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Synthesis S. Kancherla et al. Short Review

Recent Developments in Palladium-Catalysed Non-Directed C–H Bond Activation in Arenes

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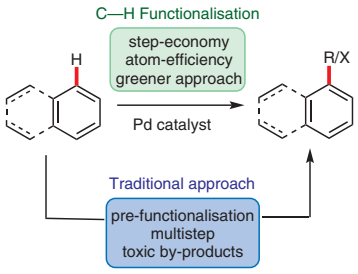

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Abstract Over the past decades, organic chemists have focussed on developing new approaches to directed C–H functionalisations, where the site selectivity is steered by the presence of a directing group (DG). Nonetheless, in recent years, more and more non-directed strategies are being developed to circumvent the requisite directing group, making C–H functionalisations more generic. This short review focuses on the latest developments in palladium-catalysed non-directed C–H functionalisations of aromatic compounds.

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2.1 C–H Arylation
2.2 C–H Alkylation
2.3 C–H Alkenylation
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Key words C–H bond activation, palladium, non-directed, arenes, catalysis

1 Introduction

Metal-catalysed C–H functionalisation is nowadays a promising strategy to introduce complexity in organic molecules in a more efficient manner since no prefunctionalisation of the starting material is required.[1] This approach brings in a single-step opportunity to have new diversification sites for almost every target molecule, allowing new strategic disconnections and late-stage diversifications.[2] Over the past decades, an enormous expansion of this strategy has been achieved with the aim of having a general synthetic tool to functionalise organic molecules. However, in the vast majority of these examples, the presence of a directing group (DG) on the substrate is required to overcome the low reactivity and selectivity observed in these processes.[3] The DGs chelate to the transition-metal (TM) catalysts and escalate the reactivity and selectivity of the substrate through complex-induced proximity effects (CIPEs). Recently, templates and transient groups have enabled the transformation of distal sites from the DG. In general, these DGs are not common functional groups in organic molecules and therefore, this approach requires additional steps before arriving at the desired product.

To realise the full potential of TM-catalysed C–H functionalisations, the development of new methodologies that allow the use of substrates lacking DGs is necessary.[4] Usually, such transformations rely on the reactivity and selectivity defined by substrate control and/or catalyst control. Unlike in heteroaromatic compounds, the reactivity between C–H bonds in aryl substrates is less differentiated and thus requires highly efficient catalytic systems. Glorius and coworkers have presented the major developments made until 2012 in this area of non-directed C–H functionalisations.[5] Considering the rapid progress being made in this field, this short review will focus on bringing together the remarkable advancements made in Pd-catalysed non-directed C–H functionalisations of arenes during the period of late 2012 to early 2018. Examples that apparently work in homogeneous phase through a defined organometallic intermediate resulting in the formation of intermolecular C–C or C–X bonds will be included. The formation of C–C bonds will be discussed in section 2 and the formation of C–X bonds will be covered in section 3. This review will conclude with a summary of the progress made and future scope of the research in this field.

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M. Ángeles (Tati) Fernández-Ibáñez (right) was born in Madrid. She received her Ph.D. in 2006 from Universidad Autónoma de Madrid (UAM), Spain, under the supervision of Prof. José L. García Ruano and Prof. M. Carmen Maestro. During her Ph.D. studies, she carried out a predoctoral stay at Boston College, USA, with Prof. Scott J. Miller. Subsequently, she joined the group of Prof. Ben. L. Feringa at the University of Groningen, The Netherlands, as a postdoctoral researcher (2006–2009). After one year at the Medicinal Chemistry Institute at CSIC in Madrid, she moved to the group of Prof. Juan Carlos Carretero at UAM as a Research Associate. In 2012, she was appointed Assistant Professor at the Department of Organic Chemistry at UAM. In January 2015, she moved to the University of Amsterdam (UvA) as an Assistant Professor (tenure-track), and in 2017 she was promoted to Associate Professor.
Kåre B. Jørgensen (centre) received his M.Eng. (1990) and Ph.D. (1995) in organic chemistry from the Norwegian University of Science and Technology under the supervision of Prof. Per Carlsen. Subsequently, he undertook postdoctoral work for two years in the lab of Professor Tadashi Nakata at RIKEN (Wacoshi Campus), Tokyo, Japan, followed by postdoctoral engagements at the University of Tromsø (Assoc. Prof. Odd Reidar Gautun) and the University of Bergen (Prof. Leiv K. Sydnes) in Norway. He was appointed Associate Professor at the then Stavanger University College in 2000, which was upgraded to the University of Stavanger in 2005. After a sabbatical stay with Prof. Victor Snieckus at Queen's University in Canada in 2008, his research has focussed on synthetic methodology for the preparation of functionalised polycyclic aromatic hydrocarbons (PAHs) and PAH metabolites.
Sindhu Kancherla (left) obtained her integrated M.Sc. degree (2013) in chemistry from Nizam College, Osmania University, India. After working for a period as a project assistant at the CSIR-Indian Institute of Chemical Technology, India, she started her Ph.D. in 2015 at the University of Stavanger under the supervision of Assoc. Prof. Kåre B. Jørgensen and Assoc. Prof. Magne O. Sydnes. Her research is currently focussed on the syntheses and functionalisations of PAHs.

2 C–C Bond Formation

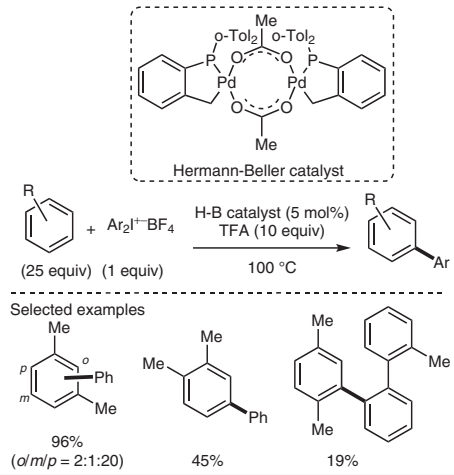
Several transformations that imply the formation of C–C bonds via Pd-catalysed non-directed C–H functionalisation of arenes have been reported in recent years. In the following subsections, new methods describing the intermolecular C–H arylation, alkylation, alkenylation and carbonylation of simple arenes will be summarised.

2.1 C–H Arylation

The direct arylation of C–H bonds in arenes has attracted considerable attention due to the abundance of biaryls in natural products and in most functional materials.[6] Various arylating reagents such as aryl halides, aryl organometallic reagents and aryl iodonium salts are employed. Nevertheless, the most concise and economical approach for the C–H arylation involves dual C–H bond functionalisations (cross-dehydrogenative coupling, CDC).[5,7] In the sections below, the latest developments on C–H arylations involving non-oxidative (ArH + ArX or $[Ar_2I]^+$ or $ArSO_2Na$), oxidative (ArH + ArM) and cross-dehydrogenative couplings are discussed based on the nature of the substrates that undergo the transformation, i.e., simple aryl derivatives, electron-deficient polyfluoroarenes and polycyclic aromatic hydrocarbons (PAHs).

2.1.1 Direct Arylation of Simple Arenes

Following the pioneering work of Sanford and co-workers for the direct arylation of naphthalene using $[Ar_2I]^+$ salts,[8] in 2013, Greaney and Storr developed a catalytic system for the direct arylation of simple arenes using symmetrical diaryliodonium salts (Scheme 1).[9] The presence of TFA was key to a successful reaction, along with the Hermann–Beller (H-B) catalyst. The protocol proceeded well with both electron-donating and electron-withdrawing groups on the iodonium salt, although the latter were preferable. *ortho*-Substitution on the iodonium salt was found to be low yielding compared to their *meta* and *para* counterparts. With regard to the aryl substrate, electron-rich arenes were arylated easily, while electron-poor arenes did not give appreciable yields. No influence on the regioselectivity was observed in the presence of the H-B catalyst, and mixtures of regioisomers were generally formed.



Scheme 1 Direct arylation of simple arenes with iodonium salts by Greaney and Storr[9]

In the same year, Loh and co-workers developed an attractive strategy for the direct C–H fluoroarylation of arenes via decarboxylative cross-coupling of perfluorobenzoic acid with simple arenes (Scheme 2).[10] The method is relatively economical and environment friendly, as the use

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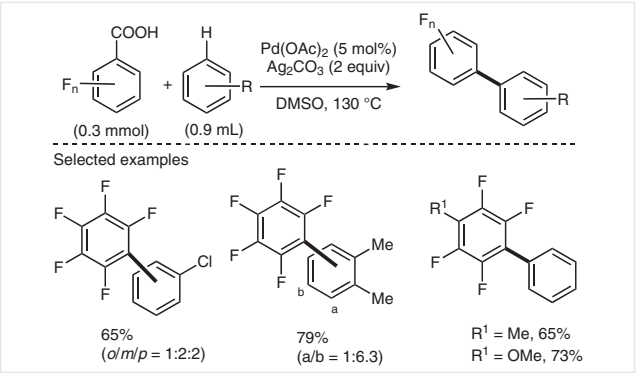
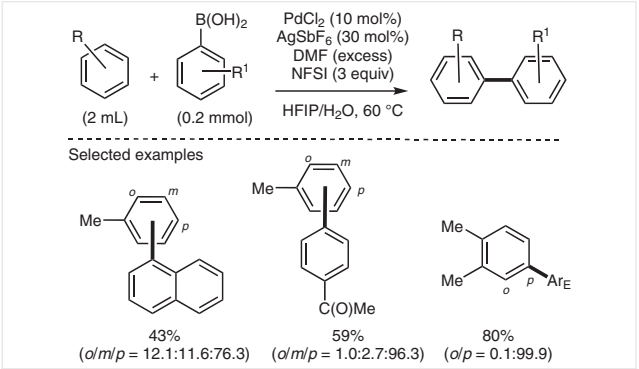
of perfluorobenzoic acids releases CO_2 as waste and seems to be a feasible pathway for the arylation of less reactive polyfluoroarenes. The reaction needs an excess of arene and mainly electron-rich arenes were tested, with the exception of chlorobenzene. The regioselectivity was dominated by steric factors, with preference for the sterically less-hindered C–H position. The reaction was catalysed by a bimetallic Pd/Ag catalytic system. The two intertwined catalytic cycles involve the reversible electrophilic palladation of the simple arene and transmetalation of perfluorophenyl to the Pd complex from the Ag-assisted decarboxylative activation pathway. At the end of the catalytic cycle, subsequent reductive elimination afforded the desired products.



Scheme 2 Decarboxylative cross-coupling of simple arenes by Loh and co-workers[10]

The highly selective arylation of mono- and disubstituted arenes with arylboronic acids was developed by Ye and co-workers in 2017 (Scheme 3).[11] Key to the success of this reaction was the observation that amide ligands influenced both the reactivity and selectivity of the reaction in the presence of $Pd(OAc)_2$ with *N*-fluorobenzenesulfonimide (NFSI) as the oxidant. Several amide ligands were screened, but DMF proved optimal. Replacing the formyl group in DMF by alkyls, ᵗbutoxy and alkylaminos reduced the reactivity and selectivity significantly. Other N-substituents on the amide were tolerated (except for phenyl substitution which gave a low yield) but did not improve the reaction. The presence of an in situ generated cationic Pd-catalyst $[Pd(SbF_6)_2$ from $PdCl_2/AgSbF_6]$ increased the yield of the reaction significantly. The experimental conditions tolerated various arylboronic acids with electron-donating and electron-withdrawing groups, resulting in extremely high *para* selectivities. Arylboronic acids with electron-donating substituents at the *para*-position gave comparatively lower yields, but still maintained the selectivity with the exception of a methoxy group, which furnished lower selectivity. In some cases, the presence of *ortho* substituents on the arylboronic acids affected the reactivity and selectivity of the process detrimentally. DMF retained its role as the ligand and the high *para* selectivity remained unaffected, even in the presence of coordinating groups such as nitro, nitrile and aldehyde. A variety of mono- and disubstituted arenes were found to be compatible with the reaction conditions, giving products in moderate to high yields with high *para* selectivity. The major drawback of the methodology is the requirement for the arene and amide ligand to be present in large excess.



Scheme 3 Oxidative direct arylation developed by Ye and co-workers[11]

In the same year, Hong and Kim reported a diimine ligand for the coupling of arenes with aryl bromides with a high turnover number (TON ≤290). The reaction was catalysed by Pd-diimine in the presence of K_2CO_3 and PivOH in benzene/DMA solution (0.1 M) (Scheme 4).[12] The substrate scope was demonstrated by engaging aryl bromides with both electron-donating and electron-withdrawing substituents, which afforded the products in good yields. The only exception found was with electron-withdrawing groups at the *para*-position that gave products in low yields. Among the simple arenes only nitrobenzene, fluorobenzene and benzonitrile were tested. Remarkably, moderate yields were obtained using only 2 to 3 equivalents of the arene. Fluorobenzene displayed an excellent selectivity affording mainly the *ortho* product. A kinetic isotope effect (KIE) value of 5.68 indicated the aryl C–H bond cleavage as the rate-determining step (RDS). The rate studies showed first-order dependence on Pd and zero-order dependence on ArBr. A series of kinetic experiments and NMR studies revealed a bimetallic pathway involving two different Pd species. However, the transmetalation between the two metal complexes is not fully understood.

