Arene Functionalization

DOI: 10.1002/anie.201001028

A Synthetic Double Punch: Suzuki–Miyaura Cross-Coupling Mates with C–H Functionalization

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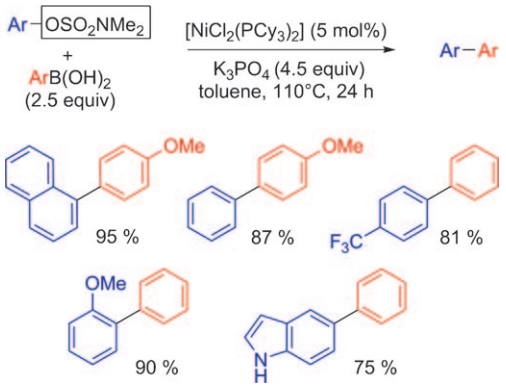
arenes · C–O activation · cross-coupling · directed *ortho*-metalation · domino reactions

In memory of Keith Fagnou

Over the past years, transition-metal-catalyzed cross-coupling reactions have matured to an impressive level of generality and complexity. Coupling reactions between virtually all possible combinations of sp-, sp^2-, and sp^3-hybridized organometallic nucleophiles and electrophilic organohalides have been realized, and in some cases have entered into industrial practice.[1] Among the various transition-metal-catalyzed cross-coupling reactions known today, the Suzuki–Miyaura coupling is characterized by mild reaction conditions, an exceptionally broad functional group tolerance, and the use of nontoxic organoboron nucleophiles.[2] Most of the research has been directed at the nature of the nucleophile (e.g. boronic acids, boronates, and trifluoroborates), while most studies employed organohalides (I, Br, Cl) as electrophilic partners. On the other hand, arene compounds with oxygen-based leaving groups represent a conceptually different class of coupling partners. They are derivatives of widely available and cheap phenols and render the overall cross-coupling a more environmentally friendly, halide-free process. Mostly aryl sulfonates (triflates, tosylates) have been used, while only a few examples of Suzuki–Miyaura reactions with aryl methylethers[3] and carboxylates[4] have been reported. Now, the research groups of Garg, Snieckus, and Shi put forth effective protocols for nickel-catalyzed Suzuki–Miyaura cross-coupling reactions with aryl (and alkenyl) *O*-carbamates,[5] which are otherwise rather stable under various reaction conditions.

Garg et al. demonstrated the competence of aryl *O*-carbamates, as well as carbonates, and sulfamates as electrophiles in the coupling with aryl boronic acids with 5–10 mol% of $[NiCl_2(PCy_3)_2]$, and 4.5–7.2 equivalents of K_3PO_4 as base in toluene at 110–130 °C (Scheme 1).[5a] Although the reactivity of aryl carbonates and carbamates were sensitive to the electronic properties, aryl sulfamates with electron-withdrawing, electron-donating, and *ortho*-substituents afforded very good yields. Snieckus et al. reported similar conditions to also bring about cross-coupling of various aryl *O*-carbamates with aryl boronic acids at 150 °C, but satisfactory yields were only

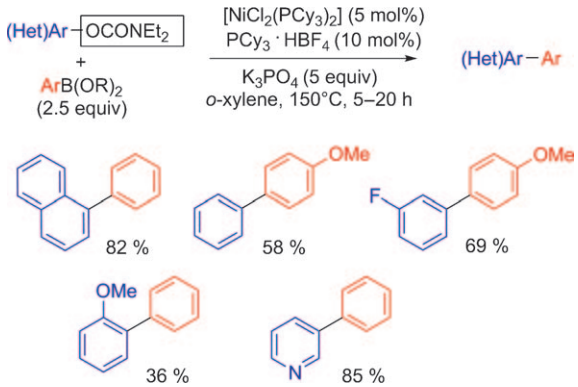


Scheme 1. Nickel-catalyzed cross-coupling of aryl *O*-sulfamates according to Garg et al.[5a] Cy = cyclohexyl.

afforded with aryl carbamates bearing electron-withdrawing substituents (Scheme 2).[5b] The nickel precatalyst used in both protocols is commercially available and exhibits high stability towards air and water.

Interestingly, Snieckus et al. observed an inhibition of the catalytic performance in the presence of palladium chloride. The *O*-carbamate moiety is even stable toward palladium-catalyzed Suzuki and Negishi cross-coupling reactions, thus providing the opportunity for chemoselective arene manipulations.[6]

In a related study, Shi et al. disclosed a practical method for the nickel-catalyzed Suzuki–Miyaura coupling of unac-



Scheme 2. Nickel-catalyzed cross-coupling of aryl *O*-carbamates according to Snieckus et al.[5b] Het = hetero.

