Arene C–H functionalisation using a removable/modifiable or a traceless directing group strategy

Fengzhi Zhang*ab and David R. Spring*b

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 a new C–C or C–X bond at a specific site within a molecule would constitute an ideal synthetic operation,1 avoiding the traditional requirement of preinstalled functional handles such as halide, triflate, boron or tin.

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”. Since then, the discovery of new methods for C–H bond cleavage by transition-metal complexes has been a long-standing goal of the synthetic community.

In 1967, Fujiwara reported the first olefination of benzene with a styrene–palladium chloride complex.2 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).

One key limitation of this transformation is the poor regioselectivity as there is little difference in reactivity between the various C–H bonds in substrates. 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.

In 1963, Kleiman and Dubcek 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

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* College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, P. R. China 310014. E-mail: fz233@cam.ac.uk
b Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK. E-mail: spring@ch.cam.ac.uk

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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.

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, 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-alkylation of aromatic ketones with olefins.

Cyclopalladation of C–H bond containing aromatic compounds has been extensively investigated and has been found to proceed along different pathways (Scheme 3). 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). Sulfonamides are important pharmacophores 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 functionalisation 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, carboxylation, olefination, iodination, arylation or the 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. These two examples demonstrate the power of the directing group assisted C–H functionalisation to the late-stage modifying 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

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**Fengzhi Zhang** received his PhD (2008) from 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 R. Spring** is currently a Professor at the University of Cambridge within the Chemistry Department. He received his DPhil (1998) from 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.
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).

### 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 of prefuctionalisation 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 traceless directing groups, 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.
Recently, Larrosa and co-workers have reported a one-pot direct meta-selective arylation of phenols with a traceless directing group relay strategy (Scheme 7). 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 iodoarene, the Pd catalyst, Ag$_2$CO$_3$, and AcOH, and further reaction at 130°C for 16 h, generated the desired meta-arylated product 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-arylphenols 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 in only three steps, an improvement over the eight steps previously required (Scheme 8). This is the ideal arene C–H functionalisation using a traceless directing group strategy since the directing group introduction/removal and C–H functionalisation take place in a one-pot process.

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

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

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 of benzaldimines with aryloboronates (Scheme 9). Remarkably, electron-deficient arenes could even be arylated at room temperature. Under 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$_3$N and AcCl in THF at room temperature to give aromatic aldehyde.

Other carbonyl-based directing groups such as amide derivatives, ketones, and oximes have also been developed for catalytic C–H bond functionalisation. In 2011, Yu and co-workers reported a Pd(II)-catalysed para-selective C–H arylation of monosubstituted arenes via cross-dehydrogenative couplings (CDC) (Scheme 10). 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 and a F$_3$CO$_2$I oxidant for the double C–H activation, the highly para-selective C–H arylation of monosubstituted arenes 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 by treating with TFA–H$_2$O at 0°C.

One limitation of this protocol is the use of arene 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.

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).
After a screening of various amide or ester based directing groups, they identified that the triazolylidimethylmethyl (TAM) amide based arene substrates 38 underwent efficient direct C–H arylation with an 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(sp³)–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 aryboronic acid esters 45 using a novel long-range directing group strategy (Scheme 12). The observed meta-selectivity was achieved through directed C–H palladation via a U-shaped nitrile template 44, which was suggested to weakly coordinate 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 was 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·H₂O, MeOH–THF, r.t.) leading to useful 3-phenylpropanoic acid 46.

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-substituted products 49 exclusively (Scheme 13). 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.

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). 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. Although 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.

Various N-containing heterocycles, such as pyrazole, oxazoline and imidazoline, have been employed as directing groups for direct C–H arylation processes. 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). Interestingly, the most efficient catalysis was achieved with catalysts derived from MesCO₂H, and when using K₂CO₃ 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.

2.2 Alkylation

Friedel–Crafts alkylation has been known for many years, yet the application of this method is typically plagued by the 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.

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. 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. 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.

In 2013, Glorius and co-workers reported a mild Rh(III)-catalysed direct ortho-C–H alkylation of arenes 61 with allyl carbonates (Scheme 17). With \([\text{Cp}^*\text{RhCl}_2\]) (2.5 mol%) as a catalyst, by tuning the amount of PtOH (1.0 equiv.) and AgSbF₆ (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.

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). Unactivated alkyl bromides and iodides reacted with various aromatic amides 64 to give the desired products 66 via a 5-membered Ni metallacycle. Ackermann and co-workers also recently reported the first nickel-catalysed direct secondary alkylations and trifluoroethylations of arenes.

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. 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). 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.
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(n)-catalysed ortho-olefination of phenylacetic acid 69 and 3-phenylpropionic acid substrates, using oxygen at atmospheric pressure as the terminal oxidant (Scheme 20).27

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 that 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 CO2H 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-methyl-aniline derivatives 77) (Scheme 21).28 The template design is predicated on a weak interaction between Pd(n) 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 20 Pd(n)-catalysed position-selective ortho-olefination.

