Direct C–H bond arylations and alkenylations with phenol-derived fluorine-free electrophiles

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Significant progress has been accomplished in direct C–H bond arylations of arenes and heteroarenes with readily accessible, inexpensive phenol derivatives. Thus, ruthenium biscarboxylate complexes and inexpensive cobalt compounds allowed for challenging C–H bond derivatizations of arenes. Further, palladium, nickel and cobalt catalysts set the stage for step-economical C–H/C–O bond functionalization with electron-rich as well as electron-deficient heteroarenes.

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Introduction

Bi(hetero)aryls are the key structural motifs of different compounds with activities of relevance to among others crop protection, medicinal chemistry or material sciences.^{1,2} Based on pioneering studies by Ullmann and by Goldberg,³ regio-selective syntheses of bi(hetero)aryls have predominantly

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Scheme 1 Strategies for sustainable biaryl synthesis.

exploited transition metal-catalyzed⁴ cross-coupling reactions between organic (pseudo)halides and stoichiometric amounts of organometallic reagents (Scheme 1a).⁵ Thereby, metal-catalyzed cross-coupling reactions have matured to being reliable tools for the formation of C_{sp}²-C_{sp}² bonds.

Lutz Ackermann

Lutz Ackermann (1972) studied Chemistry at the Christian-Albrechts-University Kiel, Germany, and obtained his PhD degree from the University of Dortmund in 2001 for research under the supervision of Alois Fürstner at the Max-Planck-Institut für Kohlenforschung in Mülheim/Ruhr. He was a postdoctoral fellow in the research group of Robert G. Bergman at the University of California at Berkeley before initiating his independent

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With the aim of expanding the scope of cross-coupling reactions, significant efforts have been made in recent decades. Prior to the late 1990s, aryl iodides and bromides were usually employed as electrophilic coupling partners in cross-coupling reactions due to their relatively high inherent reactivity.^{1,2,4} However, the synthesis of non-commercially available aryl halides may involve multiple steps and relatively harsh reaction conditions, and leads to undesired waste production. The development of pseudo-halides as an attractive alternative to halides as the electrophiles in cross-coupling reactions began in the late 1970s.⁶ Given that phenols are inexpensive and readily available, practical methods that allow for the arylations with phenol derivatives are extremely desirable. The bond-dissociation energies in Ph-H, Ph-OH, Ph-OAc, Ph-OMe, Ph-Cl, Ph-Br and Ph-I moieties are equal to 112.9, 112.4, 106.0, 101.0, 97.1, 84.0 and 67.0 kcal mol⁻¹, respectively.⁷ Typically, phenols are converted into the corresponding sulfamates, phosphates, carboxylates, or carbamates to facilitate the cleavage of the otherwise challenging C-O bonds.⁸ However, the use of the phenol-derived (fluoro)sulfonated hydroxyl group as pseudo-halide electrophiles is the most attractive.⁹ Thus, the reactivity of aryl halides and sulfonate electrophiles toward transition metals typically follows the trend ArI > ArBr ≈ ArOTf ≫ ArCl > ArOTs.¹⁰ In spite of their lower reactivities, the fluorine-free sulfonates, tosylates and mesylates are particularly valuable coupling partners for cross-coupling reactions (Table 1).

First, they are more easily accessible from phenols or carbonyl enolates and less expensive than the corresponding triflates or nonaflates. Second, aryl tosylates are usually crystalline and more convenient to use because they are more stable towards hydrolysis than are the corresponding triflates. The relatively low activity of tosylates toward oxidative addition as the crucial step in metal-catalyzed coupling reactions can be addressed by the choice of the supporting stabilizing ligands in metal-catalyzed coupling reactions.¹¹ Therefore, a number of synthetically useful protocols for cross-coupling reactions of tosylates and mesylates (Scheme 1b) have been devised during the last decade.^{8,12}

The required organometallic nucleophilic reagents, particularly when being functionalized, are, however, often not commercially available or are relatively cost-intensive. Their preparation from the corresponding (hetero)arenes usually involves a number of synthetic operations, during which undesired byproducts are formed, as are during the traditional cross-coupling reactions themselves. On the contrary, direct

