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TUTORIAL REVIEW

Arene C–H Functionalisation Using a Removable/Modifiable or Traceless Directing Group Strategy

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The use of coordinating moieties as directing groups for the functionalisation of aromatic carbon–hydrogen (C–H) bonds has become an efficient strategy for the selective construction of new carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds in arenes. However many directing groups cannot be easily removed/modified from the products after C–H functionalisation, thus limiting the structural diversity of the products. This limitation can be overcome by employing removable/modifiable or traceless directing groups which can be easily attached to the starting materials and detached from the products. In this tutorial review, we give an overview of recent advances in this emerging field which have dramatically increased the synthetic applicability of C–H functionalisation processes.

Key Learning Points

(1) Traditionally inert C–H bonds can be functionalised.
(2) Site-selective functionalisation of aromatic derivatives can be achieved with the assistance of directing groups.
(3) Carefully designed directing groups can be readily removed or converted into other useful functional groups efficiently.
(4) The functionalised aromatic compounds have use in natural product chemistry, medicinal chemistry and material chemistry.
(5) The field is fast growing and has great potential to expedite the synthesis of complex molecules.

1. Introduction

The direct cleavage of an unreactive C–H bond, followed by the formation of new C–C or C–X bond formation at a specific site within a molecule would constitute an ideal synthetic operation,[1] avoiding the traditional requirement for preinstalled functional handles such as halide, triflate, boron or tin.

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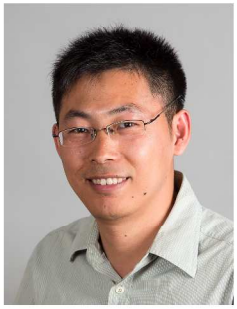
As early as 1968, the pioneering organometallic chemist Jack Halpern stated that "the development of successful approaches to the activation of C–H bonds remains to be achieved and presently constitutes one of the most important and challenging problems in this whole field".[2] Since then, the discovery of new methods for C–H bond cleavage by transition-metal complexes has been a long-standing goal in the synthetic community.

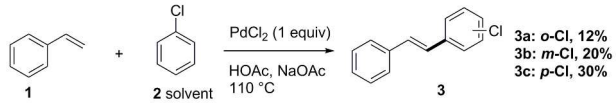
In 1967, Fujiwara reported the first olefination of benzene with a styrene-palladium chloride complex.[3] However, when mono-substituted arenes such as chlorobenzene **2** were exposed to the complex, a mixture of different isomers (**3a**, **3b** and **3c**) was obtained (Scheme 1).



Fengzhi Zhang received his PhD (2008) at the University of Nottingham (UK) under Professor Nigel Simpkins. After post-doctoral work with Professors John Moses (2008-2009, Nottingham) and Mike Greaney (2009-2011, Edinburgh), he joined the University of Cambridge working with Professors Matthew Gaunt (2011-2013) and David Spring (2013-2014). He then took up a faculty position at Zhejiang University of Technology (China). His research interests include the discovery of novel catalytic reactions and their synthetic applications.

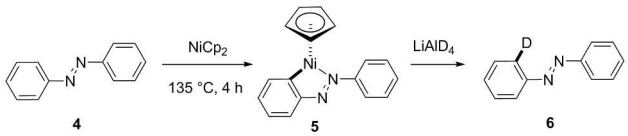
David Spring is currently a Professor at the University of Cambridge within the Chemistry Department. He received his DPhil (1998) at Oxford University under Sir Jack Baldwin. He then worked as a Wellcome Trust Postdoctoral Fellow at Harvard University with Stuart Schreiber (1999-2001), after which he joined the faculty at the University of Cambridge. His research programme is focused on synthetic chemistry and chemical biology.

One key limitation for this transformation is the poor regioselectivity as there is little difference in reactivity between the various C–H bonds in substrate. A common strategy to address this problem involves the use of substrates that contain metal-coordinating functional groups, directing the metal to activate proximal C–H bonds via cyclometallated intermediates.



Scheme 1 Pd-mediated arene C–H olefination of chlorobenzene

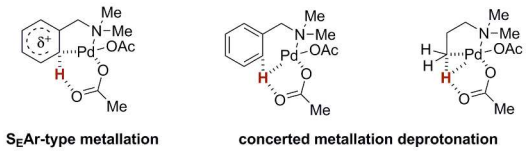
In 1963, Kleiman and Dubeck reported the formation of an azobenzenenickel complex **5** by treatment of azobenzene **4** with dicyclopentadienylnickel at 135 °C for 4 h (Scheme 2).[4] The azo functional group, working as a metal-coordinating directing group, brings the metal in close proximity to the *ortho* C–H bond to be activated, resulting in high levels of regioselectivity. After reduction of the five-membered metallacycle **5** with lithium aluminium deuteride, the metal atom in the *ortho*-position of the azobenzene was replaced by deuterium to give product **6**. Cyclic platinum and palladium complexes and their corresponding deuterium substituted products were also reported.



Scheme 2 First example of Ni-catalysed arene C–H bond activation

This was the first example of using a metal-coordinating functional group to control the regioselectivity of the transition-metal insertion into a C–H bond. This early report demonstrates the impressive reactivity of transition-metal catalysts in activating C–H bonds with the assistance of metal-coordinating directing groups, and opened the door for aromatic C–H functionalisation through this method. Since then many examples of stoichiometric C–H bond cleavage by various metals were discovered,[1] the development of a catalytic method as a key step towards a synthetically useful process was not realised until the pioneering work of Murai in 1993 on ruthenium catalysed *ortho*-alkylations of aromatic ketones with olefins.[5]

Cyclopalladation of C–H bond containing aromatic compounds has been extensively investigated and has been found to proceed along different pathways (Scheme 3).[1,6]



Scheme 3 Cyclopalladation models

A strongly coordinating nitrogen-containing directing group was typically required to promote the facile cyclopalladation, which severely limits the substrate scope. Nevertheless, these studies have served as a pivotal platform for further discovering and optimising this unprecedented mode of catalysis. Thus interest in directing group strategies for catalytic C–H bond functionalisation processes has increased dramatically.

An elegant report by Yu and co-workers in 2011 exemplifies how directing group strategies can enable the diverse C–H functionalisations of privileged molecular frameworks (Scheme 4).[7] Sulfonamides are an important pharmacophore found in nearly 200 drugs currently on the market, including the non-steroidal anti-inflammatory blockbuster drug Celecoxib **7b**. One of the potential bottlenecks in identifying promising drug candidates is the rapid access to molecular diversity. Taking advantage of the directing ability of the sulfonamide, Yu and co-workers applied their newly developed Pd(II)-catalysed C–H functionalisaton reaction to a broad range of C–C and C–X bond-forming processes. Six distinct analogues (**8**-**13**) of Celecoxib **7b** were prepared using this approach, including carboxylation, carbonylation, olefination, iodination, arylation or alkylation process. Remarkably, the coordinating ability of the sulfonamide group was able to override that of the diazine, which is itself a commonly employed heterocyclic directing group, affording exclusive site-selectivity in the presence of multiple potentially reactive C–H bonds. The *N*-aryl moiety of the sulfonamide can be kept as part of the pharmacophore or readily removed by hydrolysis with TFA in order to prepare other derivatives. Two years later, Yu and Baran successfully applied the same strategy for the divergent functionalisation of the core of bioactive natural product (+)-hongoquercin through the use of readily removable carboxylic acid and amide directing groups.[7] These two examples demonstrate the power of the directing group assisted C─H functionalisation to late-stage modify a privileged molecular framework which would have otherwise required many steps to make prior to the development of these unprecedented transformations.

