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C−O Activation

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C(aryl)−O Activation of Aryl Carboxylates in Nickel-Catalyzed Biaryl Syntheses

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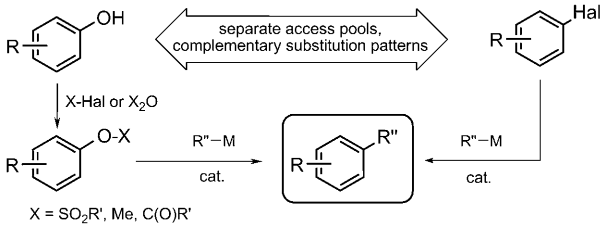
aryl carboxylates · biaryls · cross-coupling · homogeneous catalysis · nickel

Catalytic cross-coupling reactions have become indispensable tools for C−C bond formation[1] owing to their efficiency and broad applicability. Among the many known reactions of this type, Suzuki couplings are particularly popular because they tolerate a multitude of functional groups.[2] In such reactions, boronic acids, which are of low toxicity and easy to handle and store, are the most commonly used carbon nucleophiles. Among the electrophilic coupling partners, aryl halides predominate. Over the last years, the efficiency of the catalyst systems has increased to the extent that besides aryl bromides and iodides, even the substantially less reactive aryl chlorides can now be converted in high yields.[3] Although this has considerably extended the pool of available electrophiles, certain substitution patterns remain hard to access since aryl chlorides, bromides, and iodides are usually generated along the same synthetic pathways, so that their availability is often limited by the same parameters.

By contrast, phenol derivatives often originate from totally different precursors and therefore represent an invaluable extension of the spectrum of carbon electrophiles (Scheme 1).[4] In order to allow the insertion of a transition-metal catalyst into the C(aryl)−O bond, phenols are usually converted into aryl sulfonates, enabling the cross-coupling of the aryl moiety. In this context, aryl triflates, being the most reactive but also the most expensive derivatives, can be as broadly employed as aryl bromides.[5] Moreover, a series of efficient cross-coupling protocols have been reported also for the conversion of the cheaper mesylates and tosylates.[6]

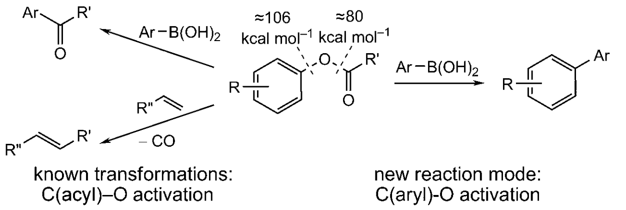


Scheme 1. Phenol derivatives as alternative carbon electrophiles in cross-coupling reactions.

Wenkert et al. showed as early as 1979 that even less reactive phenol derivatives can serve as carbon electrophiles in metal-catalyzed cross-coupling reactions with the development of a nickel-catalyzed coupling of aryl methyl ethers with organomagnesium compounds, in which alkoxides serve as leaving groups.[7] By using tricyclohexylphosphine as the ligand, Dankwardt succeeded in broadening the scope of this reaction, although it still remained limited to relatively few derivatives.[8] Shortly thereafter, Tobisu et al. disclosed the cross-coupling of some aryl methyl ethers with boronic acid derivatives employing a similar catalytic system.[9]

In light of these results, it is surprising at first glance that aryl carboxylates, which are more reactive than aryl alkyl ethers, have not yet been put to use as substrates in transition-metal-catalyzed cross-coupling reactions, especially considering that allyl carboxylates are widely used as starting materials in allylic substitutions.[10] They are easily accessible from phenols and carboxylic anhydrides or chlorides, and would thus be highly advantageous alternatives to aryl sulfonates and aryl alkyl ethers from both economical and ecological standpoints.

The magnitude of the challenge of achieving this oxidative addition becomes apparent when considering that for most phenyl acetate derivatives, the C(acyl)−O bond is substantially weaker than the C(aryl)−O bond (Scheme 2).[11] Therefore, the formation of acyl species is preferred in the reaction of low-valent metal complexes. This reaction mode is exploited in some catalytic transformations, for example, in the palladium-catalyzed coupling of phenyl trifluoroacetates with aryl halides to give trifluoromethyl ketones,[12] and in the



Scheme 2. Known and newly discovered reaction modes of aryl carboxylates.

