Scheme 4. Sequential iodination/cross-coupling of electron-deficient benzene derivatives developed by Daugulis and co-workers.[21a]

2.1.2. Oxidative Direct Arylation Using Iodonium Salts

In recent years, the use of iodonium salts (i.e., $PhI(OAc)_2$ or $[Ar_2I]^+X^-$) in transition-metal-catalyzed C–H arylation reactions has become an attractive tool, because these reagents are efficient oxidants,[22] and can also play a dual role as both substrate and oxidant.[23]

In 2011, Sanford and co-workers utilized $[Ar_2I]^+$ reagents in a highly regioselective direct arylation of naphthalene.[24] The choice of ligand for the palladium catalyst was shown to be crucial for a selective arylation process. Screening of different nitrogen atom containing ligands showed that a 2,6-dichlorinated bis(aryl)diimine ligand is superior in reactivity (70% yield) as well as selectivity, giving preferentially the α-arylated isomer (α/β = 71:1) (Scheme 5). Although a distinct



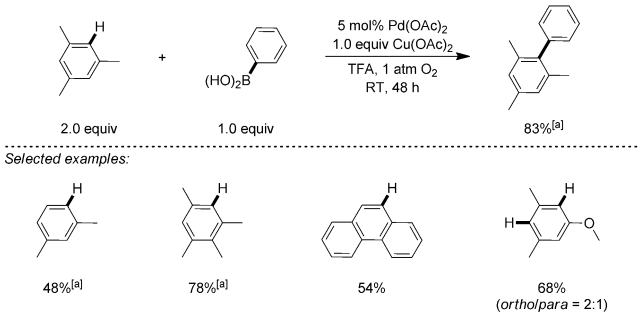
Scheme 5. Ligand-controlled regioselective arylation of naphthalene with diaryliodonium salts described by Sanford and co-workers.[24a]

correlation between ligand structure and regioselectivity remained elusive, this example elegantly demonstrates the potential power of ligand-controlled selectivity induction in C–H activation reactions.[25]

2.1.3. Oxidative Direct Arylation (Ar–H + Ar–M)

As indicated in Section 2.1.1, the direct arylation of simple arenes using organometallic reagents is a less-explored pathway.[26] However, over the last few years, several examples have been reported with some reactions proceeding under comparatively mild conditions. As oxidative addition of a late transition metal into an aryl C–H bond does not generally occur[1,14] (for an exception, see Section 3.5), stoichiometric amounts of an additional oxidant are required for these reactions to proceed.

In 2008, Shi and co-workers accomplished the coupling of electron-rich arenes and heteroarenes with aromatic boronic acids at room temperature (Scheme 6).[27,28] To avoid undesired homocoupling of the boronic acid, acidic conditions, which retard transmetalation of the boronic acid onto the catalyst, were applied. As a result, C–H activation of the unfunctionalized benzene derivative can compete more effectively, and only a slight excess (2.0 equiv) of the arene coupling partner was required to encourage cross-coupling. The higher efficiency observed for electron-rich arenes and heteroarenes in this process as well as the observed regioselectivies are consistent with a mechanism that involves most likely an electrophilic metalation-type C–H activation step. Similarly, Su and co-workers recently demonstrated that the coupling of electron-poor polyfluorinated arenes with boronic acids also requires the addition of acid to achieve high levels of selectivity for the cross-coupled product.[29]



Scheme 6. Arylation of simple arenes at room temperature using phenyl boronic acid reported by Shi and co-workers.[27] (TFA = trifluoroacetic acid). [a] Yield determined by GC analysis.

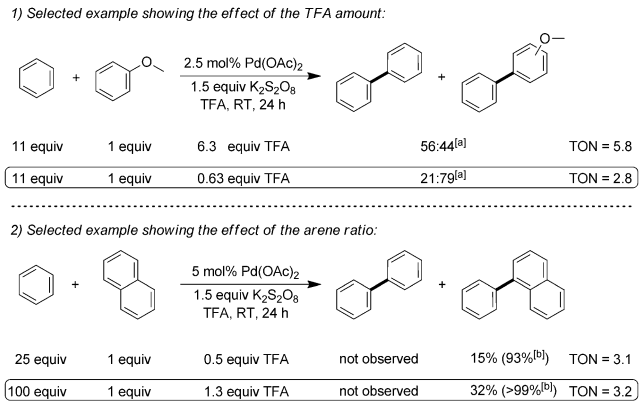
Building on earlier work on palladium-catalyzed direct arylations of polyaromatic compounds by their group,[30a] Oi, Inoue, and co-workers showed that for the coupling of arenes with aryltrimethylsilanes, the amount of $CuCl_2$ oxidant was crucial to avoid homocoupling of the organometallic reagent.[30b]

2.1.4. Cross-Dehydrogenative Couplings (CDC)

The most elegant and environmentally attractive method for the construction of the biaryl motif involves the direct cross-coupling of two arenes by dual C–H activation. In contrast to conventional transition-metal-catalyzed cross-coupling reactions, this process employs readily available arene starting materials and does not generate stoichiometric amounts of halogenated or organometallic by-products.

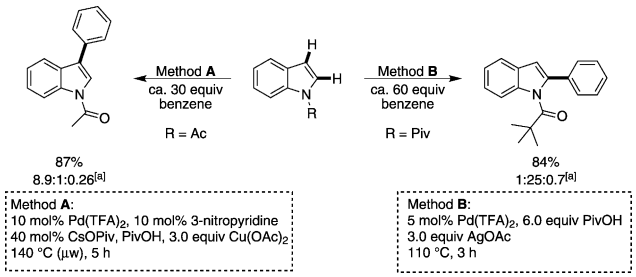
With regard to selectivity, the cross-dehydrogenative coupling (CDC) of two simple arenes constitutes the most challenging task. While direct arylations are largely complicated by the problem of how reactivity of an unreactive arene can be enhanced compared to the functionalized partner, performing an oxidative coupling requires the activation of two rather unreactive C–H bonds. In particular, it raises the question how the catalyst differentiates between the two C–H bond-containing components to achieve a chemoselective reaction, regardless of the regioselectivity issues of the reactants themselves.

Following preliminary work by Fujiwara[31] and Bercaw,[32] Lu and co-workers reported a study on palladium-catalyzed CDC of simple arenes in 2006.[33a,34] Their detailed investigation of the reaction conditions revealed two distinct chemoselectivity-determining factors: 1) the amount of trifluoroacetic acid (TFA), and 2) the ratio of the coupling partners. The latter was proposed to firstly enhance the activation of the less-reactive component, which was added in excess. A careful optimization of the amount of TFA was suggested in order to adjust the reactivity of the catalyst in such a way that the activation of the more electron-rich component is more likely in the second step (Scheme 7). Further tuning of the aforementioned factors enabled the same group to accomplish the cross-coupling of electron-deficient arenes.[33b] However, under the optimized conditions, the formation of significant amounts of homo-coupled biaryl compounds could not be avoided.