As a general trend, highly electron-rich or electron-poor arenes are easily functionalised via non-directed C–H bond activation. Simple arenes lacking these functionalities are used in excess as seen in the above examples. To overcome these challenges, in 2013, Larrosa and co-workers demonstrated the use of $Cr(CO)_3$ π-complexes of fluoroarene substrates that greatly enhanced the reactivity under the concerted metalation–deprotonation (CMD)-type arylation conditions (Scheme 5).[13] The π-complexes of fluoroarenes bearing silyl, ester or long alkyl chain groups at *ortho*-positions gave excellent yields of arylated products. Fluoro-

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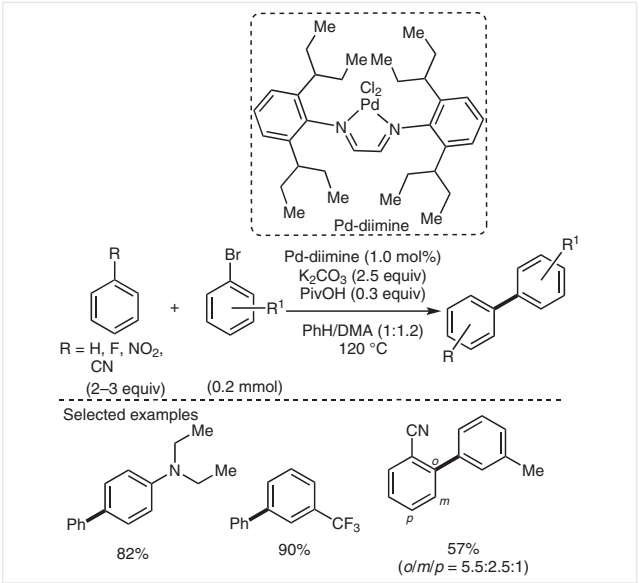
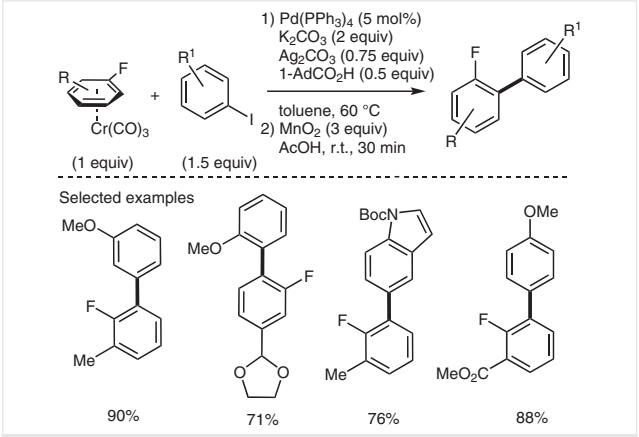


Scheme 4 Pd-diimine-catalysed arylation reported by Hong and Kim[12]

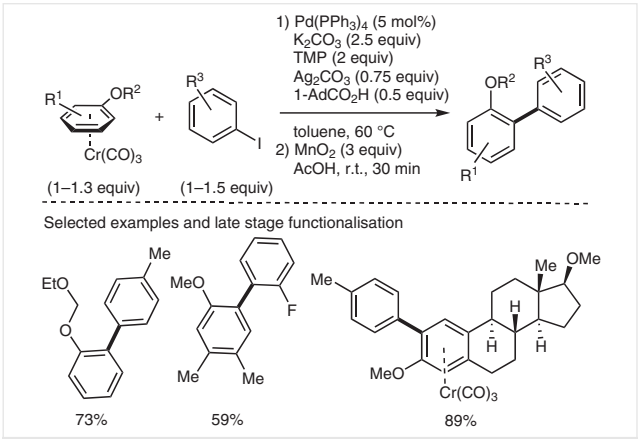
arenes with electron-donating substituents also gave good yields of arylated products. The strategy was applicable to various aryl iodides with chloro and bromo substituents. Easily oxidizable functional groups were also tolerated except alcohols, which needed protection. Computational studies indicated the role of the $Cr(CO)_3$ fragment in facilitating out-of-plane bending of the C–H bond towards the CMD transition state.



Scheme 5 Intermolecular arylation of fluoroarene-chromium tricarbonyl complexes developed by Larrosa and co-workers[13]

The method was developed further by the same research group in which π-complexed monofluoroarenes were subjected to direct arylation with either oxygen-, nitrogen- or ester-containing aryl iodides, and subsequently cyclised into oxygen- or nitrogen-containing heterocyclic and carbocyclic compounds.[14]

In 2014, the same research group expanded the scope of their π-complexation strategy from fluoroarenes to anisole and its derivatives to promote the *ortho*-arylation (CMD pathway) in place of the commonly occurring *para*-arylation (S_EAr pathway) (Scheme 6).[15] Surprisingly, various substituents on the oxygen of the anisole did not affect the reaction. The presence of strong electron-donating and electron-withdrawing groups at *para* and *meta*-positions were tolerated, while the regioselectivity was still controlled by the methoxy group. Late stage diversification of estradiol derivatives was attempted using this strategy, which afforded arylated products in excellent yields.



Scheme 6 Intermolecular arylation of anisole-chromium tricarbonyl complexes developed by Larrosa and co-workers[15]

The above discussed strategy was focused on promoting the arylation of arenes by π-complexation with $Cr(CO)_3$. Likewise, an atom-economical approach can be performed by the introduction of substituents on monofluorobenzene to enhance its reactivity considerably. In 2014, Doucet and co-workers studied the effect of electron-withdrawing and electron-donating substituents at the C-3 position of fluorobenzenes for their C-2–H arylation using 2–4 mol% of $PdCl(C_3H_5)$(dppb) in PivOK/DMA at 150 °C (Scheme 7, a).[16] In the presence of electron-withdrawing substituents on fluorobenzene, the direct arylation proceeded smoothly with regioselectivity towards the C-2 or the *ortho*-position with respect to the fluorine atom. But in the case of 3,5-difluorochlorobenzene, due to the *ortho*-directing effect of the fluorine atom, the reaction resulted in the formation of a mixture of C-2 and C-4 arylation products in an 85:15 ratio. On the other hand, the presence of electron-donating groups at the C-3 position lowered the yields and afforded mixtures of arylated products.

In the following year, the influence of electron-withdrawing and electron-donating groups at the C-4 position of fluorobenzene was investigated by using 1 mol% of phosphine-free $PdCl_2$ and 2 equivalents of PivOK in DMA (Scheme 7, b).[17] The outcome of the reaction was strongly dependent on the nature of the substituents attached to the

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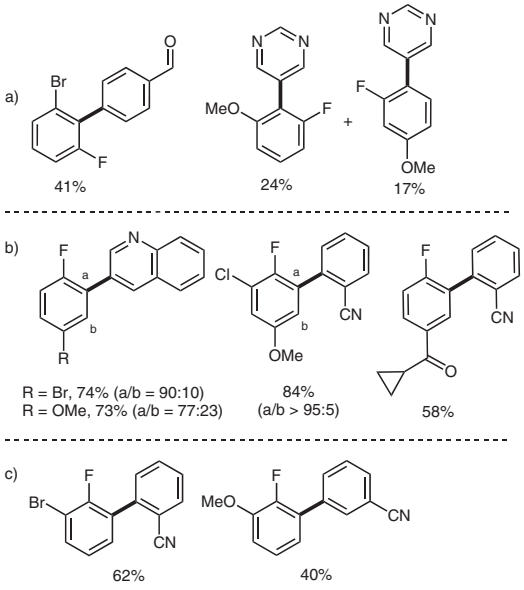
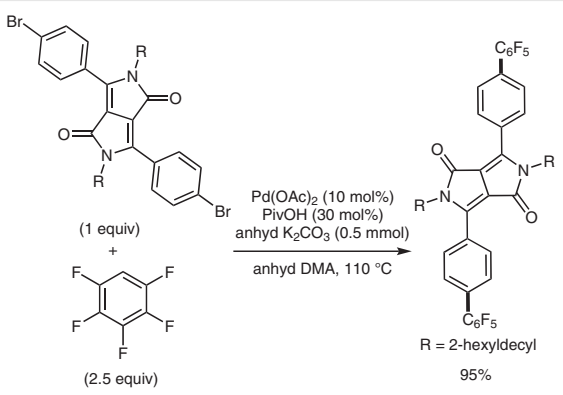
fluorobenzene. While moderate to good yields were obtained with 4-Br-, 4-Cl-, 4-F_3C- and 4-MeO-fluorobenzenes, fluoroarenes with 4-H_2N or 4-Me substituents were unreactive. In general, the reaction proceeded efficiently with regioselective arylation at the α-position to the fluorine atom. Aryl bromides with a wide variety of substituents like formyl, nitro, nitrile and cyano were also well tolerated. As a continuation of this work, in 2017, the same research group explored the effect of the *ortho*-substituent on the reactivity of fluorobenzenes using 2 mol% of $PdCl(C_3H_5)(dppb)$ and 2 equivalents of KOAc in DMA (Scheme 7, c).[18] The presence of bromo, chloro and methoxy groups at the *ortho*-position of the fluorobenzene increased the reactivity at the C-3 position, while nitro, nitrile, formyl, acetyl and amino groups inhibited the arylation reaction. On the other coupling partner, the presence of electron-withdrawing groups at *para*-position on the aryl bromide resulted in formation of the desired products, unlike in the cases with electron-donating groups.



Scheme 7 Effect of substituents on the arylation of fluoroarenes as reported by Doucet and co-workers[16–18]

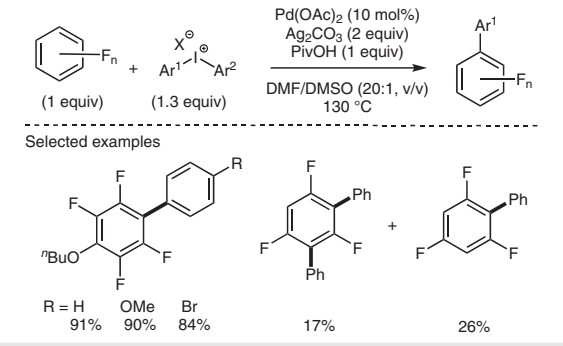
2.1.2 Direct Arylation of Electron-Deficient Polyfluoroarenes

Polyfluorobiaryl derivatives are an important structural moiety in pharmaceutical products, optoelectronic materials and pigments.[19] Therefore, the development of strategies to introduce polyfluoroarenes onto the core structure is of major interest. In 2013, Chen and co-workers developed the ligandless arylation of diketopyrrolopyrrole (DPP) derivatives with pentafluorobenzene using $Pd(OAc)_2$ (Scheme 8).[20] The presence of PivOH accelerated the reaction through a CMD pathway.



Scheme 8 Intermolecular arylation of DPPs reported by Chen and co-workers[20]

Diaryliodonium salts are found to be equally competent as aryl halides in direct arylation reactions due to their enhanced reactivity and access to higher oxidation states of palladium. Direct arylation of electron-poor polyfluoroarenes using diaryliodonium salts was reported by Wang and co-workers in 2013 (Scheme 9).[21] Most substituents, irrespective of their electronic nature, were found to be compatible with the reaction conditions. However, steric factors affected the reactivity significantly. Other polyfluoroarenes were also tested in this arylation reaction. Substrates with two or three fluorines gave the arylated products in moderate to low yields due to the lower acidities of their C–H bonds. Polyfluorobenzenes that have more than one C–H bond gave mixtures of mono- and diarylated products.



Scheme 9 Intermolecular arylation of polyfluoroarenes with iodonium salts developed by Wang and co-workers[21]

Similarly, sodium arylsulfinates have also been used as arylating reagents.[22] The stable sulfinic salts are among the most promising reagents because they are easy to handle and are accessible from sulfonyl chlorides. In 2014, Wang and Miao developed a $PdCl_2$-based desulfitative strategy for the direct arylation of polyfluoroarenes (Scheme 10).[23] The methodology was well suited to a wide range of arylsulfinates bearing electron-donating groups. It was also tolerant

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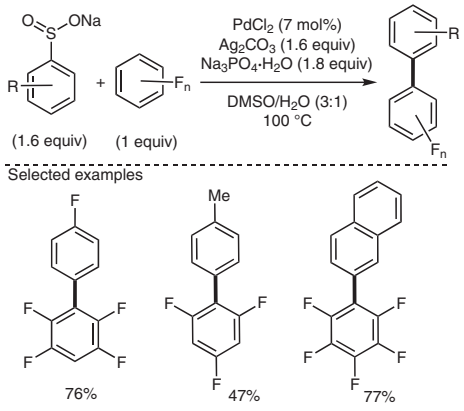
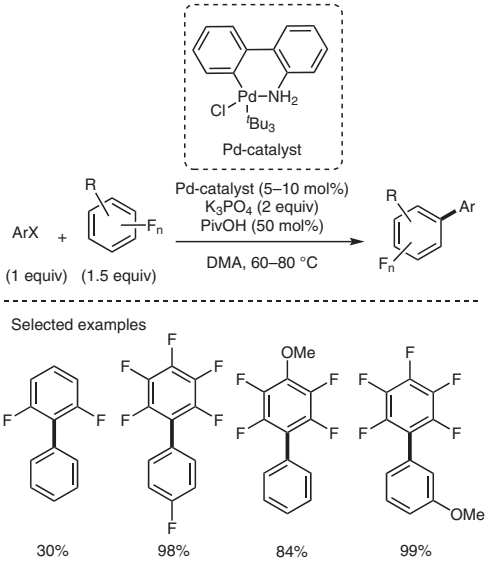
towards electron-withdrawing groups like halo and nitro. However, *ortho*-substituted arylsulfinates were unreactive, even under the optimised reaction conditions.