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

Amines can be protonated easily under acidic conditions inhibiting the coordination to metal. They can also be oxidised or form stable and unreactive bis-amino-Pd(n) 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-alkenylation products 81 were obtained in good yields by reacting with PdCl2 (5 mol%) and Cu(OAc)2 (1 equiv.) in the presence of AcOH (16 equiv.) with 2,2,2-trifluoroethanol (TFE) as a 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(n)-catalysed direct arene C–H olefination using a removable triazene directing group 83 (Scheme 23).30 With [Cp*RhCl2]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) was 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 BF3·Et2O 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. 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 establish its structure by X-ray crystallographic analysis. The successful olefination of tertiary anilines catalysed by this complex implies that 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 2-pyridylsulfonyl 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 equivalents, the diolefinated products could be obtained in high yields. Interestingly, this method could also be applied to benzylamine and phenylethylamine derivatives. The N-(2-pyridyl)sulfonyl directing group can be removed readily under acidic conditions using Zn powder to give the olefinated anilines 96.

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 a 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-pyridylmethyl directing group was removed readily by BBr₃ in CH₂Cl₂ to give the corresponding alkenylated phenols 99.

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.
In 2013, Lu and co-workers reported a mild Rh(III)-catalysed direct C–H olefination of N-phenoxyacetamides (Scheme 28).\(^{35}\) Using the \([\text{Cp}^*\text{RhCl}_2]_2/\text{CsOAc}\) catalytic system, both alkenes and alkynes could react with N-phenoxyacetamides to give the corresponding olefinated phenol products or 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.

### 2.4 Alkynylation

Alkynylation, most frequently prepared by Sonogashira–Hagihara cross coupling, are an important class of building blocks. Another complementary and powerful method for the synthesis of alkynylation 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 \textit{ortho}-C–H alkynylation of anilides (Scheme 29).\(^{36}\) Various functional groups including halogen and ester were tolerated under these reaction conditions. The alkynylation amide products can be hydrolysed readily to give the corresponding anilines. The triisopropylsilyl groups in the products can also be removed under mild conditions to liberate terminal alkynes.

Very recently, the groups of both Loh and Li reported a mild, Rh-catalysed, amide directed C–H alkynylation of arenes using a hypervalent iodine reagent (Scheme 30).\(^{37}\) Despite being demonstrated using only TIPS-substituted ethynyl benzeniodoxones, 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 alkynylation 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 direct \textit{ortho}-C–H carboxylation of anilides to form N-acyl anthranilic acids (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 could be treated with PCl\(_3\) in the presence of aniline to generate quinazoliones in excellent yields. A range of biologically active benzoaxazine and quinazolinone derivatives from simple anilides were also prepared using this reaction protocol without the need to install or remove an external directing group.

In 2009, Lloyd-Jones and co-workers reported a urea-directed, Pd-catalysed methoxycarbonylation of aniline derivatives 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. 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 \textit{ortho}-acylation of acetanilides with \(\alpha\)-oxocarboxylic acids (Scheme 33).\(^{40}\) With Pd(TFA)\(_2\) (10 mol%) as a catalyst...
and (NH₄)₂S₂O₈ as an oxidant, this new method is complementary to the classical directed lithiation/acylation process and provides useful o-acylanilides. Both aromatic and aliphatic α-oxocarboxylic acids were compatible to the reaction conditions. Various substituted anilide, with the exception of O-substituted acetanilides, were amenable to this transformation.

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 in 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 For substrates lacking an ortho-substituent, a mixture of mono- and di-halogenated products ¹¹⁷ and ¹¹⁸ was 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 O₂ or air under nonacidic conditions to give product ¹¹⁹.⁴¹ Labeling studies using both ¹⁸O₂ and H₂¹⁸O 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 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 a 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 poly-functionalised arenes were prepared successfully from the simple aryl iodides (Scheme 36).⁴³

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
3.2 C–N bond formation

Since Buchwald reported his pioneering work on Pd-catalysed intramolecular amination for the synthesis of carbazoles, many excellent transition-metal catalysed C–N bond forming protocols using directing group strategies have been developed. Recently, Daugulis and co-workers reported a Cu-catalysed aminocation 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 amines with the same quinolinylamide directing group, Nakamura and co-workers also reported an iron-catalysed ortho-C–H amination with N-chloroamines.

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). Aryl substrates with various substituents were reacted with sulphonamides and anilines to give the corresponding products in good yields. Furthermore, many heteroarenes including furan, benzofuran, pyrrole, 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. 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.

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 were prepared in one-pot from simple phenols (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.
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 an Ir catalyst (1 mol%), a pyridine-hydrazone ligand (2 mol%) and HBpin (5 mol%), various substituted arene substrates reacted with B2pin2 (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.

Recently, Krška 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 of this protocol is that secondary and ortho-substituted aniline substrates were not reactive under these conditions.

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 that 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 K3PO4. Various arenes with different functionalities (Cl, F, CF3, NO2 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.

### 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-ylalanine directing group 149 (Scheme 45).53 Almost no formation of double silylation products was 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.

In 2012, Daugulis and co-workers developed a copper promoted 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 a 1/1 mixture of mono and disulfenylated products was obtained. The 8-aminoquinoline group can be efficiently removed by base hydrolysis after amide N-methylation to give the corresponding sulfenylated aromatic carboxylic acids 152.

### 4. Conclusions and outlook

The capacity to activate a specific aromatic C–H bond and transform it into a more versatile functional group is one of the fastest growing areas in synthetic chemistry. The fundamental challenges in enhancing the reactivity and regioselectivity associated with...
these transformations are efficiently addressed by using substrates with a readily removable/modifiable or a 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, alkylation, 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 that 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 that 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/modifiable 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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References