Scheme 7. Selectivity-determining factors of the CDC developed by Lu and co-workers.[33a] [a] *Ortho*/*para* ratio is 29:71 and 31:69, respectively. [b] Selectivity related to converted naphthalene.

Following the hypothesis that chemoselective coupling of arenes might be feasible by coupling benzene with electronically different arenes, Stuart and Fagnou[35a] developed a palladium-catalyzed oxidative cross-coupling of acetyl-protected indoles with simple arenes.[36] The regioselectivity, which favored the formation of the C3-arylated indole, was remarkable. However, replacing $Cu(OAc)_2$ with AgOAc led to an inversion of the classical reactivity of indoles, with arylation occurring predominantly at the C2 position (Scheme 8).[35b] Independently, DeBoef and co-workers reported similar findings regarding the selectivity switch of the indole

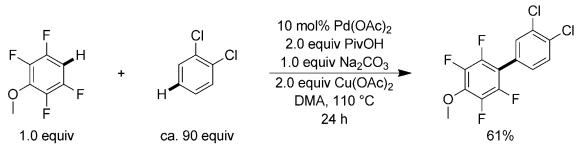


Scheme 8. Regioselectivity switch in the oxidative coupling of protected indoles with benzene reported by Fagnou and co-workers. [a] Ratio of C3/C2/double arylation.[35]

coupling partner.[37b] Through further investigations of the reaction mechanism by the same group,[37a] Fagnou and others[38] demonstrated that a CMD-type mechanism is surprisingly operative for the C–H activation of both reaction partners, thus disproving the initial hypothesis that chemoselectivity might be controlled by a difference in C–H activation mechanism.

In addition to indoles and pyrroles,[39] the dehydrogenative coupling of benzofurans[37c] and C–H acidic heteroarenes, such as xanthines,[40] has also been reported.

Moreover, Wei and Su[41] and Shi and co-workers[42] concurrently demonstrated the feasibility of a selective cross-coupling between polyfluoroarenes and different benzene derivatives, leading to the desired coupling products in moderate to good yields (Scheme 9). In both cases, regioselectivity was mainly controlled by steric factors that were imparted by the aryl substituents in such a way that for symmetrically 1,2-, 1,3-, and 1,4-disubstituted arenes only one regioisomer was generally observed.



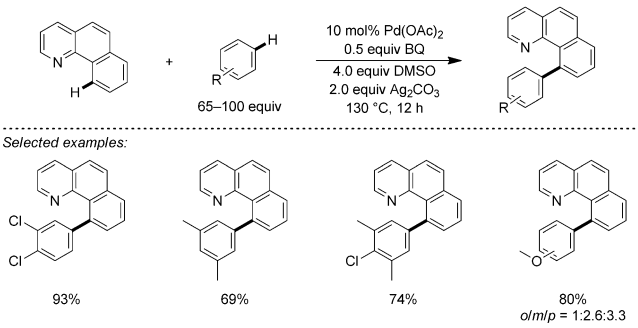
Scheme 9. Selected example for the cross-dehydrogenative coupling of simple arenes with polyfluoroarenes described by Wei and Su.[41]

2.1.5. *Chelate-Assisted Cross-Dehydrogenative Couplings*

Heteroarenes, such as indoles, and polyfluoroarenes significantly differ from other simple arenes in their reactivities, and therefore facilitate a better tuning of chemoselectivity in a cross-coupling reaction. Moreover, both compounds possess a certain intrinsic directing effect; either because of the presence of a heteroatom in the cycle or electron-withdrawing substituents on the ring, both of which provide an additional handle for regiocontrol. In contrast, the cross-coupling of two different simple arenes can be achieved when a chelating group is installed onto one coupling partner. Substantial work has already been done in this field, showing that heteroarenes, such as pyridines[43] and pyridine *N*-oxides,[44] as well as a variety of functional groups, such as acetanilides,[45,46,48b] esters,[47] carbamates,[48a] imines,[49] and amides,[48b,50,51] are suitable to direct C–H activation.

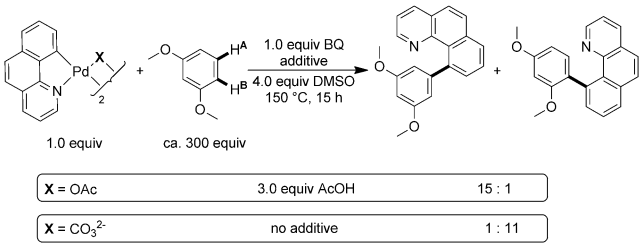
Sanford and co-workers were the first to identify the beneficial effects of utilizing a directing group in the oxidative cross-coupling of simple arenes. In 2007, they reported a highly chemoselective palladium-catalyzed arylation of benzo[*h*]quinoline, which was promoted by a substoichiometric amount of benzoquinone (BQ; Scheme 10).[43c]

Through detailed mechanistic investigations of the stoichiometric transformation, Sanford and co-workers elucidated that the course of the reaction can be influenced by three parameters: 1) the amount of BQ, 2) the acid additive,



Scheme 10. Oxidative cross-coupling of benzo[*h*]quinoline with simple arenes using a pyridine directing group reported by Hull and Sanford.[43c]

and 3) the nature of a ligand X on the metal center. More importantly, it was demonstrated that the rational variation of these three components enables tuning of reactivity and selectivity. The latter was elegantly shown for the arylation of benzo[*h*]quinoline with 1,3-dimethoxybenzene (Scheme 11).[43a] When one equivalent of BQ was used, C–H activation was reversible and complexation of BQ to the



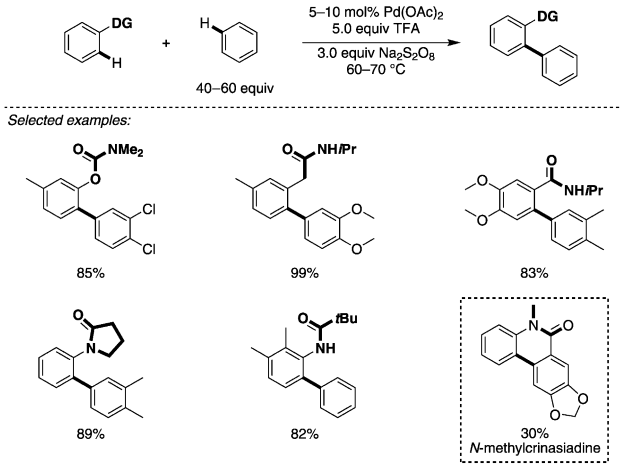
Scheme 11. Controlling regioselectivity in dehydrogenative couplings.[43a]

intermediary palladium diaryl species was proposed to be rate and selectivity determining. Under these conditions, arylation occurred predominantly at the sterically less-hindered position of 1,3-dimethoxybenzene. This effect could become further pronounced by the addition of acetic acid (3 equiv), which improved the **A**/**B** product ratio to 15:1. Exchanging the X-type ligand to carbonate led to a complete inversion of the **A**/**B** product ratio to 1:11. However, the origin of this effect still has to be elucidated. Although this study was performed in a stoichiometric fashion, it represents an exceptional example of regiocontrol in C–H activation reactions with simple arenes.