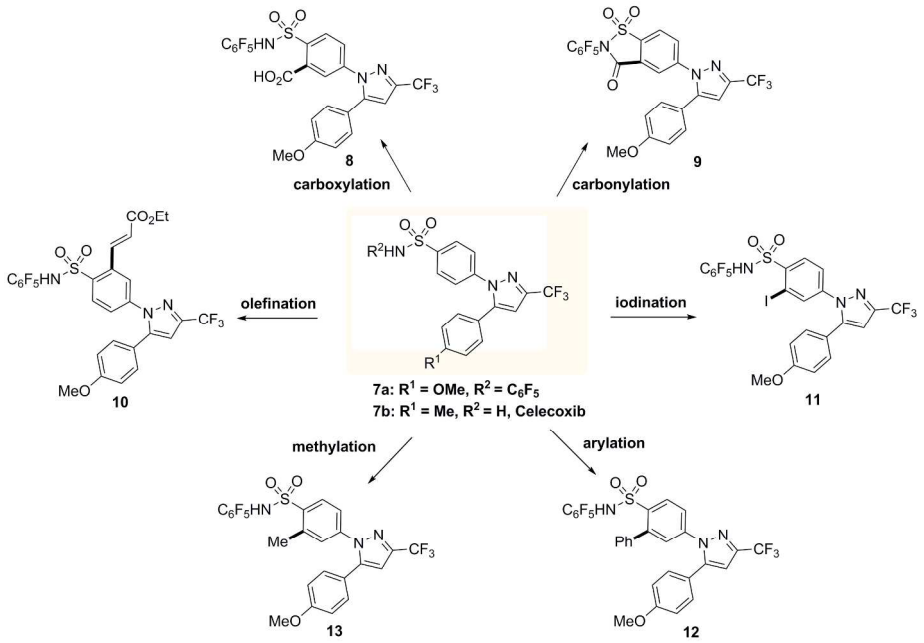
Various directing groups, such as heterocycles, carbonyl-related functional groups, amines and alcohols, have been employed for catalytic arene C–H bond functionalisation and can be categorised into three different approaches (Scheme 5):

Approach 1: After the C–H bond functionalisation of substrate **14**, the directing group remains part of the product **15**, or undergoes further cyclisation to form a heterocycle **16**. These directing groups cannot be conveniently removed or undergo further versatile transformations, which limits the structural diversity of the products.[1]

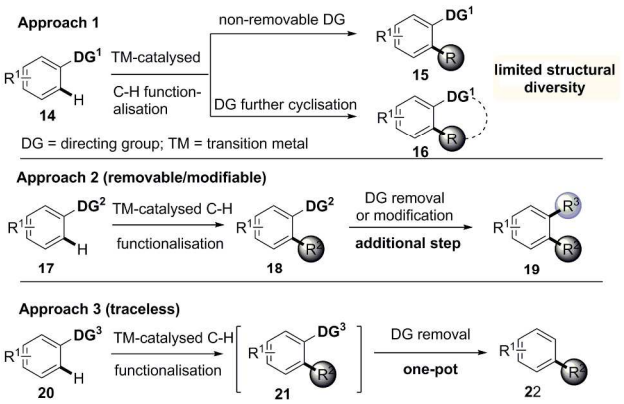
Approach 2: After the C–H bond functionalisation of substrate **17**, the directing group can be readily removed or further modified by additional steps to give functionalised product **19**. Such directing groups are classified as removable or modifiable.[8]

Approach 3: The C–H bond functionalisation of substrate **20** and directing group removal of functionalised product **21** can be carried out in one-pot. In some cases, the directing group introduction can also be done in the same pot. Such directing groups are classified as traceless.

Given the rapid expansion of this still growing field, it is not possible to cover all of the representative chemistry in the confines of this tutorial review. Therefore, in this tutorial review, we will only feature some recent representative examples of arene C–H functionalisation using removable or modifiable directing groups (Scheme 5, approach 2). We will mainly focus on the C─C and C─X bond-forming reactions based on arene substrates using traceless directing groups (Scheme 5, approach 3).



Scheme 4 Selective arene C–H functionalisation directed by a sulfonamide group



Scheme 5 Transition-Metal catalysed C–H functionalisation using directing group strategy

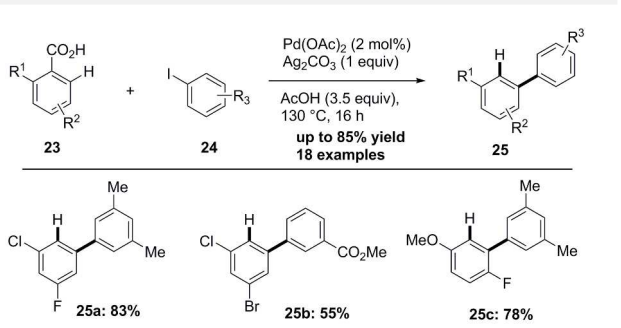
2. C–C Bond Formation

2.1 Arylation

The biaryl motif is ubiquitous in bioactive natural products, pharmaceuticals and functional materials. While Pd-catalysed cross-couplings such as Stille and Suzuki couplings have been successfully employed for biaryl synthesis, the requirement for prefunctionalisation of both coupling partners can limit their application. Direct arylation (the coupling of an unactivated aromatic C–H bond with an activated arene) using a directing group strategy has emerged as an attractive alternative to traditional cross-coupling reactions.[9]

2.1.1 Carbonyl-Derived Directing Groups

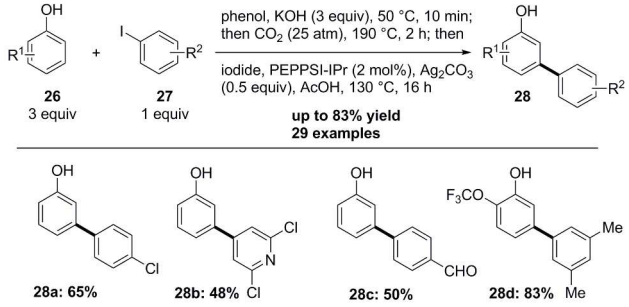
Arenes substituted with carbonyl derivatives provide an effective handle for cyclometallation. With respect to Pd-catalysis, Yu and co-workers have pioneered the use of cheap, readily available aromatic carboxylic acids in cross-coupling with arylorganometallic reagents.[10] Based on reports of protodecarboxylation of *ortho*-substituted benzoic acids under Ag catalysis and the suitability of carboxylic acids to act as directing groups to mediate *ortho*-C–H functionalisation, Larrosa and co-workers developed a formal *meta*-selective direct C–H arylation using iodoarenes **24** as coupling partners. (Scheme 6).[11] With carboxylic acids as a traceless directing group, a tandem *ortho*-arylation/protodecarboxylation process gave various *meta*-substituted biaryl compounds **25** in one step. The direct decarboxylative *ipso*-arylation and protodecarboxylation of starting material **23** before the desired arylation were successfully avoided.



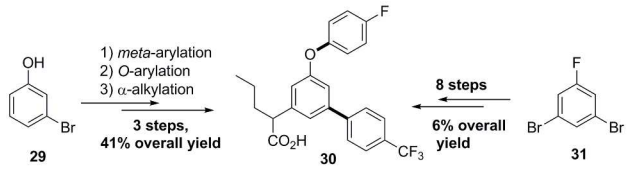
Scheme 6 Tandem *ortho*-selective arylation/protodecarboxylation of 2-substituted benzoic acids

Recently, Larrosa and co-workers have reported a one-pot direct *meta*-selective arylation of phenols **26** with a traceless directing group relay strategy (Scheme 7).[12] After extensive optimisation of conditions, it was found that treating phenol with KOH under 25 atm of CO_2 at 190 °C for 2 h, followed by the addition of the iodoarene **27**, Pd catalyst, Ag_2CO_3, and AcOH, and further reaction at 130 °C for 16 h, generated the desired *meta*-arylated product **28** successfully. Various substituents such as electron-donating and withdrawing groups, were compatible with the reaction conditions. However the

meta-NO_2-substituted phenol led to no reaction as the initial carboxylation step was prevented. Heteroarenes such as iodoindole and iodopyridine were also used as coupling partners. Thus various *meta*-aryl phenols were prepared from readily available phenols via a one-pot *ortho*-carboxylation, *ortho*-arylation and protodecarboxylation process. Finally, this methodology was applied to the synthesis of a γ-selective inhibitor **30** in only three steps, an improvement over the eight steps previously required (Scheme 8). This is the ideal arene C–H functionalisation using traceless directing group strategy since the directing group introduction/removal and C–H functionalisation take place in a one-pot process.

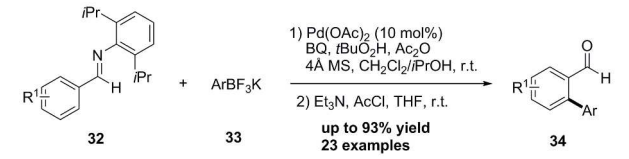


Scheme 7 One-pot *meta*-arylation of phenols with iodoarenes



Scheme 8 Efficient synthesis of γ-selective inhibitor

Compared to carbonyl-based directing groups, an imine directing group would be less electron-withdrawing, and so the C–H bond palladation event would require milder reaction conditions, which may enable the functionalisation of substrates displaying sensitive functionality. In 2011, Gaunt and co-workers developed a Pd(II)-catalysed C–H arylation for benzaldimines **32** with aryl-BF_3K salts **33** (Scheme 9).[13] Remarkably, electron-deficient arenes could even be arylated at room temperature. Using modified conditions, it was further demonstrated that the dehydrogenative cross-coupling with benzene could even be achieved on benzaldimines containing further electron-withdrawing functionality. The imine directing group itself could be removed readily using Et_3N and AcCl in THF at room temperature to give aromatic aldehyde **34**.