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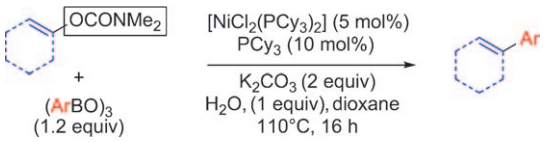
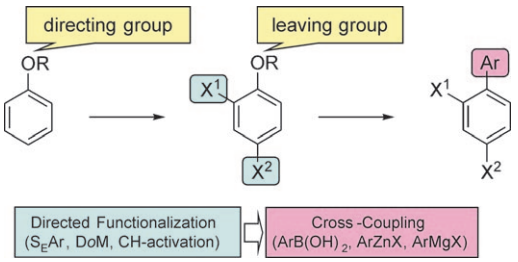
tivated alkenyl carbamates or aryl carbamates with aryl boroxines that requires lower temperatures and less base (110 °C and 2 equiv of K_2CO_3; Scheme 3).[5c] The reaction



Scheme 3. Nickel-catalyzed cross-coupling of aryl and alkenyl *O*-carbamates according to Shi et al.[5c]

conditions bring about the conversion of diverse substrate combinations; including cyclic and acyclic alkenyl carbamates, aryl carbamates, and aryl boroxines with electron-donating or electron-withdrawing substitutents.

With the use of phenol derivatives, the electron-donating character of the oxygen substituent can be exploited for the directed installation of functionality in *ortho*- and *para*-positions prior to cross-coupling (Scheme 4): 1) by electro-

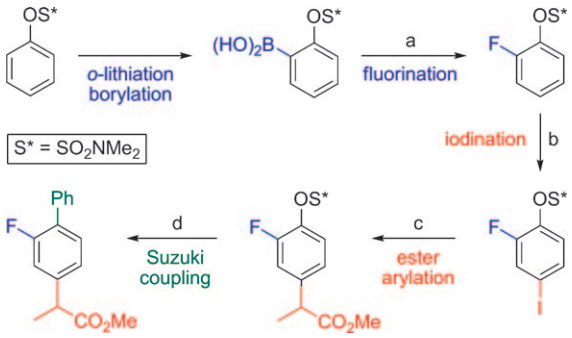


Scheme 4. The dual role of oxygen-based substituents as directing and leaving groups in the synthesis of multisubstituted arene derivatives.

philic aromatic substitution (S_EAr; mostly at the *para*-position) or 2) by metal-mediated C–H functionalization (Friedel–Crafts-type reaction or directed *ortho*-metalation, D*o*M). The D*o*M strategy was pioneered by Snieckus and operates under extremely mild reaction conditions with perfect regiocontrol.[7] In light of their potential to garnish ubiquitously available phenol derivatives with at least two vicinal substituents, sequential combinations of directed *ortho*-metalation–functionalization and *ipso*-cross-coupling reactions bode especially well for the synthesis of polyfunctionalized aromatic derivatives.[8] Such endeavors have now been fueled by the publications on nickel-catalyzed Suzuki–Miyaura coupling reactions with phenol derivatives.

The dual role of substituents as directing and leaving group has been strikingly demonstrated by Garg et al. with the synthesis of the anti-inflammatory drug flurbiprofen, which possesses a triple-functionalized benzene unit.[5a] The initially installed sulfamate moiety directs the lithiation and iodination and is stable toward borylation, fluorination, and nickel-catalyzed ester arylation. The final cross-coupling event with phenylboronic acid consumes the sulfamate and gives flurbiprofen as its methyl ester (Scheme 5).

The above publications on oxygen-based electrophiles in cross-coupling reactions in combination with powerful direct-



Scheme 5. Synthesis of flurbiprofen by Garg et al.: a) AgOTf, Selectfluor (70%); b) I_2, AgOTf (64%); c) $MeCHClCO_2Me$, $[NiBr_2(bipy)]$, Mn, TFA, 50 °C (70%); d) $PhB(OH)_2$, $[NiCl_2(PCy_3)_2]$, K_3PO_4, 130 °C (84%). bipy = 2,2′-bipyridyl, TFA = trifluoroacetic acid.

ed C–H functionalization strategies have certainly broken new grounds for the efficient derivatization of arenes. Aryl carboxylates are another attractive class of substrates that already has diverse application in directed metalation and cross-coupling chemistry.[9] Furthermore, it is likely that aniline derivatives (anilides, ureas) will be the next group of compounds to be exploited in this way. Their ability to act as powerful directing groups in electrophilic aromatic substitution and *ortho*-metalation reactions is already at an advanced stage—directed palladium-catalyzed C–H activation reactions of anilides[10] and *N*-phenylureas[11] proceed with excellent efficiency.

The interplay of orthogonal C–H functionalization and cross-coupling methods constitutes an especially attractive strategy for the construction of polyfunctional aromatic molecules.[12] Reaction sequences with extended substrate scopes and more efficient catalysts and milder reaction conditions will undoubtedly make these methods an indispensable part of sustainable syntheses.

Received: February 18, 2010
Published online: April 13, 2010

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