In 2008, Shi[45] and Buchwald[46] concurrently reported the palladium-catalyzed arylation of *meta*- and *ortho*-substituted acetanilides with benzene and various toluene and anisole derivatives with O_2 as terminal oxidant. In both cases, the regioselectivities observed for the simple arenes were mainly controlled by steric effects.

Versatile reaction conditions for the oxidative cross-coupling of benzene and symmetrically 1,2-disubstituted benzene derivatives were disclosed by Dong and co-workers.[48] The use of palladium acetate along with an excess of TFA and three equivalents of $Na_2S_2O_8$, a cheap and environmentally friendly oxidant, allowed the coupling reactions to proceed at temperatures as low as 70 °C, and were applicable to a broad range of directing groups (Scheme 12). Moreover, C–H activation of the 1,2-disubstituted arenes preferentially occurred at the least-hindered position. Interestingly, the reaction of O-phenylcarbamates was most efficient when electron-poor arenes were used, whereas other directing groups were only effective in the presence of electron-rich arenes.[48a] Additionally, stoichiometric experiments with probable palladium intermediates showed that, depending on the substrate, a change in mechanism from Pd^0/Pd^{II} (carbamate) to Pd^{II}/Pd^{IV} (acetanilide) could be observed.

Related to this observation, Thirunavukkarasu and Cheng applied very similar reaction conditions for the synthesis of

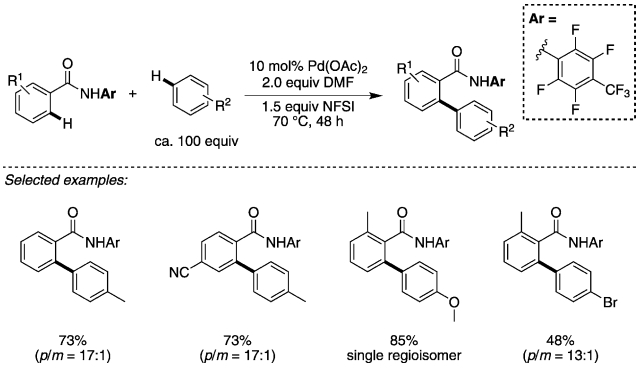


Scheme 12. Reaction conditions reported by Dong and co-workers for the dehydrogenative coupling of arenes applicable to different DGs.[48]

fluorenones from aryl oxime ethers and benzene.[49] Interestingly, when mono-substituted arenes were subjected to the reaction conditions, the products were obtained as single regioisomers.

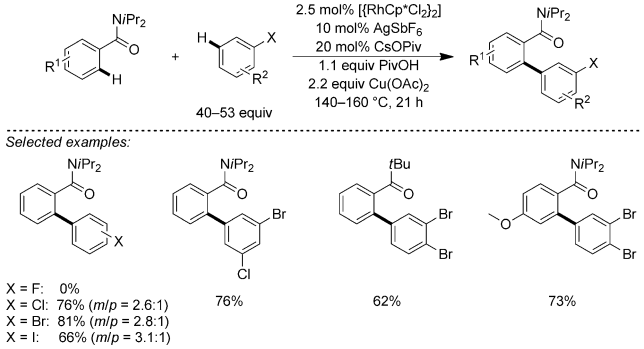
In 2011, Yu and co-workers described a highly *para*-selective arylation of mono-substituted arenes.[50] The crucial reagents that afforded this reactivity and selectivity were F^+ oxidants, which recently have been proven to promote otherwise difficult reductive eliminations from Pd^{IV} intermediates.[52] Among several F^+ reagents that were tested, *N*-fluorobenzenesulfonimide (NFSI) was superior with regard to reactivity and *para* selectivity. Combined with the versatile 4-trifluoromethyl-2,3,5,6-tetrafluorobenzamide directing group, different mono-substituted arenes, including those containing halogen atoms, were coupled with outstanding selectivity for the *para* position (Scheme 13). Since a KIE (kinetic isotopic effect) of 1.0 was observed for the simple arene, a mechanism involving electrophilic palladation was proposed. However, the involvement of a highly electrophilic $Ar^{DG}Pd^{IV}F$ species in the selectivity-determining activation step could not be clearly elucidated.

Very recently, Glorius and co-workers reported the first rhodium(III)-catalyzed oxidative biaryl formation.[51a] Using the $[\{RhCp^*Cl_2\}_2]/AgSbF_6$ catalyst system, which was pre-



Scheme 13. *Para*-selective arylation of mono-substituted arenes described by Yu and co-workers.[50]

viously shown to be effective for various coupling reactions with alkenes, alkynes,[53] allenes,[54] as well as CO,[55] chloroamines,[56] and various electrophiles,[57] the arylation of benzamides and certain acetophenones with aryl halides was achieved, leaving the halide functionality intact, independent of the halide that was employed. Notably, the *ortho* position of the aryl halide always remained untouched. Therefore, when 1,3-disubstituted bromoarenes were employed, this method constitutes a suitable handle to selectively generate valuable *meta*-bromo-substituted biaryl systems amenable to subsequent manipulations (Scheme 14). Unfortunately, although it could be demonstrated that a true C–H activation is operating on both reaction partners, a clear mechanistic understanding of the reaction is still elusive.



Scheme 14. Rh^{III}-catalyzed arylation of benzamides with bromoarenes developed by Glorius and co-workers.[51a]

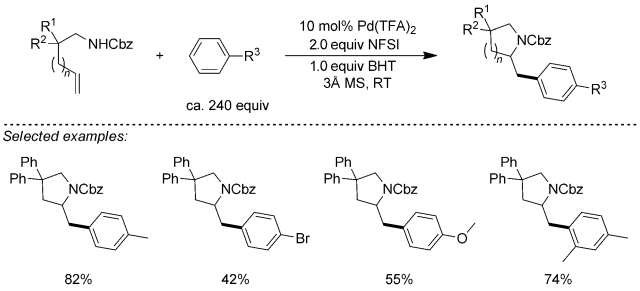
2.2. Alkylation of Simple Arenes

The classical Friedel–Crafts alkylation constitutes one of the oldest C–H functionalization methods of simple arenes.[58] Nevertheless, the well-established limitations of this transformation have encouraged the development of alternative transition-metal-catalyzed C–H alkylation methodologies, such as direct alkylations,[59,60] dehydrogenative couplings,[61] or olefin hydroarylations.[62]

A valuable example that should be highlighted in this context is the carboamination reaction developed by Michael and co-workers. The combination of $Pd(TFA)_2$ as catalyst and the F^+ oxidant NFSI resulted in the alkylation of electron-rich arenes.[63] Intriguingly, mono-substituted arenes were alkylated with exclusive *para* selectivity (Scheme 15).