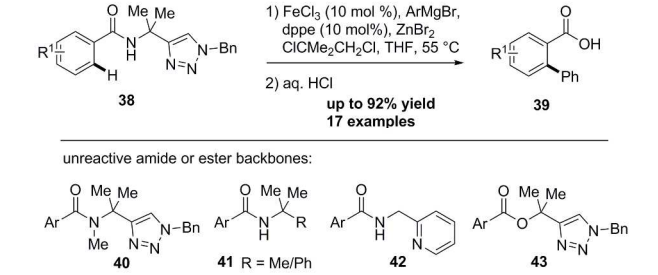


Scheme 9 Pd-catalysed *ortho*-arylation of benzaldimines

Other carbonyl-based directing groups such as amide derivatives, ketones, and oximes have also been developed for catalytic C–H bond functionalisation.[1] In 2011, Yu and co-workers reported a Pd(II)-catalysed *para*-selective C–H arylation of monosubstituted arenes **36** via cross-dehydrogenative couplings (CDC) (Scheme 10).[14] Reactions that directly couple two aryl C–H bonds have received much attention, as they require no prefunctionalisation of the coupling partners and only produce hydrogen as the sole byproduct. However the low reactivity of C–H bonds and issues of selectivity make this synthetic method particularly challenging. With $Pd(OAc)_2$ as a catalyst, an acidic amide directing group **35** and a F^+ oxidant for the double C–H activation, the highly *para*-selective C–H arylation of monosubstituted arenes **36** was achieved. No *ortho*-arylation was observed. Electron-withdrawing groups were tolerated on one of the coupling partners. The arylated amide products could be readily converted into useful carboxylic acids **37** by treating with TFA/H_2O at 90 °C. One limitation for this protocol is the use of arene **36** as the solvent. Further development to reduce this towards a single equivalent of arene could lead to practical new tools for the synthesis of *para*-substituted biaryls.

Scheme 10 Pd(II)-catalysed *para*-C–H arylation of monosubstituted arenes

In recent years, bidentate auxiliaries have attracted considerable attention owing to their unique potential for the activation of otherwise inert C–H bonds. Ackermann and co-workers recently reported an iron-catalysed direct C–H arylation using a triazole-based bidentate auxiliary (Scheme 11).[15]



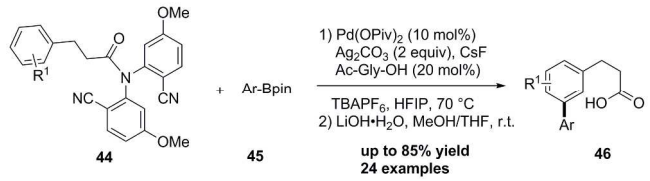
Scheme 11 Iron-catalysed direct C–H arylation

After a screening of various amide or ester based directing groups, they identified that the triazolyldimethylmethyl (TAM) amide based arene substrates **38** underwent efficient direct C–H arylation with inexpensive iron catalyst under mild reaction conditions. Tertiary amides **40**, simple amides **41** and **42** without the triazole moiety, and the corresponding esters **43** failed to give the desired products. The TAM directing group can be easily removed under acidic conditions to give the functionalised aromatic carboxylic acids. It is worth mentioning that this catalytic system also enabled the successful arylation of unactivated $C(sp^3)$–H bonds.

2.1.2 Nitrile-Containing Templates/Directing Groups

The *ortho*-functionalisation of aromatic C–H bonds is often achieved through the formation of a conformationally rigid six- or seven-membered cyclic pre-transition state by using α-chelating directing groups. This proximity-driven reactivity prevents the activation of remote C–H bonds despite the broad

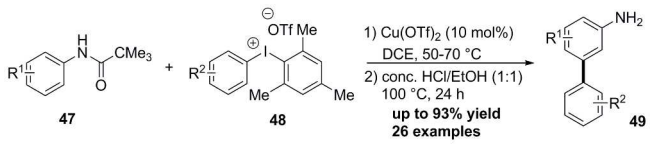
utility of this approach. Yu and co-workers extended this concept and developed the first example of Pd-catalysed cross-coupling of *meta*-C–H bonds with arylboronic acid esters **45** using a novel long-range directing group strategy (Scheme 12).[16] The observed *meta*-selectivity was achieved through directed C–H palladation via an U-shaped nitrile template **44**, which was suggested to weakly coordinated to the Pd(II) catalyst. During their investigation they found that the addition of a mono-protected amino acid (MPAA) was vital to the successful coupling. Furthermore, the addition of tetrabutylammonium salts were found to have a dramatic influence on the catalytic performance of palladium by preventing the undesired agglomeration of Pd(0) species that form the non-catalytically active palladium black. For unsubstituted or *meta*-substituted substrates, minor *ortho*- and *para*-arylated isomers were also formed. There was almost no reactivity for the di-*ortho*-substituted substrates. The template can be removed under mild conditions ($LiOH·H_2O$, MeOH/THF, r.t.) leading to useful 3-phenylpropanoic acid **46**.



Scheme 12 *meta*-Arylation of 3-phenylpropanoic acid and phenolic derivatives.

2.1.3 Amine-derived directing groups

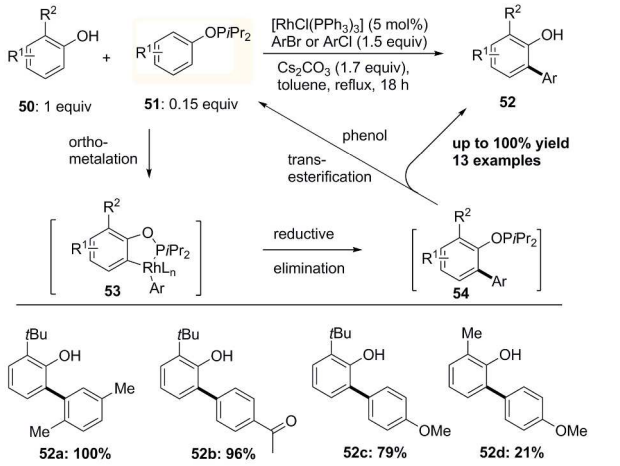
In 2009, Phipps and Gaunt found that reaction of pivanilides **47** with hypervalent iodine arylating reagents **48** in the presence of copper catalysts gave the *meta*-substututed products **49** exclusively (Scheme 13).[17] This method allowed direct access to a range of *meta*-substituted aromatic compounds in a single step, which would otherwise require multiple synthetic steps using traditional chemistry. Later, Gaunt and co-workers extended this Cu-catalysed *meta*-selective arylation method to the α-aryl carbonyl scaffold with a remote and versatile Weinreb amide directing group. A range of arenes displaying diverse substitutions, benzylic chirality and quaternary centers were prepared in one simple step under identical conditions for the arylation of pivanilides.[17]



Scheme 13 Cu-catalysed *meta*-C–H arylation of pivanilides

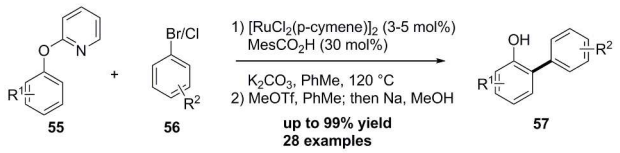
2.1.4 Phenol-Derived Directing Groups

One class of reaction that provides particular challenges for novel catalytic chemistry is the synthesis of *ortho*-arylated phenols. Currently, the most commonly used catalytic routes to these compounds employ Suzuki or Stille coupling reactions. From both synthetic and atom-economic points of view, it would be highly desirable to couple an aryl halide directly with a phenol. In 2003, Bedford and co-workers reported the first catalytic intermolecular *ortho*-arylation of phenols **50** (Scheme 14).[18] In the presence of a phosphinite cocatalyst **51**, the facile *ortho*-metalation of the simple phenols **50** occurred to give five-membered metallacycles **53**. Subsequent reductive elimination of the new ligand and the aryl group led to the reformation of the active catalyst and the liberation of a new 2-arylated aryl dialkylphosphinite ligand **54**. This ligand underwent catalytic transesterification with the starting phenol **50** to regenerate the co-catalyst **51** and liberate the 2-arylated phenol product **52**. It is necessary to have a bulky group in the 2-position of the phenol **50** for the reaction to proceed efficiently. For example, the yield of **52d** was lowered to 21% when using 2-methylphenol as the substrate, 1-Naphthol could be used as a substrate to give a 2,8-arylated product. Alhough further research is required to examine the scope of this reaction with a broad range of coupling partners, this is a very novel approach since the directing group is essentially catalytic.