Scheme 10 Intermolecular arylation of polyfluoroarenes with sodium arylsulfinates developed by Wang and Miao[23]

In 2014, Hu and co-workers reported the C–H arylation of polyfluoroarenes in the absence of silver salts using aryl iodides as well as the less reactive aryl bromides and chlorides (Scheme 11).[24] The catalytic system consists of $^tBu_3P$-coordinated 2-phenylaniline-based palladacycle complexes as precatalysts for the reaction. Fluoroarenes containing three or more fluoro groups were suitable substrates in this transformation. Among the *ortho*-, *meta*- and *para*-substituted phenyl bromides investigated, *ortho*-substituted phenyl bromides were less reactive and needed slightly higher temperatures.

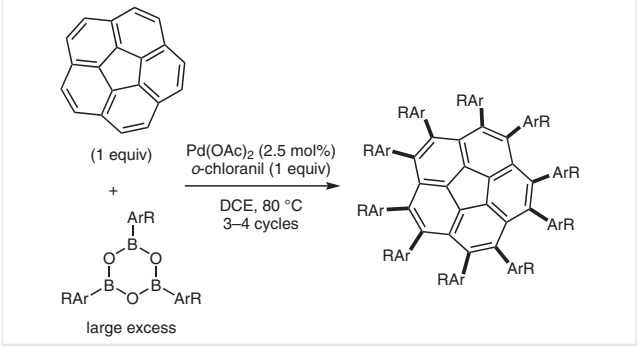


Scheme 11 Intermolecular arylation of polyfluoroarenes developed by Hu and co-workers[24]

2.1.3 Direct Arylation of Polycyclic Aromatic Hydrocarbons (PAHs)

The direct C–H functionalisation of PAHs is a significant area that has to be explored to develop methods for the synthesis of π-extended PAHs, larger graphene structures and other highly functionalised PAHs.[25] The development of catalytic systems for these substrates can be more challenging due to differential reactivity of existing K-, L- and bay regions together with steric bulkiness resulting from the large structure. The control of regioselectivity with only electronic and steric bias amidst numerous C–H bonds in PAHs can be more complicated when compared to simple arenes. The C–H activation in such complicated systems can thus reveal opportunities for distinctly controlled reactivity and selectivity. In this regard, some catalytic methods for the direct arylation of PAHs have been reported.[26]

Major contributions to C–H arylation of PAHs have been reported by Itami and co-workers, with the development of a $Pd(OAc)_2$/*o*-chloranil catalyst system, which can functionalise the outer π-bonds regioselectively.[27] In 2012, Itami, Scott and co-workers expanded the scope of the catalyst to perarylation of corannulene to synthesise decaphenylcorannulene after four rounds of phenylations (Scheme 12).[28] To relieve congestion from the fully arylated corannulene, the central core adopts a nearly planar geometry. A year later, the same research group arylated perylene with phenylboroxin using the same catalyst, giving a mixture of 3-phenylperylene (17%), di- (24%), tri- (11%) and tetraphenylperylene (0.7%).[29] The photophysical properties of 3,4,9-triphenylperylene and 3,4,9,10-tetraphenylperylene were compared with their parent compounds, in which both products showed a red shift in the absorption and fluorescence spectra.



Scheme 12 Intermolecular arylation of corannulene reported by Itami, Scott and co-workers[28]

In 2015, the double C–H activation involving a one-shot annulative π-extension (APEX) reaction on phenanthrene derivatives, catalysed by 5 mol% of a $Pd(CH_3CN)_4(SbF_6)_2$ precatalyst and 4–10 equivalents of *o*-chloranil was reported (Scheme 13).[30] The catalyst maintained its K-region selectivity even in multiple APEX reactions starting from one

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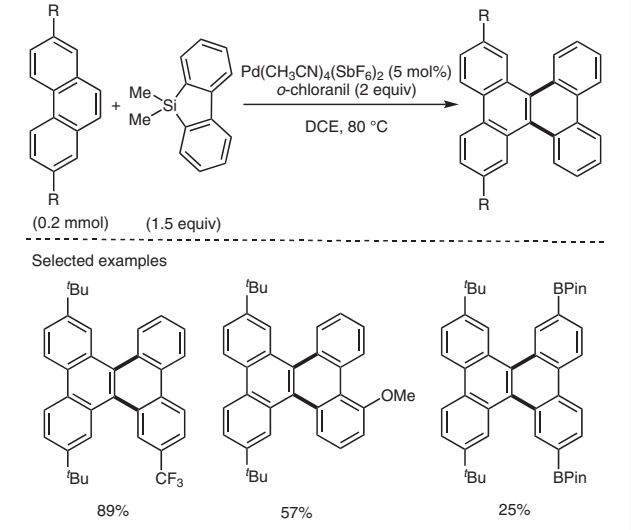
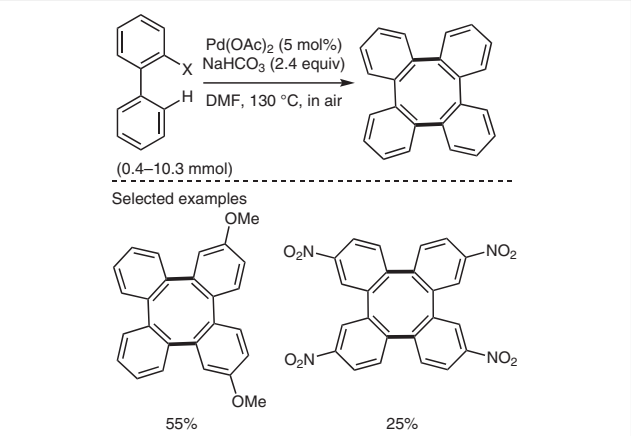
phenanthrene derivative. Following the perfect K-region selectivity in Pd-catalysed direct arylation reactions, the role of *o*-chloranil was investigated by computational studies in 2018.[31] DFT calculations for the direct arylation of phenanthrene with trimethylphenylsilane indicated that the reaction is most likely initiated by *o*-chloranil-assisted transmetalation of Pd(II) with Ar–TMS via S_EAr, followed by carbometalation of the Pd-complex by π-coordination to the K-region. The coordination of *o*-chloranil was observed to stabilise each complex. Thus, *o*-chloranil functions as a ligand, an oxidant and a base.

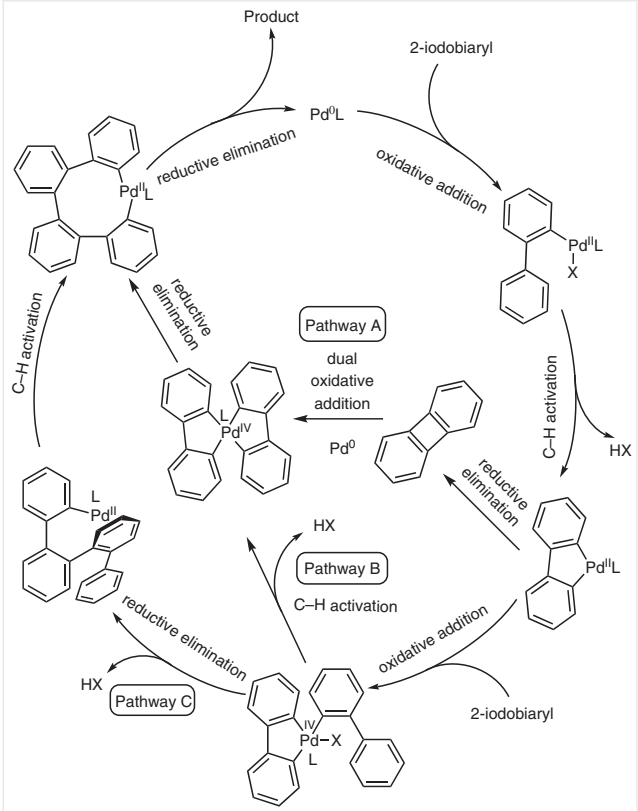
Flexible π-conjugated molecules like tetraphenylene, with special optical and physical properties for materials science, can be accessed through intermolecular dual direct C–H arylation of 2-iodobiaryls, as reported by Shi and co-workers in 2016 (Scheme 14).[32] By this method, 2-iodo-4,4′-dimethyl-1,1′-biphenyl and 2-iodo-3′,5-dimethyl-1,1′-biphenyl reacted efficiently and afforded the corresponding homo-coupled products in good yields. Interestingly, both substrates formed the same homo-coupled product, indicating that C–H activation takes place at the sterically less hindered positions. Tetraphenylenes with bulky alkyl substituents that possess special optical and electrochemical properties, and multi-methoxy-substituted tetraphenylenes with potent applications in host–guest chemistry and molecular devices were successfully prepared using this method. Electron-deficient substrates with nitro substituents were also compatible but showed lower reactivity. *o*-Iodobiaryls with differently substituted rings afforded regioisomeric product mixtures (ca. 1:1 ratios). Cross-coupling of two different *o*-iodobiaryls generated the cross-coupled compound as the main product along with minor fractions of homo-coupled compounds. The reported mechanism begins with oxidative addition of C–I to Pd(0), followed by C–H activation on the second aryl ring which might enter any of the three possible pathways (Scheme 15). Based on the unsuccessful attempts at dimerisation of the biphenylene product and cyclisation of 2-iodo-



Scheme 13 APEX reactions of PAHs reported by Itami and co-workers[30]



Scheme 14 Dual C–H arylation of *o*-iodobiaryls reported by Shi and co-workers[32]



Scheme 15 Proposed mechanism for the dual C–H arylation of *o*-iodobiaryls reported by Shi and co-workers[32]

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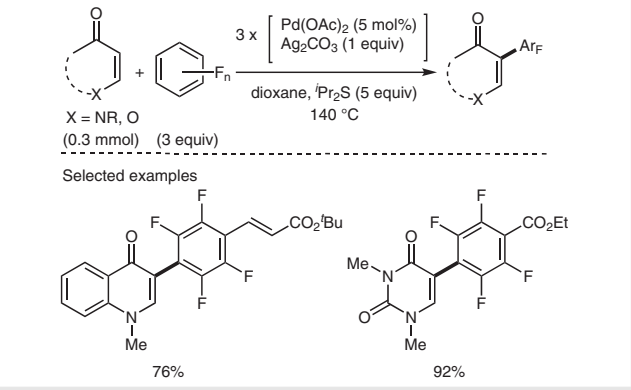
1,1′:2′,1″:2″,1‴-quaterphenyl, pathways A and C were ruled out. Hence, pathway B was proposed to be the most favourable pathway for this transformation.

2.1.4 Cross Dehydrogenative Coupling (CDC)

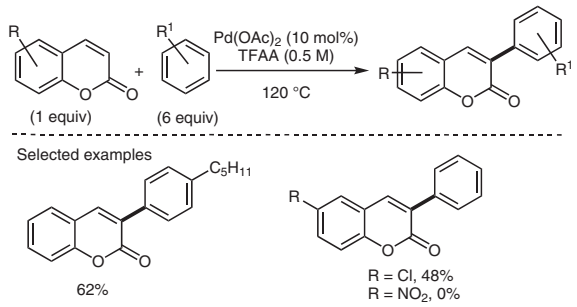
In the past few years, impressive progress has been made on the CDC approach,[33] which avoids the additional prefunctionalisation of both reactants. Not limited to the synthesis of biaryls,[34] the method was employed to arylate various heterocyclic compounds. In CDC coupling with heteroarenes, the selectivity of the C–H bond in the heteroaromatic partner is uncomplicated due to the variable distribution of electron density.

In 2012, Zhang and co-workers developed a CDC strategy for the synthesis of α-fluoroarylated enones via two-fold C–H bond functionalisation (Scheme 16).[35] The reaction tolerated a wide range of substituents on the polyfluoroarenes, such as ester, nitro, nitriles, α,β-unsaturated esters, etc. The heteroaromatic substrates also displayed an expanded scope including quinolones, chromones and pyrimidine. The reaction efficiency was improved by three consecutive additions of $Pd(OAc)_2$ and the oxidant over a period of 5 hours. KIE experiments conducted on both substrates gave values of 1.13 for C_6HF_5 and 1.66 for 1-methyl-4(*1H*)-quinolone, inferring that C–H bond cleavage is not the RDS. Based on the results from individual homocoupling reactions of fluoroarene and 4-quinolone, the catalytic cycle was believed to begin with the formation of palladated complexes of the fluoroarene and enone, which then reacted with the free reactants and underwent a subsequent reductive elimination to form the products.