2.3. Alkenylation of Simple Arenes

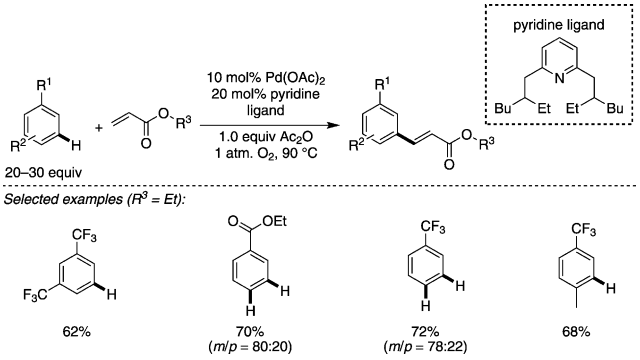
Two major classes of C–H functionalization reactions have been reported for the introduction of an olefin moiety into simple arenes:[64] 1) the hydroarylation of alkynes catalyzed by late transition metals, such as palladium,[65a–b] nickel,[65c] rhodium, iron,[65e–f] or gold,[66] and 2) the Heck reaction with a C–H analogue, also called the Fujiwara–Moritani or oxidative Heck reaction.[67]



Scheme 15. Carboamination of olefins by *para*-selective C–H activation of arenes reported by Michael and co-workers.[63] NFSI = *N*-fluorobenzenesulfonimide, BHT = butylhydroxytoluene.

Concerning the oxidative Heck reaction of simple arenes, substantial studies toward the improvement of reactivity and efficiency have been reported by Ishii,[68] Jacobs,[69] Matsumoto, and others.[70] However, achieving credible regioselectivity on the arene partner still necessitates a directing group in most cases.[53,71] Recently, a few attempts have been made to control the regioselective outcome in oxidative Heck reactions of simple arenes.[72]

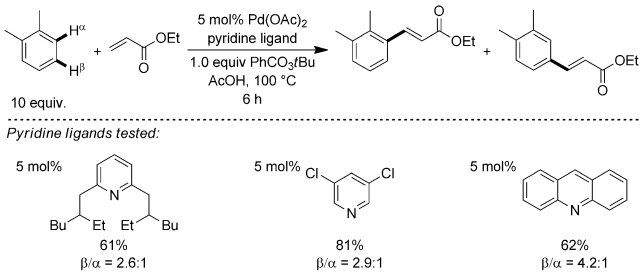
In 2009, Yu and co-workers were the first to report an appealing method for the regioselective coupling of simple arenes with acrylates. When a bulky pyridine ligand was employed, various mono-substituted electron-deficient arenes were efficiently functionalized with selectivities between 77:23 to 84:16 for the *meta* position (Scheme 16).[73] The ligand was found to be crucial for



Scheme 16. *Meta*-selective olefination of electron-poor arenes developed by Yu and co-workers.[73]

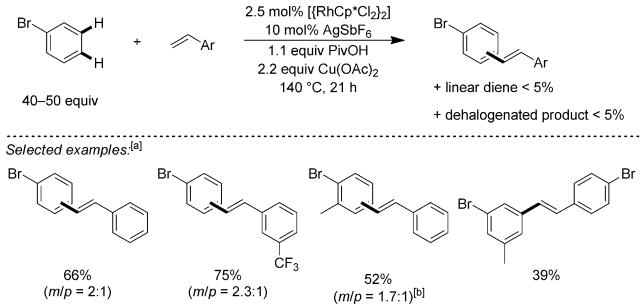
sufficient reactivity (it is bound to the palladium catalyst by a single bond, thus leaving free coordination sites for the substrate) and selectivity; the steric bulk of the ligand combined with the electronic properties of the substrates could explain the observed regioselectivity.[74]

Very recently, Sanford and co-workers similarly reported the beneficial effect of pyridine ligands on rate and selectivity of the oxidative coupling of simple arenes with acrylates.[75] Taking *o*-xylene as a model substrate, the regioselectivity was shown to be influenced by the ligand properties, thus supporting that appropriate catalyst design virtually permits site-selective C–H activation reactions (Scheme 17).



Scheme 17. Pyridine ligands that affect the regioselectivity outcome in the olefination of *o*-xylene.[75]

Based on recent work in the field of Rh^{III}-catalyzed Heck reactions,[53] Glorius and co-workers reported that $[\{RhCp^*Cl_2\}_2]$ is also an effective catalyst precursor for the oxidative Heck reaction between various styrenes and simple bromobenzene derivatives (Scheme 18).[76] Notably, the C–Br bonds of the products presumably stay untouched during the reaction. However, it was shown that the bromoarenes are not only acting as substrate, but rather have an essential role in the catalytic cycle. Regarding the regioselectivity, the reaction preferentially led to *meta* and *para* functionalization in such a way that only one isomer was obtained with 1,3-disubstituted arenes.

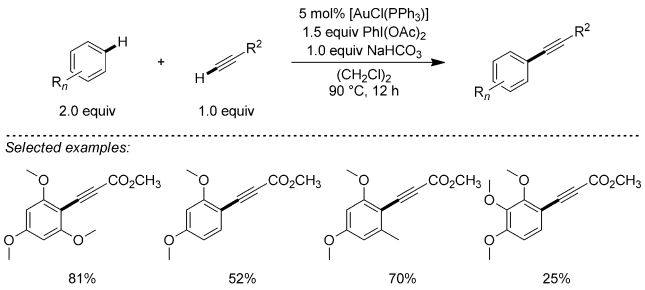


Scheme 18. Olefination of bromobenzene derivatives reported by Glorius and co-workers.[76] [a] For simplification, the amounts of by-products are not indicated. [b] *meta*/*para* selectivity with respect to the bromine substituent.

2.4. Alkynylation of Simple Arenes

In comparison to the transformations discussed above, the alkynylation of simple arenes has only been scarcely explored.[77] In a seminal work by de Haro and Nevado,[78] the first gold(I)-catalyzed oxidative coupling of electron-poor terminal alkynes with electron-rich arenes and heteroarenes was described.

The regioselectivity was controlled by mesomeric and inductive effects of the substituents, with *ortho* and *para* alkynylation occurring predominantly with these electron-rich arene substrates (Scheme 19). This regioselectivity is consistent with an electrophilic-type C–H activation mechanism that involves nucleophilic attack of the arene onto either a gold-activated alkyne species or onto gold(III) itself.[79] An electrophilic auration step of this type was first demonstrated in 1931 by Kharasch and Isbell, and has been shown to proceed under remarkably mild conditions.[1d,80]

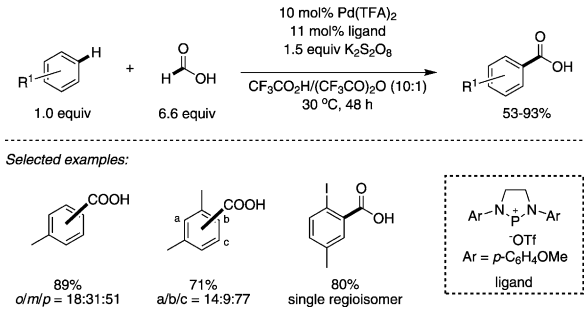


Scheme 19. Gold-catalyzed alkynylation of electron-rich arenes developed by de Haro and Nevado.[78]