Scheme 14 Catalytic *ortho*-arylation of phenols

Various *N*-containing heterocycles, such as pyrazole, oxazoline and imidazoline, have been employed as directing groups for direct C–H arylation processes.[8] Although these heterocycles are efficient directing groups for controlling the functionalisation of C–H bonds, subsequent manipulation of these motifs is difficult or restrictive. To overcome this limitation, Ackermann developed a Ru-catalysed direct arylation of arenes **55** bearing a removable pyridinyl directing group (Scheme 15).[19] Interestingly, the most efficient catalysis was achieved with catalysts derived from $MesCO_2H$, and when using K_2CO_3 as the base. Both electron-rich and deficient arenes reacted efficiently with aryl bromides or chlorides **56**. The directing group could easily be removed to give the free phenols **57**.



Scheme 15 Ru-catalysed direct arylation of 2-phenoxypyridines

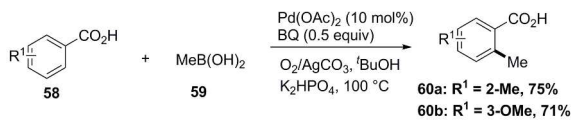
2.2 Alkylation

Friedel–Crafts alkylation has been known for many years, yet the application of this method is typically plagued by limited substrate scope, poor regioselectivity, and undesired over alkylation. However, transition-metal catalysed C–H alkylation

methodologies are able to provide access to mono-alkylated arenes with excellent regio- and chemo- selectivities.[20]

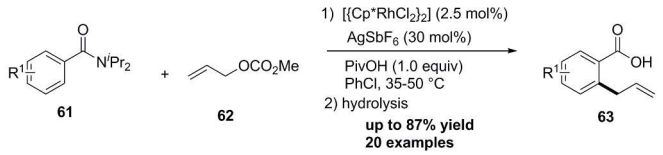
2.2.1 Carbonyl-Related Directing Groups

The directed *ortho*-alkylation of acetanilides, pioneered by Tremont in 1984, provided the conceptual basis for later approaches.[20] In 2007, Yu and co-workers reported the first catalytic protocol for the coupling of *ortho*-C–H bonds of benzoic acids **58** and *β*-C–H bonds in aliphatic acids with organoboron reagents *via* Pd(II)/Pd(0) catalysis.[21] Only two examples of the methylation of *ortho*-C–H bonds in benzoic acids were demonstrated on substrates **58**, where *β*-hydride elimination is a possible side reaction (Scheme 16). Further optimisation would be required to encompass a broad range of alkylborons. The carboxylic acid group is highly versatile, and can be removed or transformed into a variety of functional groups easily.



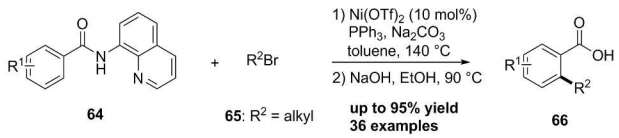
Scheme 16 Pd-catalysed methylation of benzoic acids

In 2013, Glorius and co-workers reported a mild Rh(III)-catalysed direct *ortho*-C–H allylation of arenes **61** with allyl carbonates **62** (Scheme 17).[22] With $[(Cp^*RhCl_2)_2]$ (2.5 mol%) as a catalyst, by tuning the amount of PivOH (1.0 equiv) and $AgSbF_6$ (30 mol%), the thermodynamically more stable disubstituted alkene by-products could be inhibited efficiently, leading to the desired products **63** in good yields after hydrolysis. No diallylated product was observed. Many benzamides containing various functional groups, regardless of electron-donating, neutral or withdrawing properties, were compatible with the mild reaction conditions.



Scheme 17 Rh(III)-catalysed allylation of benzamides.

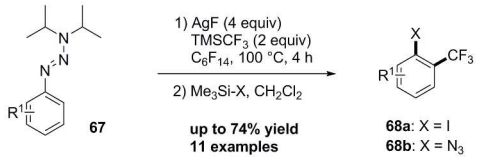
In 2013, Chatani and co-workers reported a Ni-catalysed *ortho*-alkylation of C−H bonds in benzamides and acrylamides containing an 8-aminoquinoline moiety as a bidentate directing group (Scheme 18).[23] Unactivated alkyl bromides and iodides reacted with various aromatic amides **64** to give the desired products **66** via a 5-membered Ni metalacycle. Ackermann and co-workers also recently reported a first Nickel-catalysed direct secondary alkylations and trifluoroethylations of arenes.[24]



Scheme 18 Ni-catalysed alkylation with alkyl halide via bidentate-chelation assistance

2.2.2 Amine-Derived Directing Groups

In 2010, Yu and co-workers reported a Pd(II)-catalysed *ortho*-trifluoromethylation of arenes using an electrophilic trifluoromethylating agent.[25] However, the substrate scope was limited to arenes with a *N*-containing heterocyclic directing group which is not readily removable. In 2012, Hafner and Bräse reported a highly *ortho*-selective trifluoromethylation of aromatic triazenes **67** (Scheme 19).[26] Various functional groups were tolerated, including halogens, which are not compatible with many metal-mediated trifluoromethylation reactions. Finally, triazene, a useful equivalent to a protected diazonium salt can be easily transformed into various functional groups, such as halides **68a**, azides **68b**, nitriles and phenols, or back to the starting anilines.



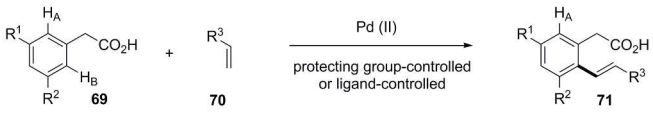
Scheme 19 Trifluoromethylation of triazenes

2.3 Alkenylation

The oxidative Heck reaction and hydroarylation of alkynes are two methodologies for the introduction of an olefin moiety into arenes, which has an advantage over the traditional Mizoroki-Heck reaction by eliminating the need for pre-activation of arenes. A number of directing groups, including *N*-oxide/nitroso, amines, alcohols and carbonyl-related functional groups, have been developed recently for this particular transformation.[1]

2.3.1 Carbonyl-Related Directing Groups

Many carbonyl-related directing groups, such as carboxylic acids, esters, ketones, aldehydes and amides, have been employed for (hetero)arene C–H olefination.[1] In 2010, Yu and co-workers developed a Pd(II)-catalysed *ortho*-olefination of phenylacetic acid **69** and 3-phenylpropionic acid substrates, using oxygen at atmospheric pressure as the terminal oxidant (Scheme 20).[27]



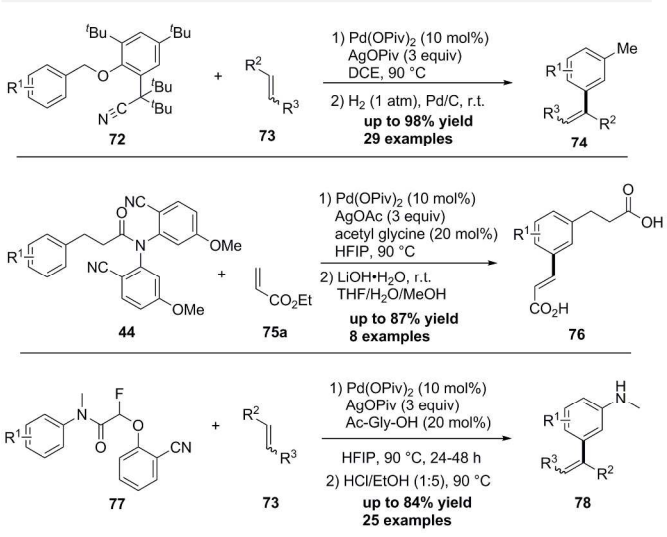
Scheme 20 Pd(II)-catalysed position-selective *ortho*-olefination

A wide range of phenylacetic acid substrates **69** were found to be compatible with this protocol by reacting with ethyl acrylate. When using 1-hexene as the olefin substrate, a class of alkenes beyond the scope of traditional Mizoroki-Heck-type chemistry, the authors found the non-conjugated product was predominantly formed as a mixture of *E*/*Z* isomers. However, the 1,2-disubstituted methyl acrylate only gave the desired product in 16% yield. Remarkably, the use of amino acid derived ligands in this reaction not only enhanced the reactivity, but also enabled the control of positional selectivity. In cases when the two *ortho* positions are equivalent, the desired product can be obtained in good yields by this approach alone. When the two *ortho* positions on the ring are different, the CO_2H directs the catalyst to the *ortho*-position, whilst the ligand is able to distinguish between the subtle electronic or

steric environments of the two *ortho*-positions. They further demonstrated the versatility of the method through direct elaboration of commercial drug scaffolds, and the efficient synthesis of 2-tetralone and naphthoic acid natural product cores.