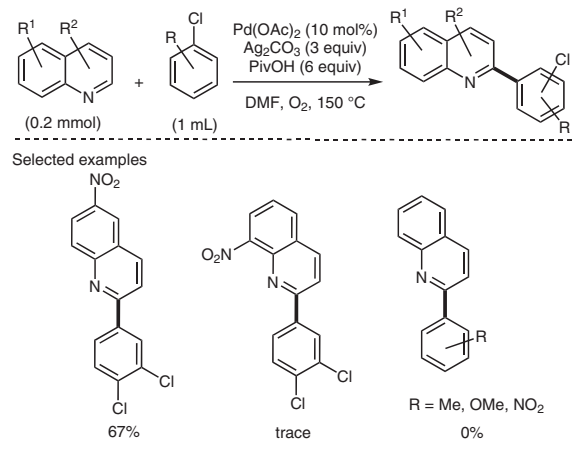
Scheme 16 Intermolecular polyfluoroarylation of enones developed by Zhang and co-workers[35]

In 2013, Shafiee and co-workers developed the dehydrogenative arylation of the O-based heterocycle coumarin, affording 3-arylcoumarins (Scheme 17).[36] The coumarins were arylated selectively at the C-3 position due to its nucleophilic character. Though electron-rich arenes were more efficient, both electron-donating and electron-withdrawing groups on the arenes and coumarins were tolerated. However, a nitro-substituted coumarin was not a feasible substrate. The plausible mechanism from the experimental results involves formation of $Pd(TFA)_2$ in situ and the subsequent electrophilic palladation of coumarin with $Pd(TFA)^+$, followed by coordination with the arene, C–H palladation and reductive elimination to give the 3-arylcoumarins.



Scheme 17 Dehydrogenative arylation of coumarins reported by Shafiee and co-workers[36]

In the context of N-based heterocycles, in 2013, Huang and co-workers presented an efficient method for the C-2 arylation of quinolones, useful for the preparation of alkaloid molecules (Scheme 18).[37] The catalytic cycle was believed to begin with Pd coordinating to nitrogen and then migrating to C-2 by metalation–deprotonation. The results were consistent with a mechanism that probably involves electrophilic palladation of the arene. Quinolines with electron-withdrawing groups reacted smoothly compared to those with an electron-donating methyl or methoxy group. However, substitution at the C-8 position was incompatible with this protocol. Non-chlorinated aryl substrates were rendered unsuitable for the reaction. The selectivity was more affected by the electronic character of the substituents than the steric factors.



Scheme 18 Intermolecular arylation of quinolines developed by Huang and co-workers[37]

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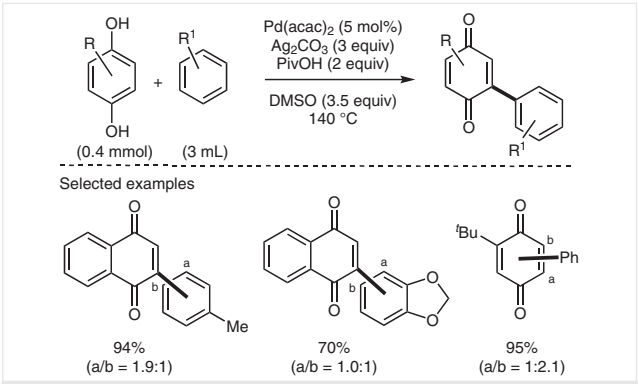
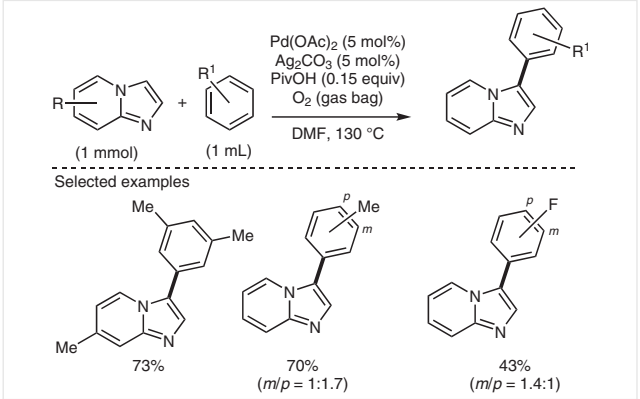
In 2013, You and co-workers reported an oxidative 'one-pot' C–H cross-coupling strategy for the synthesis of arylquinones starting from hydroquinones (Scheme 19).[38] The $Pd(acac)_2$-catalysed method was suitable for both electron-rich and electron-poor arenes. However, the latter required 10 mol% of the Pd catalyst. The scope of the hydroquinones was studied and expanded to benzannulated-, alkyl-, aryl- and methoxy-substituted examples. Based on the obtained KIE value of 2.3, the suspected mechanism was reported as a S_EAr palladation of the arene, which may then form a complex with quinone by two possible pathways: either by a Heck-type arylpalladation followed by β-H elimination, or by C–H cleavage of quinone via a carboxylate-assisted CMD pathway. At the end of the catalytic cycle reductive elimination generates the desired cross-coupled product, followed by re-oxidation of the Pd species.



Scheme 19 Intermolecular arylation of quinones reported by You and co-workers[38]

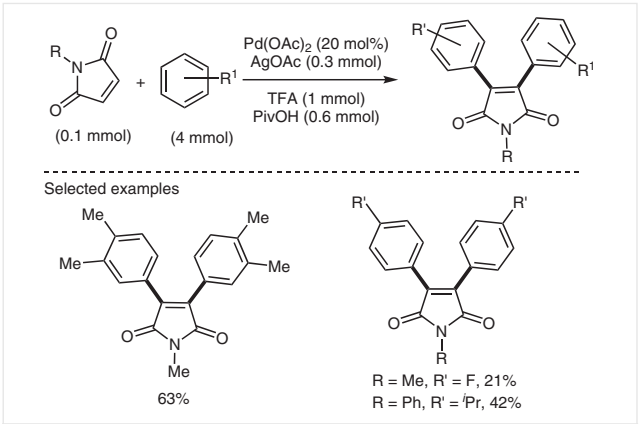
In the following year, Zhan and co-workers discovered a direct $Pd(OAc)_2$-catalysed oxidative cross-coupling of unactivated imidazo[1,2-*a*]pyridines with simple arenes via two-fold C–H bond functionalisation (Scheme 20).[39] The reaction was tolerant towards functional groups on the substrates. The C-3 position on the imidazo[1,2-*a*]pyridine ring was preferred over the C-2 position in the cross-coupling. The regioselectivity of the aryl ring was dominated by steric effects, with preference for the sterically less hindered *meta*- and *para*-positions. The catalytic cycle was expected to follow the usual mechanism of electrophilic palladation of the imidazo[1,2-*a*]pyridine, followed by C–H activation of the arene by a CMD process and reductive elimination of the cross-coupled product.

In 2016, Shamsianpour and Jafarpour described the diarylation of an olefinic bond for the synthesis of highly substituted maleimides, which represent a group of organic photochromic compounds (Scheme 21).[40] The method required AgOAc as the oxidant and followed a Pd(II)/Pd(0) catalytic cycle. The catalytic system gave good yields of diarylated products with both electron-rich and electron-poor



Scheme 20 Intermolecular arylation of imidazo[1,2-*a*]pyridines developed by Zhan and co-workers.[39]

arenes. However, a bromine substituent was an exception as the C–Br bond in bromobenzene reacted instead of the C–H bond to afford 3,4-diphenylmaleimide. No product formation was observed between *p*-nitrobenzene and *N*-methylmaleimide.



Scheme 21 Dehydrogenative cross-coupling of arenes and maleimides reported by Shamsianpour and Jafarpour[40]

Alsters and Fernández-Ibáñez recently developed an aerobic CDC coupling of *o*-xylene (Scheme 22) for the synthesis of an industrially useful monomer, 4,4′-biphthalic anhydride, under industrially relevant conditions.[41,42] The catalytic system omitted the Cu co-catalyst that was used in previous procedures,[43] and more importantly, proceeded under neat conditions. Increasing the temperature and O_2 pressure had significant effects on the yield and selectivity. Further the effect of 1:1 and 1:2 molar ratios of Pd and ligand was examined; a 1:1 ratio of Pd/ligand was found to be preferable. The preferred ligand, 2-(difluoromethyl)pyridine, is devoid of both too much steric hindrance near the N-atom and strong electron-withdrawing substituents. Evaluation of the deuterium kinetic isotope effect (KIE) provided evidence for three different rate-determining steps,

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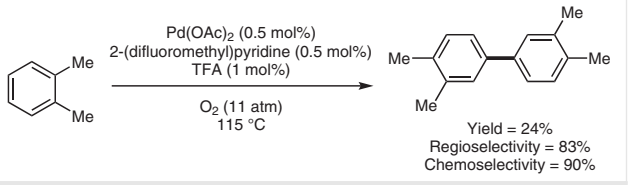
depending in particular on the reaction conditions (medium and temperature). Under the reported neat conditions, the dissociation of a carboxylate-bridged dimer to generate a more reactive monometallic Pd species was proposed to be the RDS.

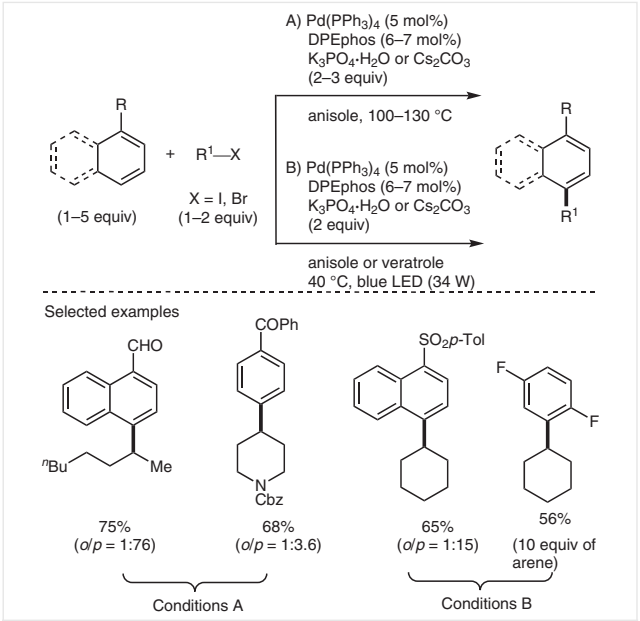


Scheme 22 Aerobic CDC of *o*-xylene reported by Alsters and Fernández-Ibáñez[41]

2.2 C–H Alkylation

Friedel–Crafts alkylation is a classical approach giving access to alkylated arenes. However, the reaction is limited to electron-neutral and electron-rich arenes, and also leads to the formation of by-products. In recent years, directed *ortho*-alkylation of arenes has made great progress. To access the remote sites, directed *meta*-alkylation of arenes through employing radical alkylation[44] and Pd/norbornene[45] approaches have also been reported.

Very recently, Zhou and co-workers reported the first examples of the alkylation of electron-deficient arenes using Pd catalysis (Scheme 23).[46] The choice of $K_3PO_4·H_2O$ as base and anisole as solvent was important to minimise the side reactions resulting in alkenes and over-alkylation side-products. Various C-1-substituted benzenes and naphthalenes with aldehyde, ketone, ester, nitrile and imide groups were alkylated at the *para* C-4 position preferentially with respect to the electron-withdrawing groups on the substrates. Naphthalenes with an electron-withdrawing group at the C-2 position were alkylated mainly at C-1. In general, naphthyl substrates were more reactive than doubly activated benzenes, followed by benzaldehydes. Both cyclic and acyclic alkyl iodides and bromides were found to be suitable as alkylating agents. However, simple linear alkyl halides did not afford the desired products due to HI elimination reactions. Steric effects also influenced the *para*-alkylation. This research group has also explored the alkylation of naphthyl and benzyl substrates, bearing single electron-withdrawing substituents, under blue LED irradiation. A tentative catalytic cycle was proposed based on DFT studies and experimental observations made from model reactions using TEMPO and *cis*/*trans* isomers of aryl iodides. It involves alkyl radical addition to the arene as the key step followed by deprotonation of the adduct to generate a radical anion. Further mechanistic studies are required to differentiate the Pd oxidation states involved in the catalytic cycle.



Scheme 23 *para*-Alkylation of electron-deficient arenes reported by Zhou and co-workers[46]

2.3 C–H Alkenylation

2.3.1 Direct Alkenylation of Simple Arenes

The palladium-catalysed C–H olefination reaction is an attractive alternative to the well-known Mizoroki–Heck reaction since prefunctionalisation of the starting material is not required. However, the vast majority of C–H olefination reactions are limited to substrates with DGs.[47] In the last few years, several contributions have been made on the direct C–H olefination, also called the Fujiwara–Moritani reaction, of simple arenes. The low reactivity of electron-poor arenes, the requirement of a large excess of the arene and poor site selectivity are the main challenges that need to be overcome for the widespread implementation of this strategy in organic chemistry labs.