2.5. Carboxylation of Simple Arenes

Various approaches have been disclosed for the transition-metal-catalyzed synthesis of benzoic acids directly from simple arenes. Pioneering studies by Fujiwara and others since the 1980s focussed on the palladium(II)-mediated carbonylation of benzene derivatives in the presence of CO gas.[81,82] Similar reactivity has also been reported using rhodium catalysts, although the substrate scope remains low at present.[83]

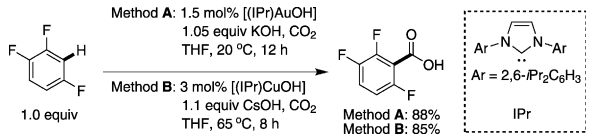
An alternative approach involves the dehydrogenative coupling of arenes with formic acid.[84–85] The combination of the palladium(II) source $Pd(TFA)_2$ and a phosphenium ligand was shown to be an effective catalytic system for this transformation, delivering benzoic acids in up to 93% yield under remarkably mild conditions (30 °C, 48 h).[85] Regioselectivities were generally moderate for a range of alkylbenzenes, with carboxylation occurring preferentially at the least sterically hindered site (Scheme 20).



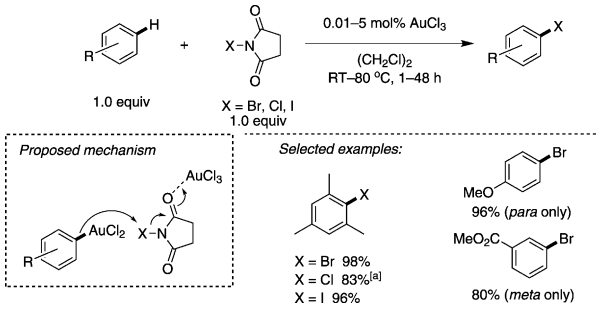
Scheme 20. Palladium-catalyzed carboxylation of arenes with formic acid described by Nozaki and co-workers.[85]

The direct carboxylation of polyfluorobenzenes with CO_2 was recently demonstrated by Nolan and co-workers, who used gold(I)[86] or copper(I)[87] catalysts stabilized by the N-heterocyclic carbene ligand IPr.[88] C–H activation in these systems is thought to occur through deprotonation of the most acidic aryl C–H bond by the highly basic hydroxide ligand,

leading to an aryl–metal species that is amenable to CO_2 insertion and hydrolysis. The exclusive formation of the 3-carboxy-substituted regioisomer from 1,2,4-trifluorobenzene is consistent with this interpretation (Scheme 21).



Scheme 21. Gold- or copper-catalyzed carboxylation of polyfluorobenzenes with CO_2 reported by Nolan and co-workers.[86,87]



Scheme 22. Halogenation of simple arenes using gold(III) chloride reported by Wang and co-workers.[92] [a] Yield determined by GC analysis.

3. C–Heteroatom Bond Formation

The construction of carbon–heteroatom bonds directly from non-activated C–H bonds in simple benzene derivatives is the most attractive method for synthesizing functionalized aromatic compounds. While transition-metal salts have long been employed as Lewis acid additives in classical arene functionalization reactions,[89] a number of carbon–heteroatom bond-forming processes in which the metal is thought to directly activate the arene C–H bond itself have been reported over the last few years. In this section, the state of the art in transition-metal-catalyzed aromatic C–halogen, C–O, C–N, C–Si, and C–B bond formation is discussed, focusing on processes in which the intermediacy of a distinct aryl–metal complex has been proposed.

3.1. C-Halogen Bond Formation

Mono-halogenated arenes are among the most versatile sources of aryl motifs available to synthetic chemists. As such, the preparation of these substrates directly from simple benzene derivatives is an attractive process and electrophilic aromatic halogenation methodologies using N-halosuccinimides (NXS, X = Cl, Br, I) as sources of "X^+" have received widespread research attention.[90,91] However, the selective halogenation of non-activated substrates by this method only proceeds in the presence of strong Brønsted or Lewis acid catalysts and typically requires high reaction temperatures and catalyst loadings.

In 2010, Wang and co-workers reported an attractive set of conditions for the halogenation of a wide range of simple benzene derivatives using gold(III) chloride as catalyst.[92,93] Using just 0.01–1 mol% of $AuCl_3$, arenes that bear electron-donating groups were generally brominated, iodinated, or chlorinated in excellent yields of up to 98% of isolated products. Notably, aromatic substrates that bear alkyl groups underwent selective halogenation of an aryl C–H bond without competitive formation of benzyl halides, which is commonly observed with Brønsted or Lewis acid catalysts. Where applicable, regioselectivities correlated well with the proposed electrophilic metallation mechanism, with *ortho*/*para* or *meta* selectivity predominating for electron-rich and electron-poor substrates, respectively (Scheme 22).

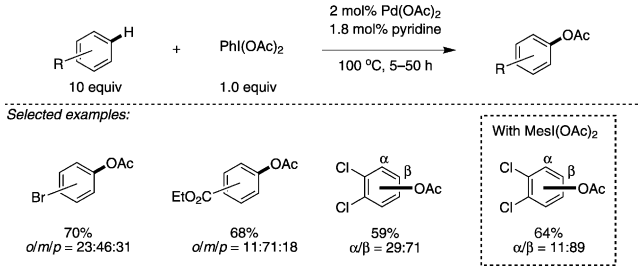
This methodology was later applied to the halogenation of arylboronate esters, leading to versatile halogenated arylboron reagents that are amenable to sequential Suzuki–Miyaura cross-couplings.[94] The high efficiency of these reactions was attributed to the dual role of gold in activating both the succinimide component (as a traditional Lewis acid) and the arene through the formation of an arylgold(III) complex.

3.2. C–O Bond Formation

A range of different transition metals have been studied as catalysts for the direct hydroxylation of aromatic compounds. This process is the most attractive method for the synthesis of phenol derivatives, which find multiple applications as building blocks in the pharmaceutical and agrochemical industries. While several *ortho*-selective C–O bond-forming reactions have been recently reported for arenes that bear directing groups, an efficient and selective C–H oxidation of aromatic substrates that do not contain a coordinating moiety has remained a major challenge.[1g,95] To date, a variety of transition metals, including iron[96] and palladium,[84,97] have been shown to have activity in the direct hydroxylation of benzene derivatives, although conversions and regioselectivities are low at present.[98] Palladium(II) acetate has also been successfully employed as a catalyst for the direct acetoxylation of simple arenes. Building on earlier work, in which dichromate[99] and peroxydisulfate oxidants[100] were used, Yoneyama and Crabtree reported an operationally simple aromatic acetoxylation process using (diacetoxyiodo)benzene (PIDA) in 1996.[101]