Table 1 Aryl triflates versus aryl tosylates and mesylates: comparison of their fundamental properties

Property	Aryl triflates Ar-OSO ₂ CF ₃	Aryl tosylates/mesylates Ar-OSO ₂ - <i>p</i> -Tol/Me
Reactivity	Very high	Low
Accessibility	Difficult	Easy
Hydrolytic stability	Unstable	Stable
Costs	Expensive	Inexpensive
Common aggregate state	Liquid	Crystalline

arylation reactions through cleavages of C–H bonds¹³ represent an environmentally benign and economically more attractive strategy (Scheme 1c). Importantly, this strategy is not only advantageous with respect to the overall minimization of by-product formation, but also allows for a streamlining of organic syntheses by significantly reducing the number of reaction steps (Scheme 1d).¹⁴

Herein, we summarize catalytic direct arylations by C–H/C–O bond cleavages with challenging fluorine-free phenol derivatives as well as mechanistically related C–H bond alkenylations until summer 2012.¹⁵

Direct arylations

Due to the general importance of bi(hetero)aryl derivatives,² direct arylations of arenes and heteroarenes have attracted significant attention in recent years.

Direct arylations of arenes

Almost all known direct arylations of arenes with arylsulfonates proceed under catalysis with ruthenium.¹⁶ Thus, the first direct arylation reactions through C–H bond activation using aryl tosylates (Scheme 2)¹⁷ has been accomplished employing a first generation ruthenium catalyst derived from an air-stable HASPO (heteroatom-substituted secondary phosphine oxides)¹⁸ bifunctional preligand (Scheme 3).

The highly efficient and chemoselective C–H bond transformations tolerated pronucleophiles with different directing groups, including pyrazole derivatives, and a wide variety of important electrophilic functional groups. The selective formation of either mono- or diarylated products was controlled through the judicious choice of the electrophile. The development of carboxylates as most efficient ligands in ruthenium-catalyzed C–H bond functionalization by our research group set the stage for second generation catalysts¹³ utilizing substoichiometric amounts of carboxylic acids¹⁹ such as MesCO₂H (**8**), which enabled ruthenium-catalyzed direct arylations with organic

Scheme 3 Ligands employed in catalyzed direct arylations of (hetero)arenes with challenging tosylates and mesylates.

Scheme 4 Direct arylations with tosylates **2** using substoichiometric amounts of carboxylic acid MesCO₂H (**8**).

halides and aryl tosylates even in apolar solvents (Scheme 4).¹⁹ With respect to both electrophiles and pronucleophiles, this catalytic system displayed an unparalleled broad scope, which allowed *inter alia* for the use of arenes displaying oxazolines in ruthenium-catalyzed direct arylations with aryl tosylates.

With respect to the step economy, it is important that the corresponding tosylates **2** could also be prepared *in situ*. Thus, phenols were directly employed as proelectrophiles in operationally simple ruthenium-catalyzed formal dehydrative direct arylations, proceeding through chemo- and regioselective functionalizations of C–H and C–OH bonds in a non-sequential fashion. Employing HASPO preligand **4**, direct arylations of simple arenes as pronucleophiles with inexpensive and readily available phenols **9** proved viable (Scheme 5).²⁰ Notably, this user-friendly formal dehydrative arylation was achieved with a highly chemo- and regioselective ruthenium catalyst and allowed for a remarkable improvement of the overall step-economy.

This highly attractive C–H/C–OH bond functionalization strategy was realized even more successfully, when employing well-defined ruthenium(II) carboxylate complex [Ru(O₂CMes)₂(p-cymene)] (**10**)²¹ as the catalyst.

Thereby efficient direct arylations of unactivated C–H bonds with easily available, inexpensive phenols were achieved (Scheme 6).²² The extraordinary chemoselectivity of the ruthenium pre-catalyst **10** set the stage for challenging C–H/C–O bond functionalizations to occur in toluene as well as under solvent-free reaction conditions, and allowed for first direct C–H bond arylations with most user-friendly diaryl sulfates as the electrophiles.