In an attempt to meet the demand for cost-effective and environment friendly approaches that generate less amounts of by-products, Bäckvall and co-workers, in 2013, demonstrated the use of electron-transfer mediators (ETMs) in C–C bond formation, by virtue of a biomimetic approach, which favours relatively low catalyst loading and O_2 at atmospheric pressure (Scheme 24).[48] The aerobic dehydrogenative coupling was successfully studied on various electron-deficient olefins like acrylates, acrylaldehydes and vinyl sulfones. Furthermore, the method was not confined to electron-rich arenes but was also demonstrated using electron-neutral and moderately electron-deficient arenes. A year later, Bäckvall extended the scope to allylic esters and reduced the amount of ETM needed for the reaction (Scheme 24).[49] The efficiency of the catalytic system was af-

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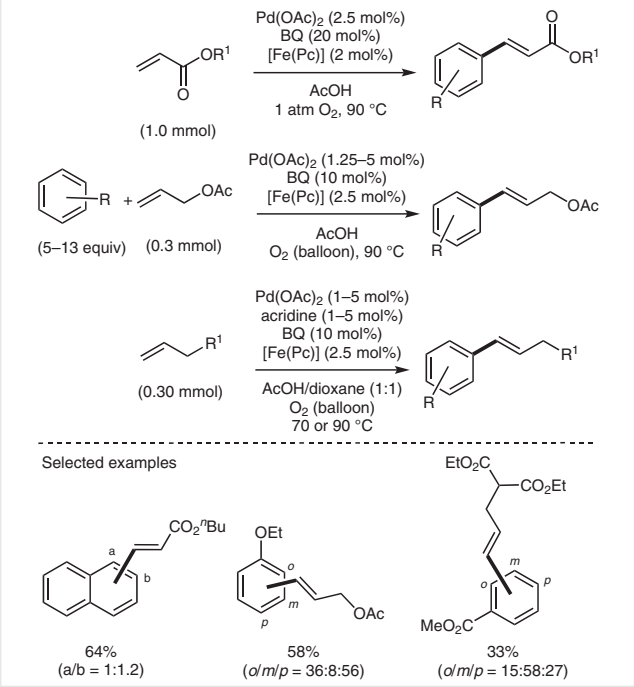
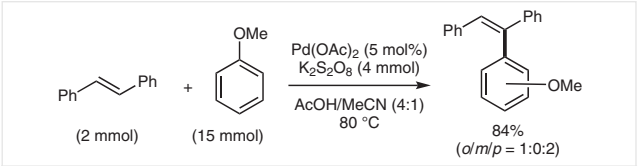
fected by the reactivity of activated and deactivated arenes to a considerable extent. In the same year, the proposed strategy was elaborated towards the arylation of unactivated alkenes, with incorporation of the nitrogen-based ligand acridine (Scheme 24).[50] The site selectivity was guided by the electronic factors of the aryl substrate with preference for the electron-rich position. In 2015, Bäckvall expanded the scope to the one-pot synthesis of tetrasubstituted olefins by increasing the amount of Pd/ligand to 5–7.5 mol%.[51] The reactivity and selectivity were controlled by steric factors around the unsaturated core and complete chemoselectivity around the double bond was achieved. For all these transformations, arenes are required in excess and mixtures of regioisomers are obtained.



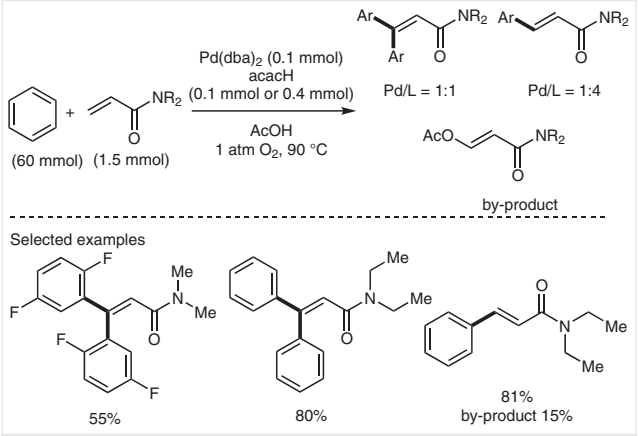
Scheme 24 The development of a biomimetic approach for the olefination of arenes by Bäckvall and co-workers[48–50]

The challenge in C–H olefination towards the synthesis of tri- and tetrasubstituted alkenes is to activate the electron-deficient arenes and less reactive 1,2-disubstituted alkenes. In 2013, O'Shea and co-workers reported the $Pd(OAc)_2/K_2S_2O_8$ catalytic system in an AcOH/MeCN solvent mixture providing an efficient route for the synthesis of trisubstituted alkenes from 1,2-disubstituted alkenes (Scheme 25).[52] The protocol was demonstrated with various activated/deactivated arenes and (*E*)-stilbene, (*E*)-chalcone and (*E*)-methyl cinnamate. Interestingly, for stilbenes with electron-donating substituents, a substituent match with the arene was crucial for the formation of coupled products. On the other hand, stilbenes with electron-withdrawing groups reacted effectively with both classes of arenes. The mechanistic aspects were investigated by MS analysis. The reported catalytic cycle had C–H activation of the arene as the first step, followed by insertion of the alkene and β-H elimination yielding the product. The palladium hydride species underwent reductive elimination to give Pd(0), which was reoxidised to Pd(II).



Scheme 25 Synthesis of trisubstituted alkenes developed by O'Shea and co-workers[52]

In 2013, Obora and co-workers reported a catalytic system for the synthesis of cinnamamides based on $Pd(dba)_2$/acacH/O_2 and AcOH (Scheme 26).[53] In this protocol, the molar ratio of Pd/acacH (L) determines the formation of monoarylated or diarylated product. Excess of the arene is required and a mixture of regioisomers is obtained under the optimised reaction conditions. The reaction was believed to follow the general catalytic cycle proposed by Fujiwara et al., beginning with electrophilic aromatic C–H activation, alkene coordination to the ArPdX intermediate, migratory insertion and product formation by β-H elimination.[54]



Scheme 26 Aerobic direct olefination of anilines and arenes developed by Obora and co-workers[53]

Further advancement in the area was brought by You and co-workers in 2014, who proposed a strategy to conduct the reaction at room temperature.[55] The strategy employs the in situ generated highly electrophilic catalyst $Pd(TFA)_2$ and $(NH_4)_2S_2O_8$ as the oxidant under air in the presence of excess arene (Scheme 27). The protocol was successfully shown to cross-couple (hetero)aryls with alkenes, coumarins or quinones, demonstrating a high *E*/*Z* selectivity. However, coupling of alkenes with electron-de-

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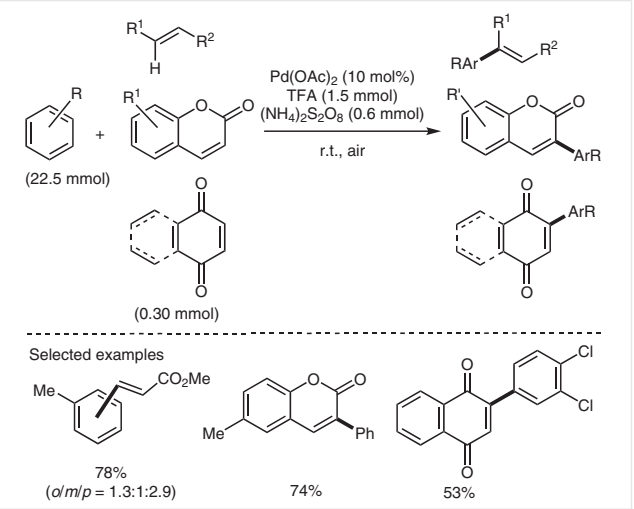
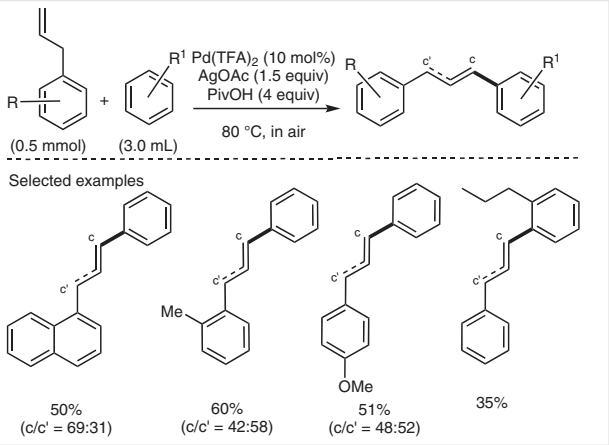
ficient arenes was not possible, but the latter was efficient in coupling with quinones. Remarkably, complete *para* selectivity was observed in the reaction with anisole.



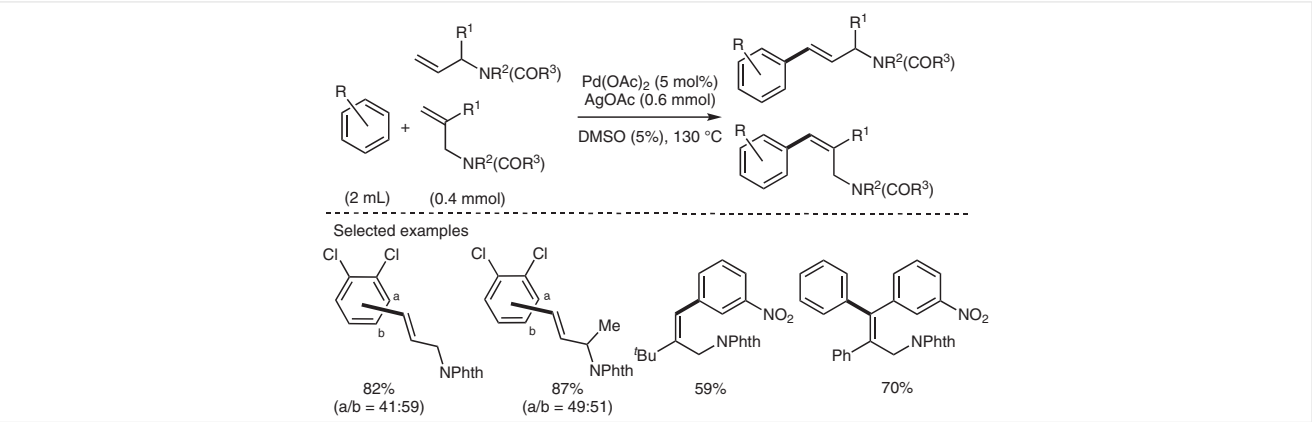
Scheme 27 Olefination of aryls at room temperature developed by You and co-workers[55]

Similarly, in 2014, Law and co-workers reported a catalytic system based on a highly electrophilic $Pd(TFA)_2$ catalyst for oxidative coupling of simple arenes with substituted allyl arenes using AgOAc as the oxidant and PivOH as the additive (Scheme 28).[56] Allyl arenes with electron-donating groups on the aromatic ring gave the desired products as mixtures of isomers in good yields. The substrate scope of simple arenes was demonstrated with alkyl, methoxy, fluoro and chloro substituents on the aromatic ring. In general, electron-deficient arenes were inefficient substrates for the reaction. Based on isotopic and intermolecular competition experiments, a plausible mechanism with in situ formation of $Pd(OPiv)_2$ was reported. The rate-determining aryl C–H activation follows a S_EAr pathway generating a σ-aryl-Pd intermediate. This then undergoes migratory insertion of the allyl arene to the Pd intermediate, which upon reductive elimination affords the vinyl arene and Pd hydride species.



Scheme 28 Allylation of simple arenes with allyl arenes reported by Law and co-workers[56]

Deng and co-workers contributed by developing a strategy in 2015 towards the arylation of allylamines where the electronic nature of the allylic substrate had significant effects on the regioselectivity and catalytic activity (Scheme 29).[57] The $Pd(OAc)_2$/AgOAc catalytic system with 5% DMSO as a co-solvent was efficacious with N-monoprotected, N,N-diprotected and β-substituted allylamines showing excellent regioselectivity and *E*/*Z* stereoselectivity towards terminal substitution. The trisubstituted olefins reacted further to give tetrasubstituted olefins in the presence of 10 mol% of Pd. However, very electron-rich allylamines were believed to cause catalyst poisoning due to strong coordination of the nitrogen to Pd, thereby inhibiting the reaction. Various electron-donating and electron-withdrawing substituents on the arenes were tolerated giving mixtures of regioisomeric products. As a common feature of this type of transformation, an excess of the arene was needed.