2.3.2 Nitrile-Containing Templates/Directing Groups

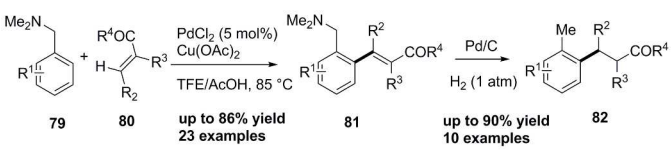
Recently, Yu and co-workers applied their nitrile-containing templates to the activation of distal *meta*-C–H bonds in three distinct classes of substrates (toluene **72**, hydrocinnamic acid **44** and *N*-methylaniline derivatives **77**) (Scheme 21).[28] The template design is predicated on a weak interaction between Pd(II) and the nitrile group. Remarkably, the template overrides the intrinsic electronic and steric biases as well as *ortho*-directing effects of the arene substrates, consistently delivering high *meta*-selectivity in most cases. After the coupling, the ether templates can be removed readily through Pd/C-mediated hydrogenolysis to give the *meta*-olefinated toluene products **74**. The amide template can be hydrolysed using LiOH as a base at room temperature to give the diacid **76**. The cleavage of the template on the aniline derivatives can be done with the mixture of HCl and EtOH (1:5) at 90 °C to give product **78**.



Scheme 21 Template-directed *meta*-selective C–H olefination of toluene, hydrocinnamic acid and *N*-methylaniline derivatives

2.3.3 Amine-Derived Directing Groups

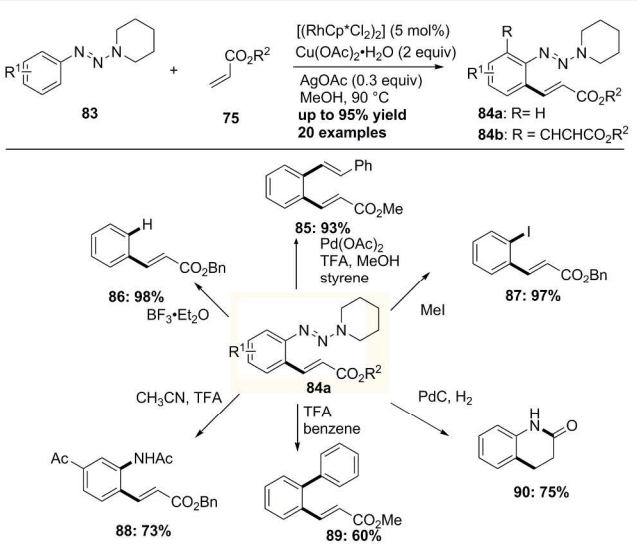
The importance of amines in organic synthesis makes them very attractive functional groups for C–H functionalisation chemistry. One of the first amine-directed C–H functionalisation reactions was reported by Shi and co-workers on the olefination of *N*, *N*-dimethylbenzylamine **79** (Scheme 22).[29]



Scheme 22 Pd(II)-catalysed arene C–H *ortho*-olefination of *N*,*N*-dimethylbenzylamine

Amines can be protonated easily under acidic condition inhibiting the coordination to metal. They can also be oxidised or form stable and unreactive *bis*-amino-Pd(II) species in the presence of a Pd catalyst. Therefore, it is critical to control the acidity of the reaction conditions. The authors found that the *ortho*-alkenylated products **81** were obtained in good yields by reacting with $PdCl_2$ (5 mol%) and $Cu(OAc)_2$ (1 equiv) in the presence of AcOH (16 equiv) with 2,2,2-trifluoroethanol (TFE) as solvent. The alkenylated products **81** could subsequently be hydrogenated to give useful substituted toluene derivatives **82**.

In 2012, Huang and co-workers reported a Rh(III)-catalysed direct arene C–H olefination using a removable triazene directing group **83** (Scheme 23).[30] With $[(Cp^*RhCl_2)_2]$ (5 mol%) as a catalyst, it was found that the addition of acetate was crucial for efficient catalyst turnover. In most cases, a mixture of mono- and di-olefinated products (**84a** and **84b**) were obtained in good yields under the optimised conditions. The electron-withdrawing effects of the two appending nitrogens on the triazene moiety, significantly weaken the C─N bond attached to the arenes, allowing for mild removal conditions and subsequent modification. For example, the triazene moiety can be quantitatively removed using $BF_3{\cdot}Et_2O$ in DME at room temperature to give **86**. The triazene group can also be converted into the corresponding iodide **87** and used in cross-coupling reactions.

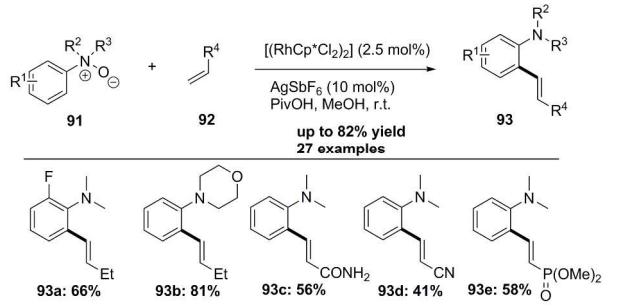


Scheme 23 Rh(III)-catalysed direct arene C–H olefination and further transformation

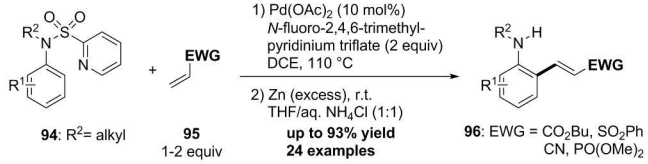
In 2013, You and co-workers reported a Rh-catalysed C–H olefination of tertiary anilines **91** using the *N*-oxide as a traceless directing group (Scheme 24).[31] For transition-metal catalysed C─H activation chemistry, an external oxidant is generally required to regenerate the catalyst. However, in this protocol, the *N*-oxide was used as both a traceless directing group and an internal oxidant. Interestingly, it was possible to isolate a five-membered cyclometalated Rh(III) complex and established its structure by X-ray crystallographic analysis. The successful olefination of tertiary anilines catalysed by this complex implies it may be one of the intermediates in the catalytic cycle. Finally, various useful 2-alkenylated tertiary anilines **93** were prepared efficiently at room temperature.

In 2011, Carretero and co-workers developed a Pd(II)-catalysed direct C─H olefination of *N*-(2-pyridyl)sulfonyl anilines **94** (Scheme 25).[32] With $Pd(OAc)_2$ (10 mol%) as a catalyst and *N*-fluoro-2,4,6-trimethylpyridinium triflate (2 equiv) as an oxidant, various *N*-alkyl derivatives **94** reacted with monosubstituted electrophilic alkenes **95** smoothly to give

the corresponding olefinated products in good yields. In some cases the formation of a minor amount of the diolefinated product was observed. By increasing the amount of both the alkene and oxidant to three equivalent, the diolefinated products could be obtained in high yields. Interestingly, this method could also be applied to benzylamine and phenylethyl amine derivatives. The *N*-(2-pyridyl)sulfonyl directing group can be removed readily under acidic conditions using Zn powder to give the olefinated anilines **96**.



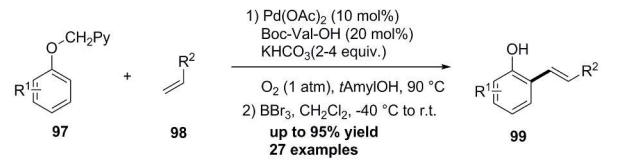
Scheme 24 Rh-catalysed C–H olefination of tertiary anilines with the *N*-oxide as a traceless directing group



Scheme 25 Pd-catalysed olefinaton of *N*-(2-pyridyl)sulfonyl anilines

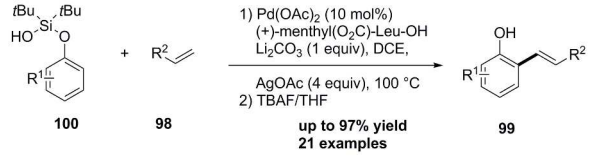
2.3.4 Phenol-Derived Directing Groups

In 2008, You and co-workers reported a Pd-catalysed C–H alkenylation of phenols using 2-pyridylmethyl ether as directing group (Scheme 26).[33] It was found that the addition of Boc-Val-OH was critical for successful olefination. A wide range of phenols **97** and alkenes **98** were employed in this transformation, affording the ortho-alkenylated products with high regioselectivity. Notably, non-activated linear alkenes could serve as coupling partners. This methodology was also applied to the diolefination of phenols, providing symmetrical or unsymmetrical divinylphenol derivatives. The 2-pyridyl-methyl directing group was removed readily by BBr_3 in CH_2Cl_2 to give the corresponding alkenylated phenols **99**.