Scheme 2 First generation catalyst for direct arylations with tosylates **2** using preligand **4**.

Scheme 5 Step-economical direct arylations using phenols **9** as proelectrophiles.

Scheme 6 Direct C–H/C–OH bond arylations with well-defined complex **10**.

Moreover, the extraordinary chemoselectivity of well-defined ruthenium complex **10** further enabled direct C–H/C–OH bond arylations to be performed in water as a green solvent (Scheme 7).^{22,23} Notably, the protocol proved to be tolerant of a wide diversity of functional groups, and chemoselectively delivered the monoarylated products not only when employing *ortho*-substituted arenes but, importantly, also with *para*-substituted substrates.

On the basis of our experimental results of mechanistic studies on carboxylate-assisted ruthenium(II)-catalyzed direct alkylations and arylations,^{13c} the working mode for these direct arylations involves initial reversible carboxylate-assisted cycloruthenation (Scheme 8).

Subsequently, the thus formed cyclometalated complex **B**^{13ff–ii} undergoes a formal oxidative addition with the *in situ* formed aryl tosylate. Thereby, a ruthenium-(aryl)(aryl) complex **C** is formed as a precursor for a final reductive elimination, which regenerates the catalytically active ruthenium species and provides the desired product **12**.

Scheme 7 Formal dehydrative arylations with water as a green solvent.

Scheme 8 Mechanistic rationalization for the formal dehydrative C–H/C–OH bond arylation (X = O₂CR, OTs).

Seminal contributions by the research groups of Nakamura and Yoshikai highlighted the power of inexpensive cobalt catalysts for direct C–H bond alkylations.²⁴ Recently, Ackermann and Song reported the first use of inexpensive cobalt catalysts for direct C–H bond arylations and benzylations with phenol-derived organic electrophiles through challenging C–H/C–O bond cleavage (Scheme 9).²⁵

The high catalytic efficacy of the versatile cobalt catalyst set the stage for unprecedented metal-catalyzed direct arylation and benzylation of arenes **13** with easily accessible fluorine-free aryl sulfamates **14**, carbamates, and phosphates. Interestingly, intermolecular competition experiments with differently substituted

Scheme 9 Cobalt-catalyzed direct arylations with aryl sulfamates **14**.

arenes provided strong support for a non-S_EAr-type reaction manifold for this catalytic transformation.

Direct arylations of heteroarenes

In contrast to the direct arylation of aromatic carbocycles, arylations of heterocycles with arylsulfonates proceed mostly under palladium catalysis. Hence, the first direct arylation of azoles **16** through C–H bond functionalization with aryl tosylates **2** as electrophiles was performed with a palladium catalyst derived from Pd(OAc)₂ and the ligand X-Phos (**5**) (Scheme 10).²⁶ This highly active palladium complex enabled a broadly applicable C–H bond functionalization of various heterocycles with aryl tosylates **2**, and also proved to be applicable to the unprecedented direct arylations using mesylates.

The use of 1,2,3-triazoles **18** as the pronucleophiles in the palladium-catalyzed direct arylation using tosylates **2** turned out to be viable with the palladium complex derived from X-Phos (**5**), proceeding with excellent chemo- and site-selectivities through C–H bond functionalizations on the heterocyclic moieties. Monosubstituted 1,2,3-triazoles **18** gave rise to the 1,5-disubstituted compounds **19** as the sole products (Scheme 11).²⁶

According to the generally accepted mechanism of palladium (0)/(II)-catalyzed direct arylations, these functionalizations are proposed to occur through initial oxidative addition of the aryl tosylate, along with subsequent C–H bond metalation and reductive elimination (Scheme 12).

Scheme 10 Palladium-catalyzed direct arylations of heteroarenes.

Scheme 11 Direct arylations of 1,2,3-triazoles **18** using tosylates **2**.

Scheme 12 Proposed mechanism of direct arylations of 1,2,3-triazoles **18** using tosylates **2**.