Scheme 29 Direct arylation of allylamines with simple arenes developed by Deng and co-workers[57]

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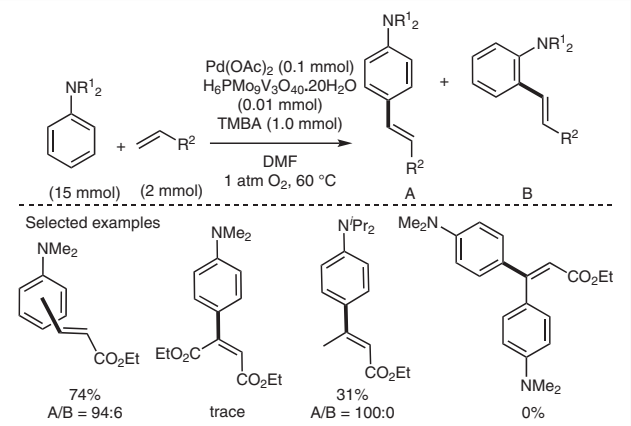
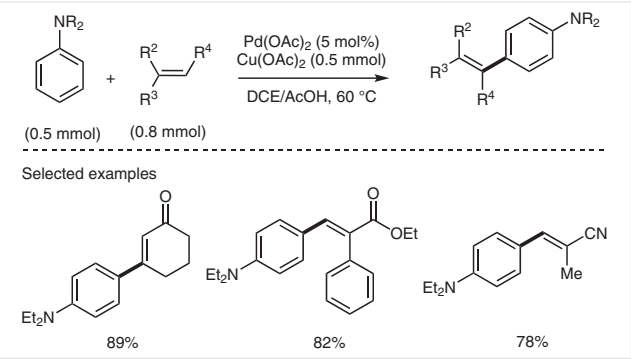
In 2012, Ishii and co-workers, reported a combination of Pd/HPMoV/O_2 in DMF (non-acidic solvent) with 2,4,6-trimethylbenzoic acid (TMBA) as an additive for the highly *para*-selective aerobic C–H olefination of aniline derivatives (Scheme 30).[58] The requirement for an excess amount of the aniline and a narrow substrate scope limited to unsubstituted anilines are the main limitations of this protocol. The authors highlighted that the use of TMBA as a co-solvent is essential to achieve high yields of (*E*)-*para*-alkenyl-substituted aminobenzenes.



Scheme 30 Aerobic direct olefination of anilines and arenes developed by Ishii and co-workers[58]

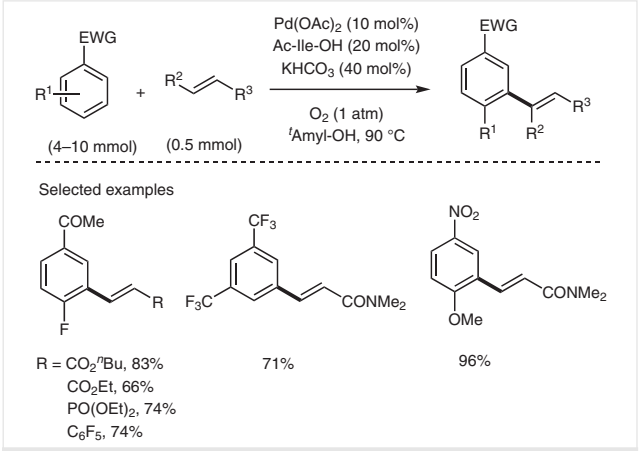
In 2017, Karimi and co-workers demonstrated the *para*-selective alkenylation of anilines under mild conditions using $Pd(OAc)_2$ and $Cu(OAc)_2$ (Scheme 31).[59] The presence of AcOH was crucial in maintaining the acidic conditions to diminish the strong binding of the nitrogen atom of aniline to the Pd(II) ion. Both terminal and internal alkenes were suitable for this transformation. Other olefinic substrates such as acrylic esters, cyclic alkenones, acrylonitrile, and styrene gave good yields of *para*-selective *trans* isomers. Regarding the scope of the arene, only *N*,*N*-dimethyl-, *N*,*N*-diethyl- and *N*,*N*-diisopropylaniline were subjected to the reaction.



Scheme 31 Non-chelation assisted *para*-olefination of anilines reported by Karimi and co-workers[59]

As seen from the above examples, there has been a lot of research to develop more efficient, robust, green and economical catalytic systems for alkenylation of various substituted aryl derivatives. However, an excess of the arene is needed in these examples, and mixtures of regioisomers are obtained. The substrate scope is generally limited to electron-neutral or electron-rich arenes. In the last couple of years, major efforts have been devoted towards overcoming these limitations by developing appropriate ligands. Some of these ligands will now be discussed below in the context of this review.

In 2013, Zeng and co-workers described the acceleration effect of mono-N-protected amino acids (MPAAs) on Pd-catalysed dehydrogenative Heck reactions (Scheme 32).[60] The authors conducted experimental and computational studies on non-chelate-assisted olefination of pyridines and elaborated the experiments to analogous electron-deficient arene substrates. The electron-deficient arenes were comparatively more reactive with the transformation occurring at lower temperatures. The catalytic activity of Pd(II) was highly altered by N-protecting groups and α-alkyl substituents on the MPAA ligands. Higher yields of olefinated products were obtained with MPAA ligands having a *N*-acetyl protecting group and a *sec*-butyl group (Ac-Ile-OH) at the α-position for electron-deficient substrates and an ^{i}Pr group (Ac-Val-OH) for the pyridine derivatives. The catalytic system gave *meta*-selective/C-3 selective alkenylated products. Various substituted alkenes were also employed affording the products in good yields. More challenging internal alkenes resulted in the formation of trisubstituted *E*-olefins. KIE experiments indicated a thermodynamically unfavourable C–H activation step involving a CMD mechanism and the possibility of the enhancement of the electrophilic character of palladium by the MPAA ligands, which thereby promote C–H bond cleavage. DFT studies revealed



Scheme 32 MPAA-promoted dehydrogenative Heck reactions reported by Zeng and co-workers[60]

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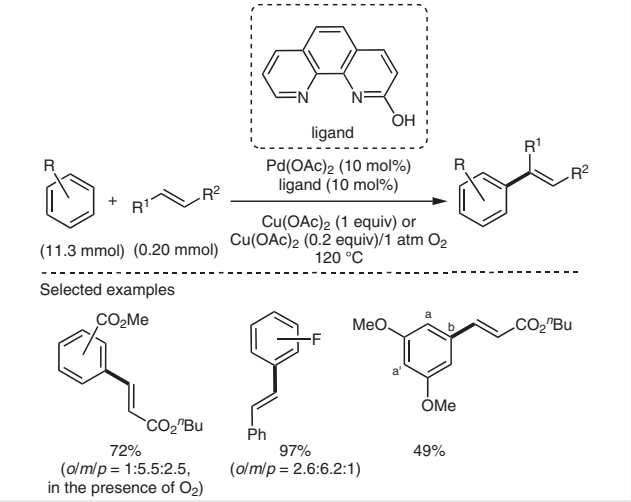
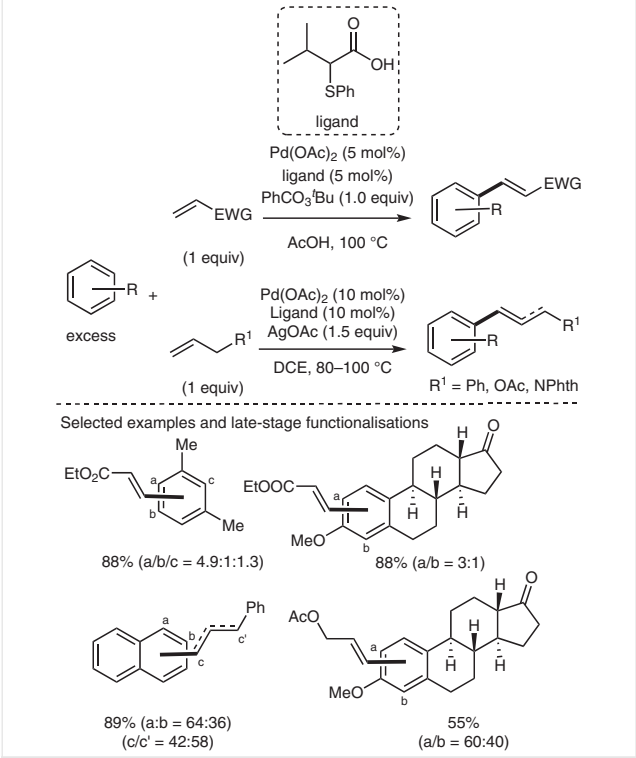
conversion of the amino group of the MPAA ligand to X-type and L-type during the catalytic cycle to facilitate the transformation.

In 2014, Duan and co-workers reported an acceleration effect on a Pd-catalysed oxidative Heck reaction using a bidentate 2-hydroxy-1,10-phenanthroline ligand. In the presence of the ligand, the reaction proceeds with substrates having various electron-withdrawing and electron-donating groups (Scheme 33).[61] Remarkably, arenes bearing a nitro, ester, or nitrile group were tolerated and afforded the corresponding products in good yields. However, the reaction gave a mixture of regioisomers. A clear preference towards C–H olefination at the *meta*-position was observed in all examples independent of the electronic nature of the arene. The alkene counterparts with β-substituents also reacted smoothly. Key to the success of this transformation is the use of the bidentate monoanionic nitrogen ligand. A KIE value of 2.5 ascertained the aryl C–H bond cleavage to be the rate-determining step. However, the role of the ligand and the mechanism involved in this transformation are unclear.



Scheme 33 The 2-hydroxy-1,10-phenanthroline-accelerated olefination developed by Duan and co-workers[61]

Recently, in 2017, a significant contribution in the field of C–H olefination of arenes was reported by Fernández-Ibáñez and co-workers using an unprecedented hemilabile bidentate thioether carboxylic acid ligand (Scheme 34).[62] The reaction proceeded efficiently with bulky arenes as well as with electron-rich and electron-deficient arenes in the presence of the bidentate S,O-ligand. The substrate scope of the alkenes was elaborated by using acrylates, cinnamates and various electrophilic alkenes. Although the reaction using the new catalytic system furnished a mixture of regioisomers, the presence of the S,O-ligand clearly affects the site selectivity of the process. It is worth mentioning that the C–H olefination takes place preferentially at the more electron-rich position of the arene regardless of steric hindrance, in contrast to the examples illustrated below (see Schemes 35 and 36).[63] In addition, the new catalytic system showed higher activity and had a greater influence on the site selectivity than the previous well-established Pd/pyridine-based catalytic systems.[64] Importantly, the reaction can be performed using 1 equivalent of the arene as proven in the late-stage olefination of estrone and naproxen derivatives. Further, the scope of the ligand was expanded to the C–H olefination of various substituted arenes with allylic substrates using slightly modified reaction conditions (Scheme 34).[65] Although the role of the ligand in this transformation remains unclear, it has been hypothesised that the S,O-ligand increases the stability of the catalyst and promotes C–H bond cleavage.



Scheme 34 S,O-Ligand-promoted olefination and allylation developed by Fernández-Ibáñez and co-workers[62,65]

Also in 2017, Yu and co-workers developed a new catalytic system based on the use of an electron-deficient 2-pyridone ligand that did not require an excess of the arene substrate (Scheme 35).[63a] Both electron-rich and electron-deficient aryl derivatives were olefinated at the electron-rich position of the ring with excellent to moderate yields. α,β-Unsaturated and 1,2-disubstituted α,β-unsaturated olefins with electron-withdrawing groups were all found to be amenable with the catalytic system. Although, the electronic and steric properties dominate the site selectivity of substituted arenes, the 2-pyridone ligand has a substantial in-

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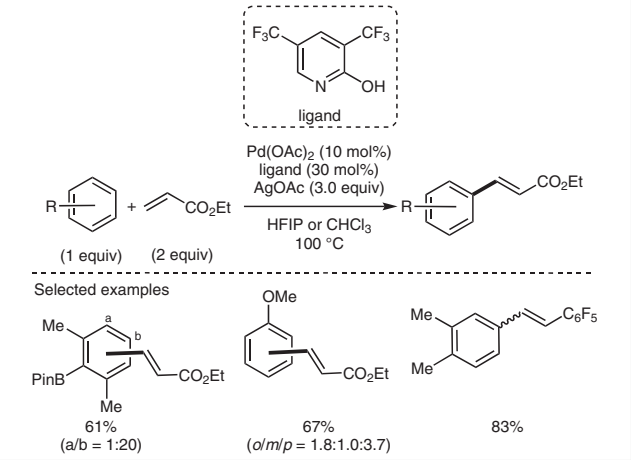
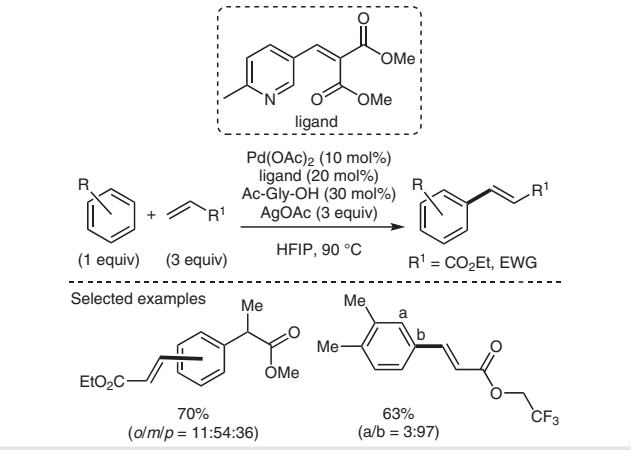
fluence on the site selectivity in a few classes of arene substrates. Mechanistic studies showed that the ligand has a dual role in this transformation, preventing catalyst decomposition as well as accelerating the reaction.