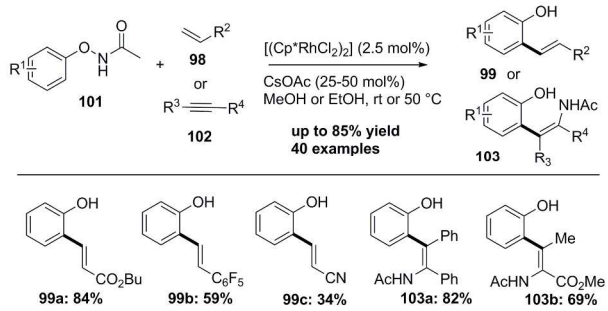
Scheme 26 Pd-catalysed direct C–H olefination of phenol ethers

Inspired by successful C–H functionalisation directed by alcohol or silicon-tethered directing groups, Gevorgyan and co-workers developed a Pd-catalysed *ortho*-alkenylation of phenols **100** with electron-deficient alkenes **98** directed by a traceless silanol functional group (Scheme 27).[34] This reaction is monoselective because the bulky *tert*-butyl groups at the silanol moiety prevent orientation of the silanol directing group towards the less hindered C–H site. A range of alkenylated phenols **99** including benzofuranone and alkenylated estrone derivative were prepared efficiently using this semi-one-pot process.



Scheme 27 Pd(II)-catalysed silanol-directed alkenylation of phenol derivatives

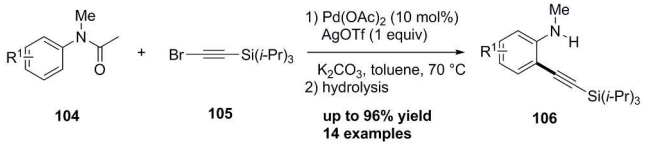
In 2013, Lu and co-workers reported a mild Rh(III)-catalysed direct C─H olefination of *N*-phenoxyacetamides **101** (Scheme 28).[35] Using $[(Cp^*RhCl_2)_2]$/CsOAc catalytic system, both alkenes **98** and alkynes **102** could react with *N*-phenoxy-acetamides **101** to give the corresponding olefinated phenol products **99** or **103** in one step. It is worth mentioning that the high atom economy was achieved when alkynes were reacted with *N*-phenoxyacetamides. The acetamido group was employed as both a directing group and an internal oxidant in these protocols.



Scheme 28 Rh-catalysed direct C─H olefination of *N*-phenoxyacetamide

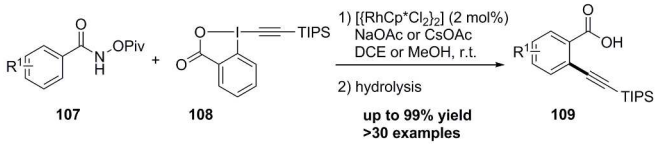
2.4 Alkynylation

Alkynylarenes, most frequently prepared by Sonogashira-Hagihara cross coupling, are an important class of building blocks. Another complementary and powerful method for the synthesis of alkynylarenes is catalytic aromatic C–H bond functionalisation using a readily available alkynyl source.[1] In 2009, Chatani and co-workers reported a Pd-catalysed direct *ortho*-C–H alkynylation of anilides **104** (Scheme 29).[36] Various functional groups including halogen and ester were tolerated under this reaction conditions. The alkynylated amide products can be hydrolysed readily to give the corresponding anilines **106**. The triisopropylsilyl groups in the products can also be removed under mild conditions to liberate terminal alkynes.



Scheme 29 Pd-catalysed direct alkynylation of aromatic *ortho*-C–H bonds in anilides and further transformations

Very recently, the groups of both Loh and Li reported a mild, Rh-catalysed, amide directed C–H alkynylation of arenes **107** using a hypervalent iodine reagent **108** (Scheme 30).[37]

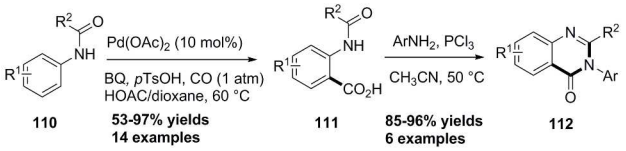


Scheme 30 Rh-catalysed direct C─H alkynylation of arenes

Despite being demonstrated using only TIPS-substituted ethynyl benziodoxones, the compatibility of heterocycles and various functional groups, the very mild reaction conditions (room temperature) and high mono-selectivity would make these protocols powerful tools for the late-stage functionalisation of complex molecules. Li also demonstrated that many other commonly used directing groups could be used for this Rh-catalysed arene C─H alkynylation. Furthermore, an Ir(III)-catalysed C─H alknylation of *N*-methoxycarboxamides with TIPS-substituted ethynyl benziodoxones was further developed.

2.5 Carbonylation

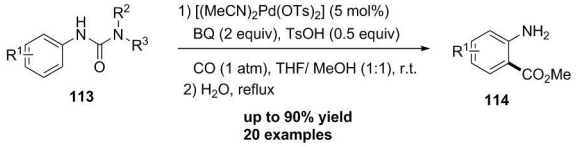
Carbonylation of organic compounds is an attractive synthetic transformation since it utilises CO as an economical carbon source for the formation of a new C–C bond with concomitant introduction of a highly oxidised functional group. Yu and co-workers developed a Pd(II)-catalysed reaction for the direct *ortho*-C–H carboxylation of anilides **110** to form *N*-acyl anthranilic acids **111** (Scheme 31).[38] During their investigation, it was found that the presence of toluenesulfonic acid monohydrate (0.5 equiv) in the solvent mixture of acetic acid and dioxane was crucial for the reaction. Interestingly, the *N*-benzoylanthranilic acids **111** could be treated with PCl_3 in the presence of aniline to generate quinazolinones **112** in excellent yields. A range of biologically active benzoxazinone and quinazolinone derivatives from simple anilides were also prepared using this reaction protocol without the need to install or remove an external directing group.



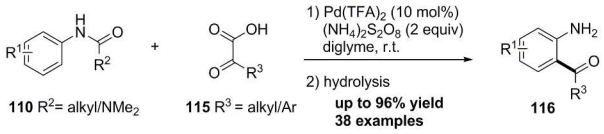
Scheme 31 Pd(II)-catalysed carboxylation of anilides and further manipulation

In 2009, Lloyd-Jones and co-workers reported a urea-directed, Pd-catalysed methoxycarbonylation of aniline derivatives **113** at room temperature (Scheme 32).[39] The diisopropyl urea moiety can be selectively removed under neutral conditions in the presence of an ester group to give the methoxycarbonylated anilines **114**. Methoxycarbonylation followed by the addition of potassium carbonate and heating afforded the one-pot synthesis of quinazolinone, a key heterocyclic pharmacophore in many drug substances.

In 2010, Ge and co-workers reported a Pd-catalysed decarboxylative ortho-acylation of acetanilides **110** with α-oxocarboxylic acids **115** (Scheme 33).[40] With $Pd(TFA)_2$ (10 mol%) as a catalyst and $(NH_4)_2S_2O_8$ as an oxidant, this new method is complementary to the classical directed lithiation/acylation process and provides useful o-acylacetanilides. Both aromatic and aliphatic α-oxocarboxylic acids were compatible to the reaction conditions. Various substituted acetanilide, with the exception of *O*-substituted acetanilides, were amenable to this transformation.



Scheme 32 Pd(II)-catalysed methoxycarbonylation of aniline derivatives



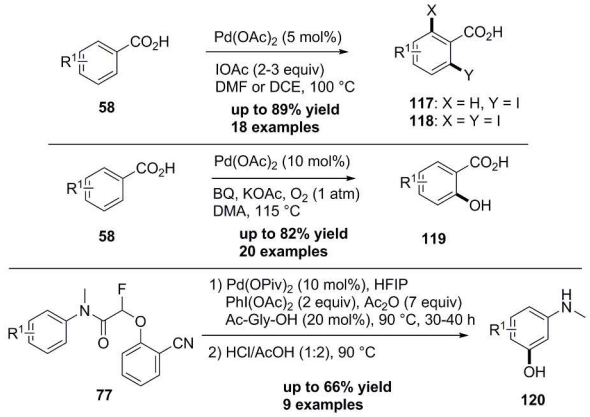
Scheme 33 Pd-catalysed *ortho*-C–H acylation of acetanilides

3. C–X Bond Formation

The construction of C–X bonds directly from arene C–H bonds is of great importance because the C–X functionalities can be further modified to introduce interesting molecular complexity.[1] In this section, recent progress on the C–O, C–halogen, C–N, C–B and C–Si bond formation using removable or traceless directing groups will be discussed.