The significantly lower molecular weights of the corresponding aryl mesylates **21** render processes utilizing these electrophiles more atom-economical than those employing tosylates **2**. However, as a result of the decreased inherent activity of aryl mesylates **21**, metal-catalyzed direct C–H bond arylations with these sulfonates as electrophilic substrates have remained elusive until very recently. Hence, in the presence of substoichiometric amounts of pivalic acid, a catalytic system comprising Pd(OAc)₂ and the ligand X-Phos (**5**) allowed for the efficient functionalization of benzoxazole (**20**) with mesylates **21**, thereby regioselectively yielding heterocycles **22** (Scheme 13).²⁶

Arylation of electron-deficient heteroarenes was considered a particular challenge in C–H-bond activation chemistry.^{13*r–t*,27}

Scheme 13 Direct arylations of benzoxazole (**20**) using mesylates **21**.

Yet, the high catalytic efficacy of the optimized palladium complex was found to enable direct arylations of electron-deficient arenes and heteroarenes with aryl and alkenyl tosylates or mesylates. Under the reaction conditions described above, but applying CsF as the base, direct arylations of pyridine *N*-oxides **23** with both electron-deficient as well as electron-rich aryl tosylates **2** as electrophiles did selectively provide the desired products **24** (Scheme 14).²⁸ Furthermore, intramolecular competition experiments indicated a dependence of the site-selectivity on the kinetic C–H bond acidity. Thus, the 2-arylated products **24** were exclusively formed when employing 3-fluorosubstituted substrate **25**.

Importantly, the optimized palladium catalyst also enabled general direct functionalizations of electron-deficient heteroarene **25** with more atom-economical aryl mesylates **21** (Scheme 15).²⁸ In contrast to the direct arylation of benzoxazole **20**, a wide variety of mesylates, including electron-rich and/or *ortho*-substituted derivatives **21**, furnished the arylated products **26**.

More recently, the use of CM-phos (**7**) in lieu of X-Phos (**5**) as the ligand in palladium-catalyzed direct arylations with aryl mesylates was reported by Kwong *et al.*²⁹ It is particularly noteworthy that the palladium catalyst derived from CM-phos (**7**) smoothly catalyzed direct arylations without the use of cesium fluoride (Scheme 16).

Caffeine, 1-(4-methoxyphenyl)-1,2,3-triazole, and benzothiazole were effectively functionalized to give the desired products

Scheme 14 Direct arylations of electron-deficient *N*-oxides **23** with tosylates **2**.

Scheme 15 Direct arylations of *N*-oxide **25** with aryl mesylates **21**.

Scheme 16 CM-phos (**7**) as the ligand for direct arylations with aryl mesylates **21**.

in moderate to good yields. Specifically, the direct arylation of 1-(4-methoxyphenyl)-1,2,3-triazole with 3,5-dimethylphenyl mesylate occurred in a highly regioselective manner, and only the 5-arylated product was thus obtained.

A catalytic system consisting of Pd(OAc)₂ and bidentate ligand dppe was, on the contrary, found to be the optimal one for the first direct arylations of heteroarenes with moisture-stable aryl imidazolyl sulfonates **20** as electrophiles (Scheme 17).³⁰ This protocol was found not to be restricted to benzoxazoles, but could also be applied to C–H bond functionalizations on oxazoles. Competition experiments between differently substituted benzoxazoles **20** revealed that more electron-deficient heteroarenes reacted preferentially, and indicated the following series in the order of decreasing reactivity of electrophiles: ArOSO₂Im > ArBr > ArCl.

Notably, this catalytic system proved to be applicable to unprecedented C–H bond functionalizations with easily accessible alkenyl as well as benzyl phosphates, thus allowing for direct benzylations and alkenylations as well (see below).^{30,31}

Recently, elegant nickel-catalyzed C–H bond arylations of azoles with phenol derivatives were developed by Itami and coworkers.^{8c}

The catalytic system based on Ni(cod)₂ and the ligand dcype [dcype = Cy₂P(CH₂)₂PCy₂] was found to be active for the

Scheme 17 Direct arylations with imidazolylsulfonates **27**.