Scheme 35 Ligand-promoted olefination reported by Yu and co-workers[63a]

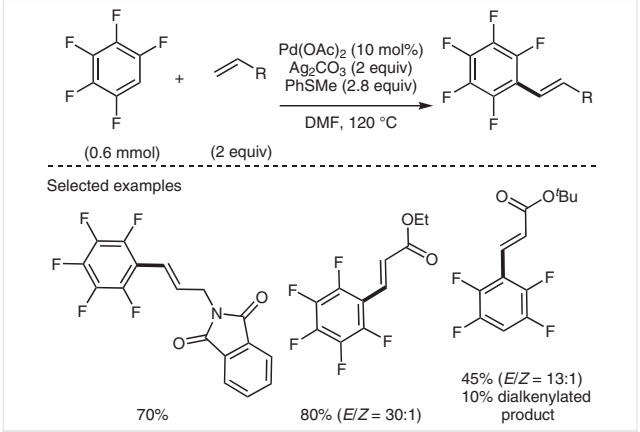
N-Acetyl amino acid[66] and pyridine-based ligands[61] have separately been described to accelerate the C–H olefination reaction. In 2018, van Gemmeren and co-workers found that a combination of an amino acid derived ligand and a pyridine ligand can efficiently promote the C–H olefination of non-directed arenes which are used as limiting reagents (Scheme 36).[63b] Control experiments indicated that the *N*-acetylglycine ligand was crucial for catalytic activity with a minor influence on the regiochemistry of the reaction, while the pyridine ligand was essential for efficient catalysis and has an influence on the regioselectivity. The dual-ligand catalytic system was compatible with arenes possessing electron-withdrawing and electron-donating substituents. Reactions with monosubstituted arenes afforded mixtures of isomers with mostly *meta* and *para* products, presumably due to the combined effect of steric and electronic control. Similarly, β-selectivity was preferred in reactions with di- and trisubstituted arenes. The protocol showed a broad applicability with acrylates, acroleins, acrylamides, phenyl vinyl sulfone and diethyl vinyl phosphonate.



Scheme 36 Dual-ligand-promoted olefination reported by van Gemmeren and co-workers[63b]

2.3.2 Direct Alkenylation of Electron-Deficient Polyfluoroarenes

Direct olefination[67] and allylation[68] of electron-deficient substrates like polyfluoroarenes are sparsely explored due to the 'inert' nature of the C–H bonds in these compounds. A previous observation by the Zhang group in 2010[67a] on the importance of DMSO for reaction efficiency[69] eventually led to the development of a thioether ligand that promoted olefination of polyfluoroarenes 2013 (Scheme 37).[70] For substrates having more than one reactive site, the catalytic system furnished products with considerable stereoselectivity and regioselectivity. Alkenes with electron-donating substituents resulted in higher yields. Both electron-rich and electron-deficient alkenes were successfully coupled with polyfluoroarenes.



Scheme 37 Thioether-promoted olefination reported by Zhang and co-workers[69]

Very recently, Breit and Zheng developed an efficient method for the allylation of polyfluoroarenes with alkynes as the source of the allylic electrophiles (Scheme 38).[71] The main challenge in developing such a procedure was the addition of a Brønsted acid to generate metal hydride species under basic reaction conditions. The metal hydride was responsible for a secondary catalytic cycle to isomerise the alkyne into an allene. It was thought that polyfluoroarenes might be deprotonated with a weak base, and the acid formed thereafter could generate the required Pd hydride species. Based on this prediction, results with excellent regioselectivity were obtained using $Pd(OAc)_2$/SPhos and

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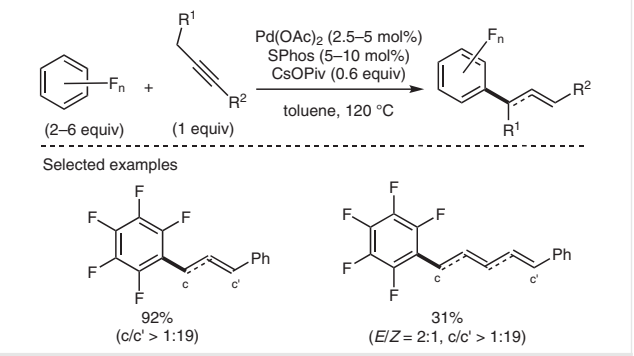
CsOPiv as the base in toluene. Pentafluoro- and tetrafluoroarenes were allylated efficiently under these reaction conditions. However, fluoroarene substrates bearing two or three competing sites required 3–6 equivalents of the arene to promote formation of the monoallylated product over the diallylated product. Aryl alkenes containing electron-donating and electron-withdrawing substituents were compatible with the reaction conditions affording excellent yields and regioselectivity, although the latter were comparatively less efficient. H/D-Exchange and other experiments provided some mechanistic insights. The reaction might begin with deprotonation of the fluoroarene generating a fluoroarene anion that reacts with the allene species formed during the reaction.



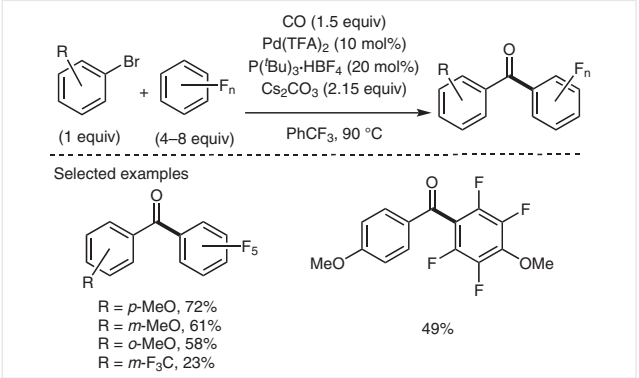
Scheme 38 Direct allylation of polyfluoroarenes with alkynes reported by Breit and Zheng[71]

2.4 C–H Carbonylation

The majority of the research studies conducted on the palladium-catalysed C–C bond formation with arenes constitute arylation and to some extent olefination, while reports on carbonylative couplings are scarce. Reactions that are dependent on initial C–H bond activation by a Pd(II) species are generally found to be incompatible with the reducing capabilities of CO.

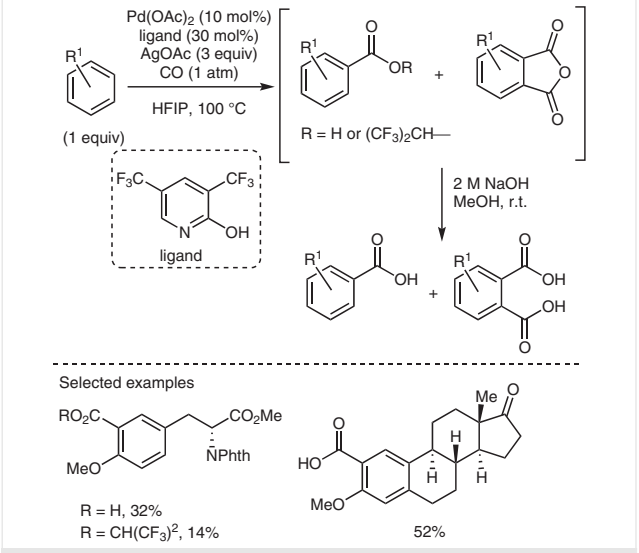
In 2015, Skrydstrup and co-workers reported the first Pd-catalysed intermolecular carbonylative coupling of polyfluoroarenes with aryl bromides via C–H activation (Scheme 39).[72] In this procedure, both electron-rich and electron-deficient aryl bromides were tolerated and performed well, although electron-rich substrates gave higher yields. On the other hand, replacing fluorine in pentafluoroarenes with hydrogen or methoxy groups resulted in reduced yields. The experimental results were consistent with the involvement of a Pd(II)/Pd(0) species. An initial oxidative addition of ArBr to Pd(0) was followed by coordination and insertion of CO and subsequent C–H bond activation of ArF_n.

In 2017, Yu and co-workers expanded the scope of their 3,5-bis(trifluoromethyl)pyridin-2(1*H*)-one ligand from C–H olefination to carbonylation (Scheme 40).[63a] In all their



Scheme 39 C–H carbonylation reported by Skrydstrup and co-workers[73]

transformations the arene was used as the limiting reagent. The C–H carbonylation was conducted under a CO atmosphere using HFIP as the solvent. The reaction catalysed by $Pd(OAc)_2$ with AgOAc as the oxidant afforded a mixture of the mono-HFIP ester and phthalic anhydride derivatives, which upon treatment with 2 M NaOH in MeOH resulted in mono- and diacids. This methodology was also suitable for late-stage functionalisation of natural products and drug molecules.



Scheme 40 Ligand-promoted carbonylation reported by Yu and co-workers[63a]

3 C–Heteroatom Bond Formation

Transition-metal catalysis is a powerful method for the generation of C–heteroatom bonds, which comprise transformations such as acetoxylation, benzoxylation, imidation, amination, borylation, silylation, etc. As discussed in the previous sections, direct functionalisation of C–H bonds employing these heteroatom-based transformations gives

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access to functionalised aromatic building blocks in a step-economical manner. Some of the above-mentioned C–heteroatom bond formations, relevant to the topic covered by this review, are discussed in the following sections.

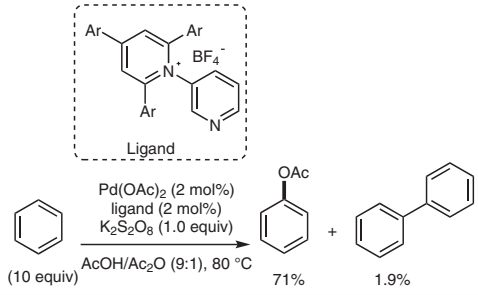
3.1 C–O Bond Formation

Hydroxylated arenes and aryl alkyl ethers constitute an important structural scaffold present in agrichemicals, pharmaceuticals, polymers, natural products and many other commercial products.[73] Hydroxylated compounds are also among the reactive substrates for functional group transformations, making C–O bond formation one of the most interesting research areas in catalysis. In 1996, Crabtree and Yoneyama were the first to report the palladium-catalysed acetoxylation of arenes employing $PhI(OAc)_2$ as the oxidant.[75]

Sanford and co-workers reported that the use of a pyridine ligand with $Pd(OAc)_2$ and $PhI(OAc)_2$ improved the catalyst performance (TON >4500).[76] Later on, they described detailed mechanistic studies on the catalytic species involved in the acetoxylation of benzene, where the key effect of the molar ratios of $Pd(OAc)_2$ and the pyridine ligand (1:1 and 1:2) in the reaction were studied.[77]

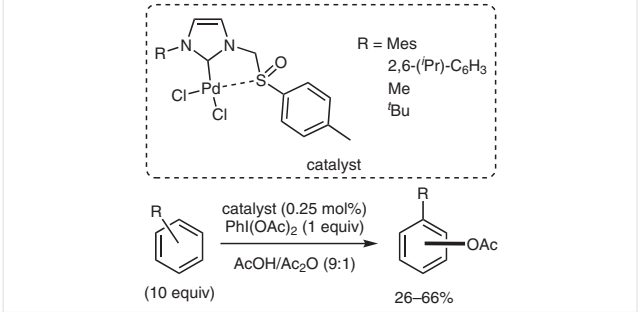
In 2013, the same group reported a synergistic effect of an acridine ligand in the presence of $MesI(OAc)_2$ as the terminal oxidant to control the site selectivity in the C–H acetoxylation of simple arenes.[78] The catalytic system with $Pd(OAc)_2$/acridine (3:1) was studied on various mono-, di-, and trisubstituted arenes. In contrast to the general ligand-free $Pd(OAc)_2/PhI(OAc)_2$ conditions, the new conditions favoured acetoxylation at the sterically less hindered site, deviating from the electronic-effect bias from the functional groups on the arene substrates. However, the catalytic system was ineffective in selecting between *meta*- and *para*-positions on monosubstituted arenes and instead afforded a 1:1 mixture.

Under the scope of ligand-promoted acetoxylation, Sanford and co-workers reported an efficient C–H oxygenation of benzene using $K_2S_2O_8$ as the terminal oxidant. The presence of a monodentate cationic pyridinium substituted pyridine ligand was crucial for obtaining an efficient catalyst in this reaction (Scheme 41).[79] Mechanistic studies pointed out that the cationic ligand serves as a phase-transfer catalyst for the $K_2S_2O_8$ oxidant.



Scheme 41 Pyridinium-ligand-promoted acetoxylation reported by Sanford and co-workers[79]

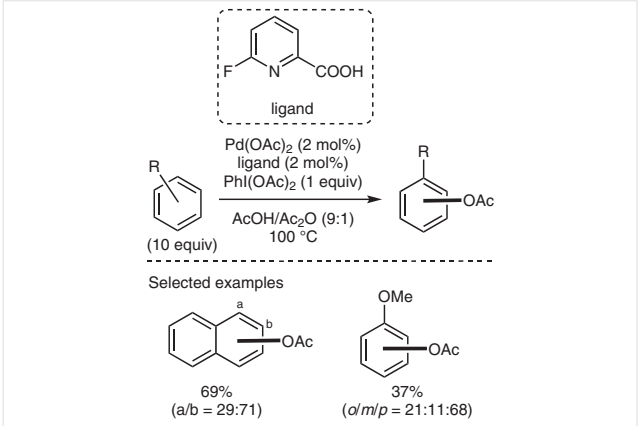
In the same year, Cárdenas and co-workers reported a novel series of sulfinyl-NHC-Pd catalysts with differently N-substituted imidazoles for the acetoxylation of simple arenes using $PhI(OAc)_2$ as the terminal oxidant (Scheme 42).[80] The method required a low catalyst loading (0.25 mol%), but only provided useful yields with electron-rich arenes which are used in excess.