3.1 C–O/C–Halogen Bond Formation

In 2008, Yu and co-workers developed the Pd(II)-catalysed *ortho*-C–H halogenation of aromatic carboxylic acids **58** (Scheme 34).[41]

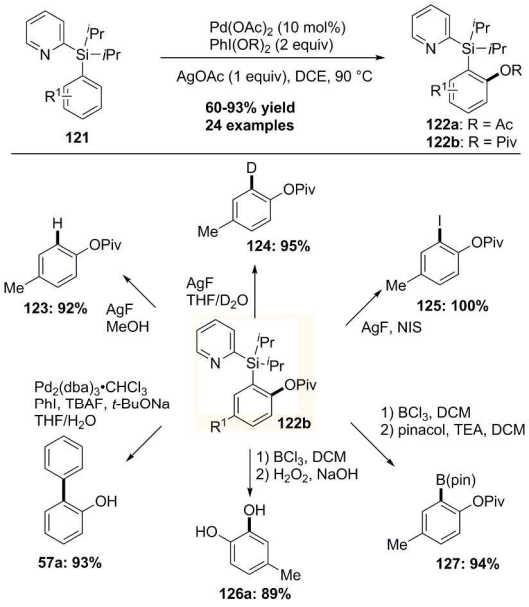


Scheme 34 Pd(II)-catalysed C–H halogenation/hydroxylation of aromatic carboxylic acids and aniline derivatives

For substrates lacking an *ortho*-substituent, a mixture of mono- and di-halogenated products **117** and **118** were obtained. It was found that the use of tetra-alkyl ammonium salts could boost monoselectivity. They also developed a Pd(II)-catalysed *ortho*-C–H hydroxylation of aromatic carboxylic acids **58** using 1 atm of O_2 or air under nonacidic

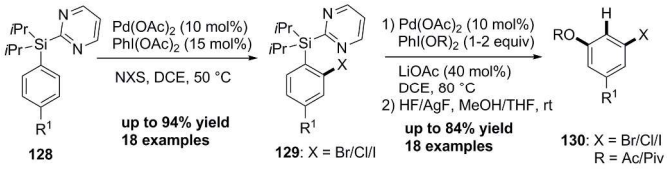
conditions to give product **119**.[41] Labelling studies using both $^{18}O_2$ and $H_2{}^{18}O$ supported a direct oxygenation of the arylpalladium intermediates rather than an acetoxylation-/hydrolysis pathway. More recently, they applied their nitrile-containing template-directed remote C─H functionalisation approach to the acetoxylation of *N*-methylanilines **58**.[28] Excellent levels of *meta*-selectivity were obtained with various substituted anilines using $Pd(OAc)_2$ (10 mol%) as a catalyst and $PhI(OAc)_2$ as an oxidant. Notably, these transformations proceed via Pd(II)/Pd(IV) redox chemistry as opposed to the Pd(0)/Pd(II) catalytic cycle in the C─H olefination. The hydrolytic removal of the template also converted the acetate to a hydroxyl group of aniline **120** in one pot (Scheme 34).

In 2010, Gevorgyan and co-workers developed an efficient Pd(II)-catalysed acetoxylation/pivaloxylation of aromatic C–H bonds of **121** using a silicon-tethered directing group (Scheme 35). Only the mono-oxygenated product **122** was obtained in this reaction. For the substrates containing *meta*-substituents, the acetoxylation and pivaloxylation took place only at the less hindered *ortho*-position. The directing group can be efficiently cleaved or converted into various synthetic useful functional groups such as iodide **125** and boronate **127** etc.[42]



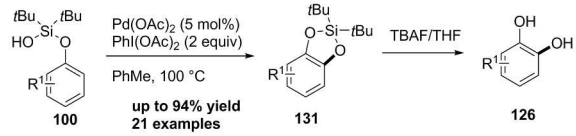
Scheme 35 Pd(II)-catalysed *ortho*-C–H oxygenation of arenes and further transformation

By using 2-pyrimidyldiisopropylsilyl as a directing group they further achieved the *bis*-oxygenation of aromatic C–H bonds in the presence of LiOAc as cocatalyst. The tolerance of *ortho*-substituents in the oxygenation reaction with the 2-pyrimidyldiisopropylsilyl directing group allowed for the development of a twofold unsymmetrical C–H functionalisation process. Twofold aromatic C–H functionalisation is synthetically appealing as it allows for the introduction of two substituents in a one-pot or a two-step procedure. Prior to this report however, twofold C–H functionalisation has been used only for the introduction of the same or similar functionalities. By combining the Pd(II)-catalysed C–H halogenation reaction with the C–H oxygenation reaction, substituted *meta*-halophenols **130** as well as polyfunctionalised arenes were prepared successfully from the simple aryl iodides (Scheme 36).[43]



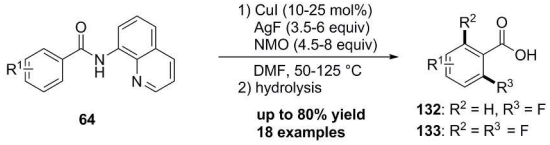
Scheme 36 Pd(II)-catalysed sequential halogenations/oxygenation of of arenes

Gevorgyan and co-workers further developed a Pd(II)-catalysed silanol-directed C–H oxygenation of phenols **100** into catechols **126** (Scheme 37).[44] This method operates via a silanol-directed acetoxylation, followed by a subsequent acid-catalysed cyclisation reaction into a cyclic silicon-protected catechol **129**. A routine desilylation of the silacyle with TBAF unveils the catechol product **126**. In contrast to other alcohol and phenol directed C–O cyclisation methods, where the directing group also serves as the oxygen source, the oxygen atom of the newly installed hydroxyl group in this method was delivered by the oxidant.



Scheme 37 Pd(II)-catalysed C–H oxygenation of phenol derivatives

Fluorine can provide many beneficial properties when incorporated into a molecule. Recently, Daugulis and co-workers developed a Cu-catalysed aminoquinoline directed selective mono-fluorination protocol with AgF as the fluoride source to give the fluorinated aromatic carboxylic acid (Scheme 38).[45]



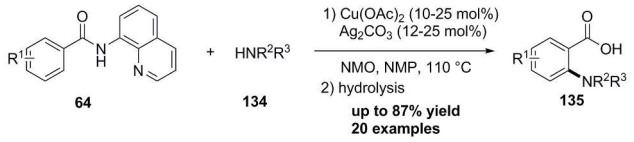
Scheme 38 Cu-catalysed fluorination of benzamide

Both electron-rich and deficient benzamides **64** containing various functional groups were compatible with the fluorination conditions. Heterocyclic carboxamides containing indole and pyridine moieties were also fluorinated in good yields. The clean difluorination can also be achieved simply by increasing the Cu catalyst, fluoride source loading and the reaction time. Given that the aminoquinoline amides stabilise high oxidation states in transition-metal complexes, it was proposed that the Cu-catalysed aminoquinoline amide fluorination proceeds via a Cu(III) intermediate.

3.2 C–N Bond Formation

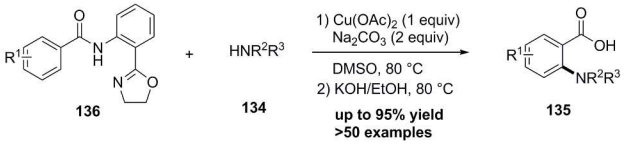
Since Buchwald reported his pioneering work on Pd-catalysed intramolecular amination for the synthesis of carbazoles,[46] many excellent tranisition-metal catalysed C–N bond forming protocols using directing group strategies have been developed.[1] Recently, Daugulis and co-workers reported a Cu-catalysed directed amination of carboxylic acid derivatives with a removable aminoquinoline directing group (Scheme 39). Simple amine coupling partners such as morpholine can be

used to install the nitrogen moiety in the presence of an inexpensive Cu-Ag catalytic system. The aminoquinoline directing group can be removed readily under basic conditions. Using arenes with the same quinolinylamide directing group, Nakamura and co-workers also reported an iron-catalysed *ortho*-C–H amination with *N*-chloroamines.[47]



Scheme 39 Cu-catalysed C─H amination of arenes.