Recently, Sanford and co-workers reported a greatly improved set of conditions for this reaction, using a $Pd(OAc)_2$/pyridine catalytic system.[102,103] The metal/ligand ratio was found to have a dramatic effect on the reaction efficiency, with 0.9 equivalents of pyridine per equivalent of $Pd(OAc)_2$ leading to the highest yields of the acetoxylated products. This effect was attributed to the in situ formation of a Pd^{II} active catalyst of the form $[(py)Pd^{II}(OAc)_2]$, which contains a free coordination site available for aryl C–H activation. Under these conditions (2 mol% of Pd, 1.8 mol% of py), comparatively electron-deficient arenes could be successfully oxidized in yields up to 70%, whereas the analogous reactions that

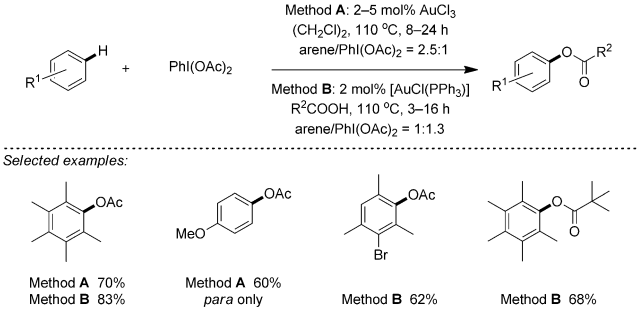
were performed using $Pd(OAc)_2$ alone or with $Pd(OAc)_2$/pyridine in a ratio of 1:2.1 delivered the acetoxylated products in less than 8% yield. The presence of the pyridine additive also led to an improvement in regioselectivity with a general increase in *meta* selectivity for electron-deficient substrates. Intriguingly, switching the oxidant to the more sterically demanding (diacetoxyiodo)mesitylene also led to a slight increase in regioselectivity, thus indicating that the nature of the hypervalent iodine reagent may also affect the product distribution (Scheme 23).



Scheme 23. Palladium acetate/pyridine catalyzed acetoxylation of arenes using PIDA developed by Sanford and co-workers.[102]

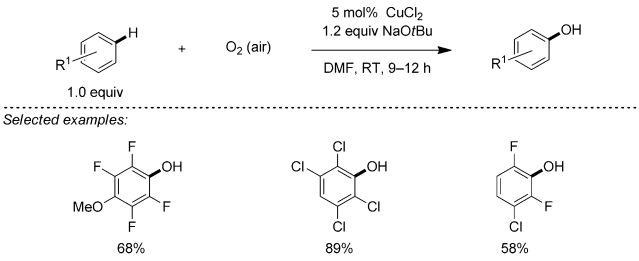
Independent studies by the groups of Wang[104] and Michelet[105] demonstrated that gold salts can also catalyze the formation of acetoxylated arenes directly from simple benzene derivatives in the presence of PIDA. Mechanistically, this process is thought to involve an intermediate arylgold(III) complex formed upon electrophilic attack of the arene substrate onto gold(III). Nucleophilic substitution of the aryl moiety onto gold-activated PIDA or C–O bond-forming reductive elimination from a gold(III) aryl acetate species would then deliver the acetoxylated products. In the latter scenario, re-oxidation of gold(I) by PIDA would complete the catalytic cycle and regenerate gold(III) acetate. The acetoxylation process could be performed on a range of electron-rich aromatic substrates in generally moderate to good yields of up to 83% upon heating to 110°C in the presence of 2–5 mol% of either a gold(I) or gold(III) precatalyst. Electron-neutral or electron-deficient arenes, such as toluene, were not suitable substrates, while compounds containing two adjacent nonsubstituted carbon atoms suffered from competitive oxidative aryl homocoupling.[106] Alkyl carboxylates other than acetate could be successfully coupled upon performing the reaction (with $[AuCl(PPh_3)]$) in different carboxylic acid solvents. Regioselectivities were consistent with the proposed Friedel–Crafts-type electrophilic activation mechanism with strongly *ortho*/*para*-directing substituents, such as methoxy, determining the site of acetoxylation (Scheme 24).

Very recently, Lei and co-workers reported a copper-catalyzed hydroxylation of polyfluoro- and polychloroarenes using air as the oxygen source.[107] The use of NaO*t*Bu as a basic additive was essential to encourage product formation, because C–H activation is thought to occur through deprotonation of relatively acidic polyhalogenated arenes by an external base to afford an aryl–Cu^I species.[21c] Oxidation to afford the corresponding phenols occurred under notably



Scheme 24. Gold-catalyzed acyloxylation of arenes using PIDA described by Wang[104] and Michelet[105] and their respective co-workers.

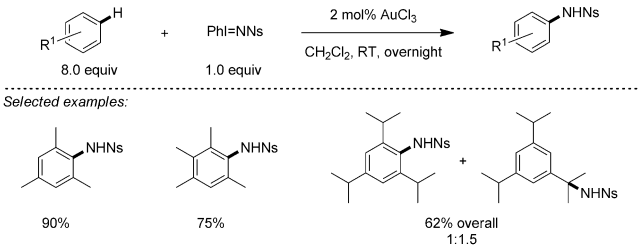
mild conditions, with complete conversion using $CuCl_2$ as catalyst (5 mol%). Moderate to good yields of up to 89% were obtained with these arene substrates, while the process was also successful with heteroaromatic benzothiazoles, benzoxazoles, purines, and oxadiazoles (Scheme 25).[4i]



Scheme 25. Copper-catalyzed hydroxylation of polyhalogenated arenes with air reported by Lei and co-workers.[107]

3.3. C–N Bond Formation

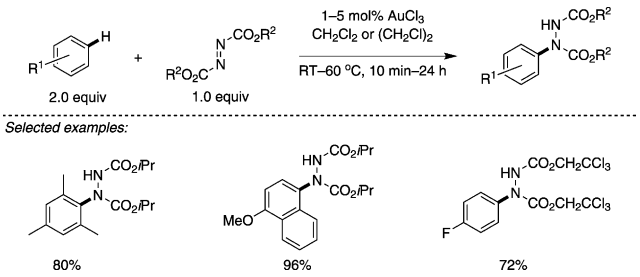
Electrophilic activation of aryl C–H bonds by gold(III) salts was exploited by He and co-workers to prepare anilines directly from simple arenes.[108,109] In the presence of the nitrene precursor PhI=NNs (Ns = *para*-nitrosulfonyl) and 2 mol% of $AuCl_3$, aromatic substrates that bear three or more alkyl groups could be converted into the corresponding anilines in up to 90% yield (Scheme 26). In contrast to the related copper-catalyzed process,[110] high selectivity for the aromatic C–H functionalization product was observed for most arenes with competitive benzylic amination only occur-



Scheme 26. Gold-catalyzed amination of arenes using PhI = NNs developed by He and co-workers.[108]

ring with substrates that possess very weak benzyl C–H bonds. This selectivity mitigates in favor of a mechanism that involves an arylgold(III) intermediate derived from direct electrophilic auration of the arene.

A related gold-catalyzed aromatic amination process was recently reported by Zhang and co-workers using azodicarboxylates as a source of electrophilic nitrogen.[111,34] While analogous Brønsted or Lewis acid catalyzed processes require harsh reaction conditions, the $AuCl_3$-catalyzed reactions proceeded at room temperature, and an increased scope of electron-rich and poor arene substrates could be employed (Scheme 27). Where applicable, regioselectivities were high, with electron-donating substituents leading to predominantly *para* selectivity. This observation is consistent with the proposed "dual activation" mechanism, in which gold(III) both reacts with the arene to form an arylgold(III) complex and activates the azodicarboxylate as a Lewis acid.