Scheme 42 N-Heterocyclic carbene ligand promoted acetoxylation reported by Cárdenas and co-workers[80]

In 2015, Choudhury and co-workers reported the synthesis and use of bis-N-heterocyclic carbene (NHC)-chelated palladium(II) complexes in the acetoxylation of simple arenes.[81] Acetoxylated products in the mixtures of regioisomers were obtained in moderate yields. An intermolecular KIE value of 4.5 demonstrated that C–H bond breaking was the rate-determining step.

In 2016, Fernández-Ibáñez and co-workers reported a new catalytic system employing a bidentate picolinic acid ligand for $Pd(OAc)_2$-catalysed acetoxylation of simple arenes (Scheme 43).[82] The bidentate ligand enhanced the reactivity (TON = 7800). The method was tolerant towards



Scheme 43 Picolinic acid promoted acetoxylation reported by Fernández-Ibáñez and co-workers[82]

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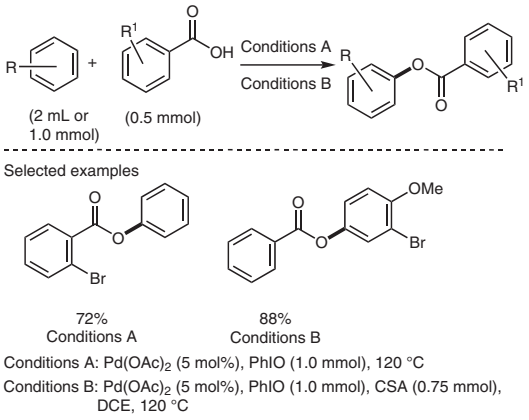
both electron-donating and electron-withdrawing substituents on the arene. The site selectivity was guided by both electronic and steric factors.

Liu and co-workers, in 2015, reported a $Pd(OAc)_2$-catalysed benzoxylation of non-directed arenes using carboxylic acids as the coupling partners (Scheme 44).[83] A large excess of the arene was required in the reaction, apart from cases with electron-rich arenes bearing a methoxy group. For the last example using reaction conditions B, 2 equivalents of the arene in the presence of camphorsulfonic acid (CSA) as an additive and DCE as the solvent were employed. Unlike the general acetoxylation procedures where $PhI(OAc)_2$ was used as the terminal oxidant, these conditions performed well with PhIO as the oxidant.

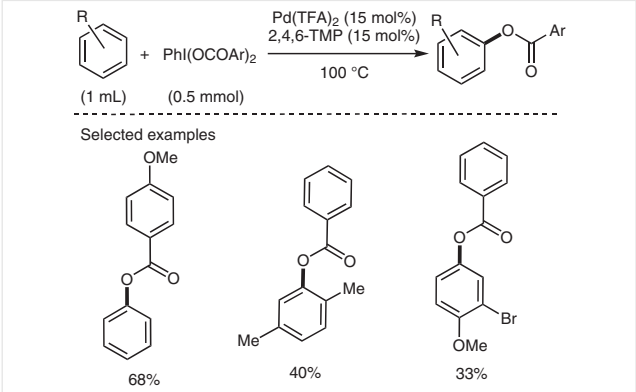


Scheme 44 Benzoxylation of arenes reported by Liu and co-workers[83]

In the following year, Li and co-workers described the benzoxylation of arenes employing iodobenzene dibenzoates as both the oxidant and the benzoxylation agent (Scheme 45).[84] Key to the success of this transformation was the use of a pyridine-based ligand. The paramount requirement for high catalyst efficiency was to maintain the 1:1 ratio of Pd/ligand, in agreement with Sanford's previous study.[76] The reaction gave the desired products in moderate yields even when using a large excess of the arene substrate. Both electron-withdrawing and electron-donating substituents on the benzoyl ring were suitable for the protocol. The reaction was expected to follow a Pd(II)/Pd(IV) mechanism with C–H bond cleavage being the rate-determining step.

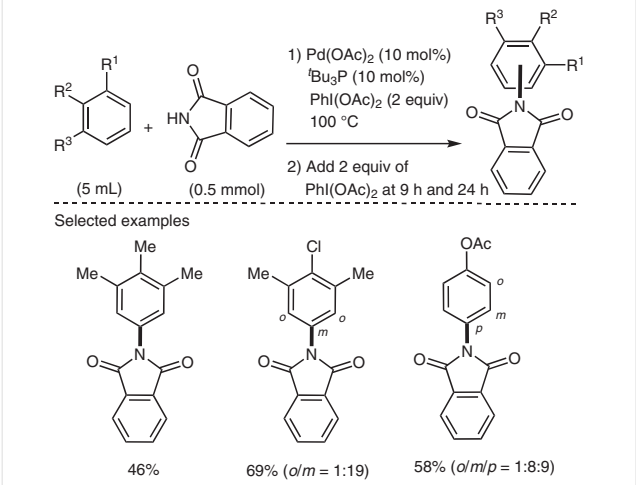
3.2 C–N Bond Formation

Together with the known difficult regioselectivity and poor reactivity, non-directed C–N bond formation in simple arenes faces an additional challenge with electrophilic metal catalysts vulnerable to the parent amine.[85] Consequently, the developments in this area are few.



Scheme 45 Benzoxylation of arenes reported by Li and co-workers[84]

In 2013, Hartwig and co-workers devised a $Pd(OAc)_2$-catalysed intermolecular imidation of simple arenes in the presence of $PhI(OAc)_2$ as the oxidant (added at two intervals during the reaction) to afford *N*-arylphthalimides (Scheme 46).[86] The reaction was highly efficient with mono-, di- and trisubstituted arenes undergoing imidation. Steric effects on simple arenes controlled the regioselectivity predominantly with preference for sterically less hindered products. With regard to the scope of the nitrogen source, electron-rich imides performed better than electron-poor imides such as saccharin and succinamide. Amines and amides gave low conversions. KIE experiments indicated that the C–H bond was cleaved irreversibly. The regioselectivity was disparate from the related acetoxylation reactions of arenes previously reported in the literature. This indicates to a different species being involved in the cleavage of the C–H bond and further mechanistic studies will be useful to develop more robust and practical catalysts.



Scheme 46 Amination of arenes reported by Hartwig and co-workers[86]

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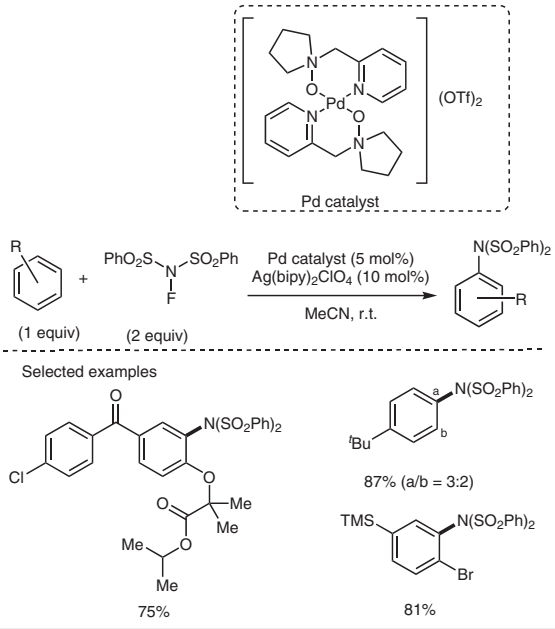
Ritter and co-workers synthesised an amine *N*-oxide-ligated palladium complex from tetrakis(acetonitrile)palladium(II) triflate and a *N*-(2-pyridylmethyl)pyrrolidine *N*-oxide ligand for the imidation of arenes (Scheme 47).[87] The catalyst worked efficiently in the presence of $Ag(bipy)_2ClO_4$ as a co-catalyst for the functionalisation of C–H bonds in simple arenes with N-fluorobenzenesulfonimide (NFBS). Moreover, the arene was required as the limiting reagent. The regioselectivity depends on the electronic factors of the arene substrate similar to electrophilic aromatic substitution. Substrates with inductive donors and lack of a strong directing bias resulted in a mixture of constitutional isomers. Electron-poor arenes were less reactive than electron-rich arenes. In cases of extremely electron-rich arenes, competitive C–H fluorination and double imidation occurred as side reactions. However, these side reactions were substantially reduced at lower temperatures (4 °C). A mechanistic study revealed an unusual radical mechanism without the formation of commonly observed organometallic intermediates, where C–H bond functionalisation occurred at a high oxidation state [Pd(III)] of the catalyst.

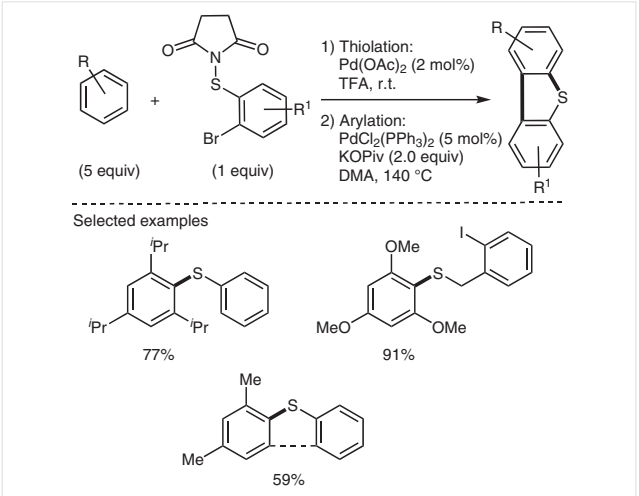


Scheme 47 Imidation of arenes developed by Ritter and co-workers[87]

3.3 C–S Bond Formation

Diaryl sulfides are commercially significant molecules since they are ubiquitous subunits of many organic semiconductors, important natural products and drug molecules. General methods for the syntheses of diaryl sulfides include deprotonative thiolation[88] and cross-coupling of arylmagnesium halides,[89] aryl boronic acids (Chan–Lam type)[90] or aryl halides[91] with an electrophilic aryl sulfur reagent. Literature on direct thiolation of C–H bonds by a chelation-assisted mechanism[92] or non-directed, as in simple arenes, is limited. A plausible reason could be catalyst poisoning due to strong coordination of organosulfur compounds to the TM. Lately, some developments in metal-free arylthiolation[93] and in DG-assisted thiolation using Ni,[94] Cu[95] or other metal catalysts have been reported.[96]

Regarding undirected thiolation of C–H bonds in simple arenes, in 2014, Anbarasan and Saravanan developed a method for the synthesis of unsymmetrical diaryl sulfides from simple arenes with an electrophilic sulfur reagent derived from succinimide (Scheme 48).[97] The unsymmetrical diaryl sulfide was subsequently subjected to intramolecular arylation, resulting in the formation of dibenzothiophene derivatives in good yields. The method worked well for the thiolation of sterically hindered substrates such as 1,3,5-triisopropylbenzene and many other di- and trisubstituted arenes. The scope of substitutions on the sulfur reagent was also examined. Both electron-donating and electron-withdrawing groups on the aryl thiol partner were tolerated, affording products in excellent yields. In addition, alkyl thiols were employed to afford the corresponding products in good yields. Based on previous reports, it was believed that highly electrophilic in situ generated $Pd(TFA)_2$ is involved in the proposed Pd(II)/Pd(IV) catalytic cycle, which includes C–H functionalisation of the arene, oxidative insertion into the N–S bond, reductive elimination and ligand exchange to generate the active Pd species.



Scheme 48 Thiolation of simple arenes developed by Anbarasan and Saravanan[97]

4 Conclusion

Reactions involving C–H activation represent cost-effective, atom-economic and low chemical-waste-generating methods to functionalise organic compounds. This multifaceted research area reveals numerous new strategies every year. Among the many directions C–H activation has

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been growing into, non-directed functionalisations of simple arenes are much less reported, but not for the lack of effort. The challenges in this area are reactivity and selectivity in general. This short review has presented various discovered and developed approaches to attain high yields and maximum regioselectivity possible with simple aryl derivatives. Most procedures described here depend on the electronic and steric bias of the substrate to afford selectivity. A few reports explain the importance of Pd/ligand combinations in controlling the selectivity, irrespective of the electronic effects of substituents on the aryl moieties. In general, the undirected transformations have often demanded the use of excess arenes for obtaining high yields. However, there are procedures reported using the arene as the limiting reagent that enable the use of undirected C–H activation in more elaborate syntheses.

The non-directed C–H activation has advanced further with the unravelling of new catalyst systems such as Pd-NHC complexes and heterogeneous-based catalysts. Most reactions have been demonstrated on aryl and naphthyl derivatives. The substrate scope has been sparsely extended towards PAHs, which if successful, will save lots of time and reduce the steps for building complex structures and functional materials. The development of new methods that allow the use of the arene as the limiting reagent, that broaden the substrate scope and that increase the selectivity of these processes is key for the tangible implementation of these strategies in academia and industry.

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