Scheme 18 Nickel-catalyzed coupling of azoles **20** and **29** with phenol-derived electrophiles.

coupling of various phenol derivatives, such as esters, carbonates, sulfamates, triflates, tosylates, and mesylates (Scheme 18). Using the C–H/C–O biaryl coupling, a series of privileged 2-arylazoles **31**, including biologically active alkaloids, were step-economically accessed. Moreover, the power of the optimized catalytic system was illustrated by directly functionalizing estrone and quinine.

Contrarily, Song and Ackermann recently disclosed inexpensive cobalt catalysts for direct C–H bond arylations of heteroarenes through C–H/C–O bond cleavages. Thus, the inexpensive catalyst was not limited to arylations of arenes (*vide supra*), but also allowed for cobalt-catalyzed C–H bond arylations of heteroarenes with readily accessible aryl sulfamates **14**. Indeed, mono-*N*-substituted indoles **32** were selectively arylated at the C2 position (Scheme 19).²⁵

This allowed for the synthesis of among others sterically encumbered heterobiaryls, a feature that should prove instrumental for future applications to asymmetric C–H bond arylations.

Scheme 19 Cobalt-catalyzed direct arylations of indoles **32** with aryl sulfamates **14**.

Direct alkenylations

The catalytic system consisting of $\text{Pd}(\text{OAc})_2$ and the ligand dppe (*vide supra*) was also found to be suitable for direct C–H bond alkenylation reactions of benzoxazoles **20**.³⁰

Indeed, readily available and moisture-stable phosphates **34** turned out to be alkenylation reagents of choice. Thereby, various alkenylated products could be obtained in good yields and with excellent chemoselectivities (Scheme 20).³⁰

Moreover, Hirano, Miura and co-workers discovered efficient copper-catalyzed allenylations of oligofluoroarenes **36** with propargyl phosphates **37** for the synthesis of highly fluorinated arylallenes **38** (Scheme 21).³¹ While smaller primary alkyl groups *R* gave satisfactory γ -selectivities, the use of bulky *tert*-butyl-substituted propargyl phosphate resulted in the α -substituted allene as the major isomer.

Under ruthenium catalysis, arenes **1** bearing different directing groups were site-selectively alkenylated with alkenyl acetates and butyrates **39** to give π -conjugated aromatic compounds **40** (Scheme 22), as reported by Kakiuchi and co-workers.³²

These ruthenium-catalyzed direct C–H bond alkenylation reactions proceeded under ligand- and base-free reaction conditions.

Scheme 20 Direct alkenylation with phosphates **34**.

Scheme 21 Copper-catalyzed coupling of polyfluoroarenes with propargyl phosphates **37**.

Scheme 22 Ruthenium-catalyzed direct alkenylation with alkenyl acetates and butyrates **39**.

Conclusions

Recent years have witnessed a tremendous development in catalytic C–H bond functionalizations. Thus, challenging C–H/C–O have proven to be viable with ruthenium(II) biscarboxylate complexes as well as with palladium catalyst derived from electron-rich phosphine ligands. Furthermore, inexpensive nickel and cobalt complexes were very recently discovered as highly efficient catalysts for direct arylations with easily accessible phenol derivatives as arylating agents.

While direct C–H bond arylations with *inter alia* sodium arylsulfonates,^{33a} aryltrimethoxysilanes^{33b} or arylsulfonyl hydrazides^{33c} were recently reported, fluorine-free sulfonates, such as aryl tosylates and mesylates, are undoubtedly among the most synthetically useful reagents for direct arylations. Thus, it does not come as a surprise that applications of these easily accessible, moisture-stable and inexpensive electrophiles were devised in the recent years (Fig. 1). Given the user-friendly

nature of readily available, inexpensive phenol derivatives, the use of challenging aryl tosylates and mesylates in the direct arylation reactions could open a new horizon for future C–H bond transformations. Considering the practical importance of atom- and step-economical C–H bond catalytic arylations for natural product synthesis,³⁴ drug discovery and crop protection, further progress is expected in this rapidly developed research area.

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