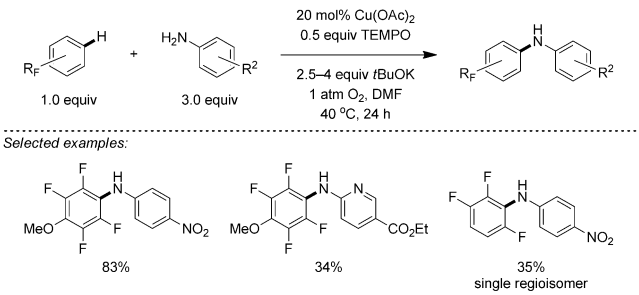


Scheme 27. Gold-catalyzed amination of arenes using azodicarboxylates described by Zhang and co-workers.[111]

Several impressive publications have focussed on the copper-catalyzed direct amination of fluorinated benzenes using simple amines as the nitrogen source. Aromatic C–H activation in these systems is thought to occur through deprotonation of the relatively acidic carbon–hydrogen bond by basic additives in the reaction mixture, leading to an arylcopper intermediate. In 2009, Wang and Schreiber reported that copper(II) acetate could mediate the oxidative coupling of polyfluoroarenes with pyrrolidinone when reacted at 120–140 °C in toluene.[112] The range of nitrogen coupling partners was extended by the group of Su to electron-deficient anilines upon using *t*BuOK as base and a TEMPO/O_2 system as oxidant.[113] Under these conditions, the reaction temperature could be lowered to 40 °C, while yields of the diarylamine products ranged from 29–83%. However, arene coupling partners with comparatively few fluorine substituents and consequently less-acidic C–H bonds, such as 1,3,5-trifluorobenzene, were not reactive, while 1,2,4-trifluorobenzene reacted exclusively at the most acidic C–H bond (Scheme 28).[114–115]

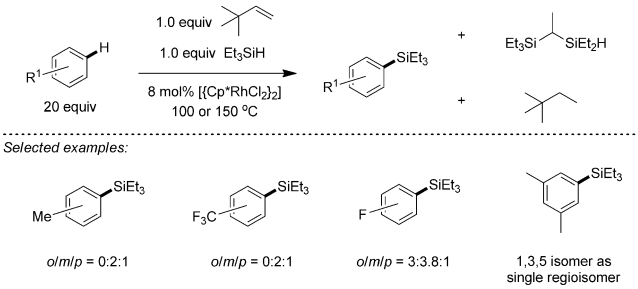
3.4. C–Si Bond Formation

A number of late transition metals have shown activity as catalysts for the C–H activation/silylation of aromatic compounds.[116] As early as 1982, Curtis and co-workers reported



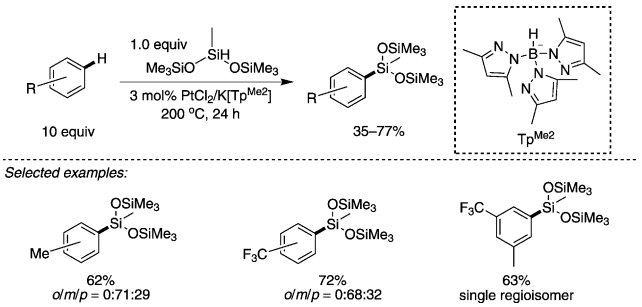
Scheme 28. Copper-catalyzed amination reaction of polyfluoroarenes reported by Su and co-workers.[113]

the iridium-catalyzed formation of phenylsiloxanes directly from benzene and hydridosiloxanes,[117] while subsequent reports by the groups of Tanaka[118] and Ishikawa[119] disclosed related transformations catalyzed by nickel, platinum, or rhodium complexes. However, these pioneering reactions either suffered from low yields, worked only for a limited number of arene substrates, and/or required the use of specific silane coupling partners. In 1998, Berry and co-workers reported a rhodium-catalyzed dehydrogenative transfer coupling of benzene derivatives and triethylsilane.[120] The presence of one equivalent of *tert*-butylethylene as a hydrogen acceptor was essential for the coupling to proceed and reaction temperatures of 100 °C or 150 °C were required. Competitive formation of the carbosilane dimer was also observed, although time–course studies revealed that over extended reaction times this species could be converted into the desired arylsilane and one equivalent of triethylsilane. The selectivity for the arene silylation product was increased upon switching to ruthenium(II) precatalysts although these reactions were around 20 times slower than the corresponding rhodium-mediated processes. Interestingly, the electronic properties of the arene substituents had little effect on the silylation regioselectivity, with comparatively electron-rich toluene and electron-deficient trifluorotoluene delivering a statistical 2:1 mixture of the *meta*- and *para*-substituted products. Carbon–silicon bond-formation was not observed in *ortho* position to the more sterically demanding methyl and trifluoromethyl substituents in either of these substrates (Scheme 29).



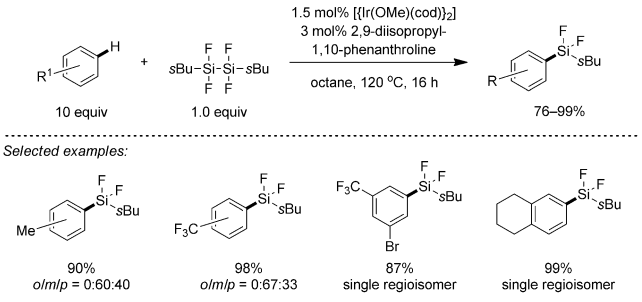
Scheme 29. Rhodium-catalyzed silylation of arenes with triethylsilane developed by Berry and co-workers.[120] Yields of isolated products were not reported.

In 2005, Tsukada and Hartwig developed a platinum-catalyzed benzene silylation protocol, which does not require stoichiometric amounts of a hydrogen-accepting additive.[121] The range of suitable arene substrates in this process was expanded in a later report by Murata and co-workers. using 1,1,1,3,5,5,5-heptamethyltrisiloxane as the silicon coupling partner (Scheme 30).[122] A sterically controlled regioselectivity pattern similar to that observed in the rhodium-catalyzed process above was also noted for this transformation with both electron-rich and electron-poor substrates, leading to essentially statistical mixtures of the *meta*- and *para*-substituted products.



Scheme 30. Platinum-catalyzed silylation of arenes with 1,1,1,3,5,5,5-heptamethyltrisiloxane described by Murata and co-workers.[122]

An efficient iridium-catalyzed silylation process for simple benzene derivatives was described by Miyaura and co-workers using 1,2-di-*tert*-butyl- or 1,2-di-*sec*-butyl-1,1,2,2-tetrafluorodisilane as the silicon source.[123] A range of substituted arenes (10.0 equiv) could be converted into the corresponding arylhalosilanes in good to excellent yields. As in the previous samples, steric factors dominated the regioselectivity of the process, with statistical mixtures of *meta* and *para* products being observed for mono-substituted substrates, and 1,3-disubstituted arenes leading exclusively to 1,3,5-trisubstituted products. The arene electronics also had a minimal effect on their relative reactivities, with an equimolar mixture of toluene and trifluorotoluene undergoing silylation with essentially equal efficiency (Scheme 31).