Yu and Dai recently reported a Cu(II)-mediated amination and amidation of (hetero)arenes through the use of a readily removable amide-tethered oxazoline directing group (Scheme 40).[48] Aryl substrates **136** with various substituents were reacted with sulphonamides amides or anilines to give the corresponding products in good yields. Furthermore, many heteroarenes including furan, benzofuran, pyrole, indole and pyridine, reacted smoothly to give the corresponding amidation products in moderate to good yields. The amide-oxazoline directing group can be removed under basic conditions to give the corresponding functionalised aromatic carboxylic acids **135**. While this protocol is stoichiometric in copper at this stage, the unprecedented level of compatibility of this reaction with heterocyclic arenes and amine donors is a practical and important feature for medicinal chemists.

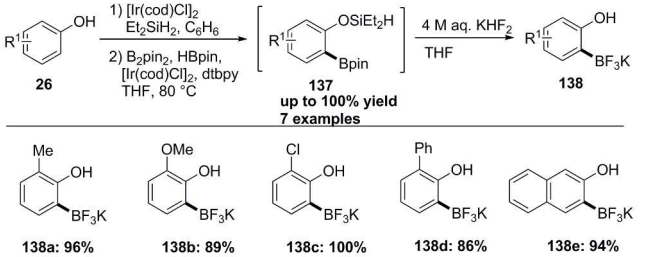


Scheme 40 Cu-mediated C–H amidation/amination of arenes

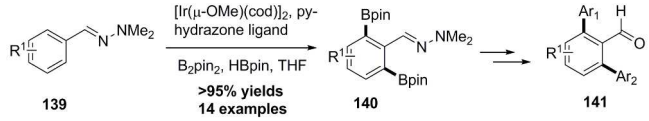
3.3 C–B Bond Formation

Traditionally, arylboron reagents were prepared by the addition of organolithium or magnesium species to borates. In 2008, Hartwig and Boebel developed a silyl-directed, Ir-catalysed *ortho*-borylation of arenes. Substituted aryl trifluoroborate salts **138** were prepared in one-pot from simple phenols **26** (Scheme 41). However, only seven examples were demonstrated in this reaction. They further extended this methodology to the borylation of nitrogen-containing heterocycles such as indole, carbazole, phenothiazine, and tetrahydroquinoline.[49]

In 2012, Lassaletta and co-workers reported an Ir-catalysed diborylation of benzaldehyde derivatives **139** with hydrazone as the directing group (Scheme 42).[50] Remarkably, in the presence of Ir catalyst (1 mol%), pyridine-hydrazone ligand (2 mol%) and HBpin (5 mol%), various substituted arene substrates reacted with B_2pin_2 (2 equiv) to give the desired diborylated products **140** in excellent yields. Interestingly, the diborylated products can undergo sequential Suzuki–Miyaura cross coupling with two different aryl bromides to give densely functionalised arenes, which was attributed to the unsymmetrical interaction of the hydrazone with the two Bpin moieties. The hydrazone directing group itself can be transformed into aldehyde **141** or nitrile by ozonolysis or oxidative cleavage using magnesium monoperoxyphthalate.

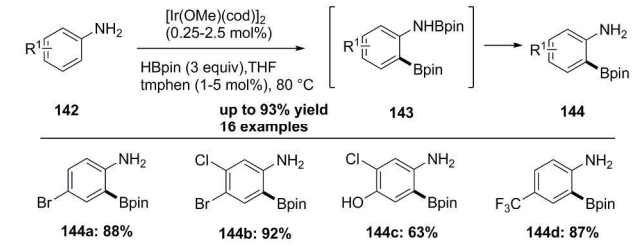


Scheme 41 One-pot *ortho*-borylation of phenols and heterocycles



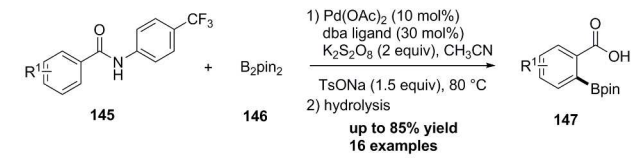
Scheme 42 Ir-catalysed diborylations of benzaldehyde derivatives

Recently, Krska and co-workers demonstrated that the (pinacolato)boron (Bpin) group can be employed as a traceless directing group for C–H borylation of anilines **142** and aminopyridines (Scheme 43).[51] Traceless Bpin protection enables the regioselective functionalisation of C–H bonds in the parent compound without the need for separate installation and removal of a directing group. The resulting reactions are operationally simpler and generally higher yielding than Boc-directed counterparts previously developed by the group. One of the limitations for this protocol is that secondary and *ortho*-substituted anilines substrates were not reactive under these conditions.



Scheme 43 Traceless Bpin-directed *ortho*-borylation of anilines

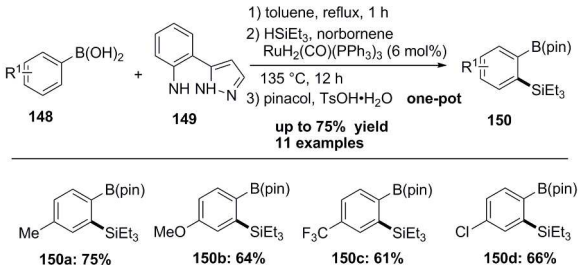
In 2012, Dai and Yu reported the first example of Pd-catalysed oxidative *ortho*-C─H borylation of arenes **145** with a diboron reagent **146** using an amide auxiliary (Scheme 44).[52] It was found the use of a weak base such as TsONa was essential for obtaining good yields, as both the diboron reagent and the arylboronate decomposed in the presence of K_3PO_4. Various arenes with different functionalities (Cl, F, CF_3, NO_2 and OAc) were borylated in good yields. In most cases only the monoborylated products were isolated. The borylated products can be further converted into various useful synthons using known transformations.



Scheme 44 Pd-catalysed borylation of *N*-arylbenzamides

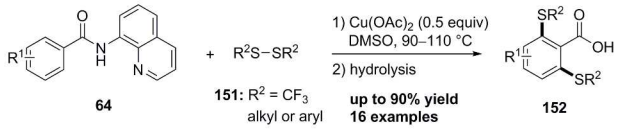
3.4 C–Si/C–S Bond Formation

In 2009, Suginome and Ihara reported a Ru-catalysed *ortho*-C–H silylation of aromatic boronic acids **148** with an easily attachable and detachable 2-pyrazol-5-ylaniline directing group **149** (Scheme 45).[53] Almost no formation of double silylation products were detected in these reactions. Highly regioselective silylation at the less sterically hindered *ortho*-position was observed for the *meta*-substituted boronic acids. After acid treatment, the corresponding boronic acid can be used as a handle for further transformations.



Scheme 45 One-pot *ortho*-silylation of arylboronic acids using pyrazolylaniline as a directing group

In 2012, Daugulis and co-workers developed a copper mediated sulfenylation of benzoic acid derivative **64** using 8-aminoquinoline auxiliaries as removable directing groups (Scheme 46).[54] In the presence of $Cu(OAc)_2$ (0.5 equiv), various carboxylic acid derivatives with different functionalities were sulfenylated by employing aryl or alkyl disulfides **151** (2.5 equiv) in DMSO. Selective monosulfenylation of substrates without *ortho*-substituents could not be achieved. Either low conversion or about 1/1 mixture of mono and disulfenylated products 152 were obtained. The 8-aminoquinoline group can be efficiently removed by base hydrolysis after amide *N*-methylation to give the corresponding sulfenylated aromatic carboxylic acids.



Scheme 46 Copper-promoted sulfenylation of benzoic acid derivatives

4. Conclusions and Outlook

The capacity to activate a specific aromatic C–H bond and transform it to a more versatile functional group is one of the fastest growing areas in synthetic chemistry. The fundamental challenges of enhancing the reactivity and regioselectivity associated with these transformations are efficiently addressed by using substrates with a readily removable or traceless directing group capable of pre-coordinating the metal catalyst. Various directing groups have been designed and employed successfully for the arene C–H bonds *ortho*- and *meta*-functionalisations (arylation, alkylation, olefination, alkynylation, carbonylation, oxygenation and halogenations). However, very few directing groups can be applied to a broad range of transformations. The use of carbonyl-derived directing groups for C–H functionalisation is probably the most versatile and successful approach investigated to date. In the future, we expect more elegant traceless directing groups will be developed, so that C–H bonds can be activated as required in any molecule, and applied to diverse arene C–H functionalisations. Furthermore, we anticipate the development of more powerful novel catalytic processes, with lower catalyst loadings under mild conditions, and greater functional group compatibility, will be further developed.

In summary, functionalisation of unactivated aromatic C–H bonds with removable or traceless directing groups is an efficient strategy for the rapid generation of relatively complex molecules from simpler starting materials. Advances in these areas will change the way we approach the synthesis of arenes and find their way into industrial applications.

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