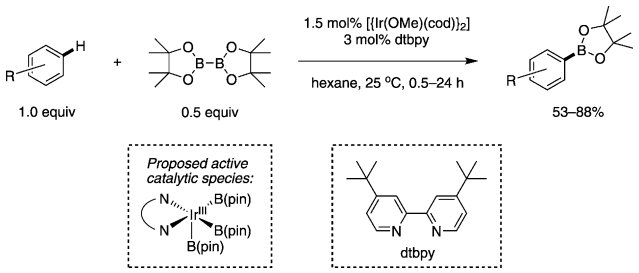


Scheme 31. Iridium-catalyzed silylation of arenes with 1,2-di-*sec*-butyl-1,1,2,2-tetrafluorodisilane developed by Miyaura and co-workers.[123b]

3.5. C–B Bond Formation

The selective borylation of aromatic C–H bonds is a powerful transformation that gives access to versatile arylboron reagents amenable to a wide range of subsequent manipulations. While rhodium has been shown to mediate this transformation,[124] iridium complexes have emerged as the catalysts of choice for most applications with HB(pin) or $B_2(pin)_2$ (pin = pinacol) acting as the borylating reagents. This topic has been excellently reviewed recently,[116a,125] and only a brief overview highlighting the key features of the process will be discussed here.

Although the initial reports of Ir-catalyzed arene C–H borylation employed Cp*Ir complexes,[124b,126] a series of studies by the groups of Hartwig, Ishiyama, and Miyaura identified the Ir^I dimer $[\{Ir^IOMe(cod)\}_2]$ (cod = 1,5-cyclooctadiene) as the optimal precatalyst for this transformation when used in combination with the 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) ligand.[127] Using this catalytic system (3 mol% [Ir]/dtbpy), a wide range of electron-rich, electron-neutral, and electron-deficient arenes could be borylated in high yields (Scheme 32). Furthermore, the reaction proceeded at room temperature and an excess of the aromatic



Scheme 32. Iridium-catalyzed borylation of arenes with $B_2(pin)_2$ reported by Hartwig, Ishiyama, Miyaura, and their respective co-workers.[127a]

substrate relative to boron (i.e., 2.0 equiv of arene per 1.0 equiv of $B_2(pin)_2$) was not required. Detailed mechanistic investigations[127a,d,128] identified the triborylated Ir^{III} complex as the active catalytic species in this process with C–H activation of the arene occurring either by oxidative addition to afford an Ir^V species or by σ-bond metathesis with a boronate ligand. Theoretical studies on a simplified system by Sakaki and co-workers[128a] offered support for a mechanism involving oxidative addition of the arene C–H bond to Ir^{III}.[128c]

The electronic nature of the arene ring substituents has only a marginal effect on the regioselectivity of the process. Instead, the site of borylation is essentially completely determined by steric factors.[125c] Mono-substituted or unsymmetrically 1,2-disubstituted arenes typically give rise to statistical mixtures of the *meta*- and *para*-boronate products, while 1,3-disubstituted or symmetrically 1,2-disubstituted substrates lead to a single regioisomer with borylation occurring at the least-hindered site (Figure 2).[129]

This sterically controlled regioselectivity pattern stands in contrast to the standard *ortho* selectivity imparted by DG-

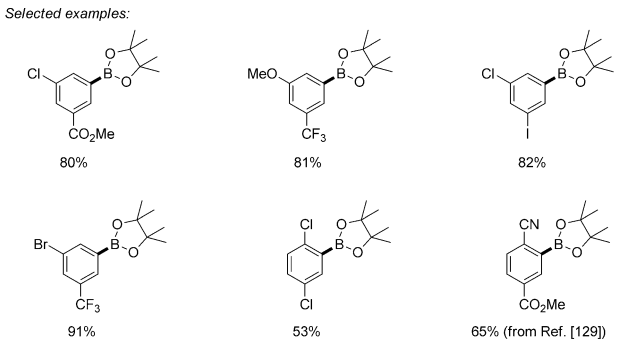
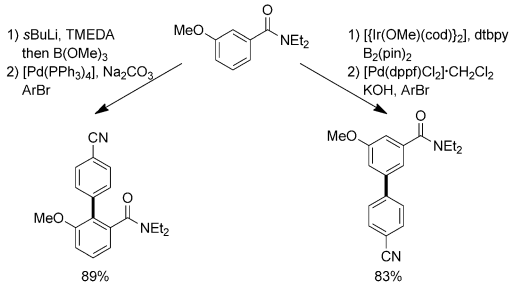


Figure 2. Selected examples of sterically controlled iridium-catalyzed borylation of arenes.[127b,129]

assisted transition-metal-catalyzed arene C–H functionalization processes or by stoichiometric *ortho*-lithiation protocols. The synthetic utility of these complementary methodologies was elegantly demonstrated by Snieckus and co-workers in 2010 in the preparation of benzamide-substituted biaryl compounds.[130] While an *ortho*-lithiation approach led to the corresponding 1,2,3-trisubstituted arene, iridium-catalyzed borylation followed by palladium-catalyzed Suzuki–Miyaura arylation delivered the 1,3,5-trisubstituted biaryl compound as a single regioisomer in 83% yield (Scheme 33). Similar synthetic applications of this methodology, which make use of the versatility of arylboron reagents, have also been reported.[125]



Scheme 33. Complementary methods for the regioselective arylation of simple arenes described by Snieckus and co-workers.[130]

4. Conclusion

Transition-metal-catalyzed processes that involve the direct activation of aromatic C–H bonds are among the most elegant, cost-effective, and environmentally friendly methods to functionalize benzene derivatives. The dual challenges of enhancing reactivity and regioselectivity inherent to these transformations are most commonly addressed by using substrates that bear directing groups capable of precoordinating the metal catalyst. However, more general processes that do not require the pre-installation of a directing group on the simple benzene derivative are much less widely reported. In these cases, the efficiency and site of C–H functionalization is governed by factors such as the electronic and steric profiles of the arene. Consequently, aryl C–H activation can occur with regioselectivity that is complementary to *ortho*-selective DG-assisted processes. For example, the regioselectivity of functionalization reactions that proceed through electrophilic metalation mechanisms typically follow classical Friedel–Crafts-type patterns, while iridium-catalyzed borylation of 1,3-disubstituted benzenes occurs exclusively at the least sterically hindered 5-position. Furthermore, several reports demonstrate that the selectivity can be improved upon judicious selection of the catalyst and ligand combination. Although this field remains in its infancy, further studies that build on the examples presented herein should allow the development of more active catalytic systems that are capable of achieving the same levels of predictability and robustness observed for DG-assisted transformations.

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