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decarbonylative Heck reaction of aromatic carboxylic acid derivatives.[13]

A few months ago, two groups achieved a possible breakthrough nearly simultaneously in the activation of the C(aryl)−O bond of phenol derivatives, thus adding another reaction mode to the rich chemistry of carboxylic acids in catalysis.[14] Garg et al. showed that a series of aryl pivalates can be coupled with arylboronic acids to form unsymmetrical biaryls.[15] The Shi group achieved such cross-couplings by way of C(aryl)−O activation using aryl esters of different carboxylic acids.[11] They obtained the best results with aryl boroxines, again in combination with aryl pivalates.

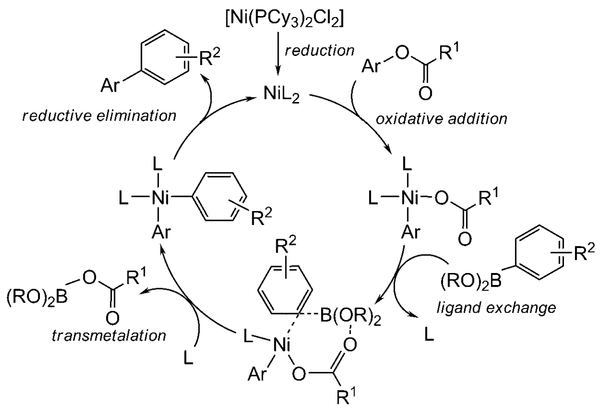
Both groups used commercially available $[Ni(PCy_3)_2Cl_2]$ (Cy = cyclohexyl) as the precatalyst and K_3PO_4 as the base. This surprisingly simple catalyst system is not only cheap but also easy to handle, an essential advantage over in situ generated systems of low-valent Ni^0 species. No other transition metal tested was able to activate the C(aryl)−O bond in this manner. The choice of tricyclohexylphosphine as the ligand proved to be essential as well; other phosphine ligands did not give even remotely comparable results. The proposed mechanism of this transformation is illustrated in Scheme 3. It consists of the oxidative addition of the aryl ester to a Ni^0 species, followed by a transmetalation step for which Shi et al. postulated an unusual intermediate,[16] and finally the reductive elimination of the product.

The two research groups chose naphthol derivatives as especially active test substrates for their initial experiments—1-naphthyl pivalate in the case of Garg and 2-naphthyl acetate in the case of Shi. The high reactivity of condensed arenes had already been noted in the context of the activation of the aryl methyl ethers. It can be explained based on the hypothesis that the oxidative insertion into the C−O bond gives rise to an intermediate in which the aromaticity of the arene is lost, such as a η^2-arene complex or a kind of Meisenheimer complex.[9] Either way, the complexation of naphthalene derivatives would be easier than that of benzene derivatives because the aromaticity of the substrate would not be completely sacrificed.

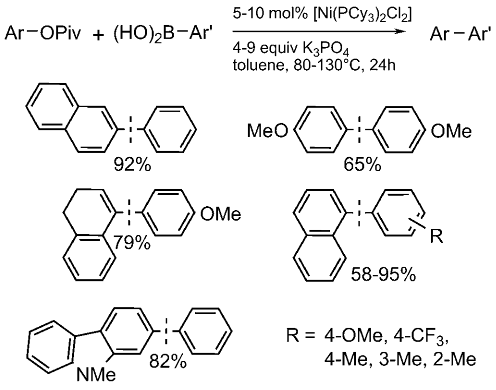
Simarly to related couplings of organoboron compounds, the control of the hydrolysis equilibrium between free boronic acid and the substantially less reactive boroxine played a major role in the development of this reaction.[17] Commercially available boronic acids often contain large amounts of the cyclic anhydrides and the condensation of the boronic acids continues in solution, thus making it hard to control the amount of boronic acid and water in the reaction. The two groups employed different strategies to perform the coupling of moisture-sensitive aryl carboxylates in good yields despite the described correlation. Garg et al. used unmodified boronic acids as carbon nucleophiles and performed the reaction in the nonpolar solvent toluene without controlling the water content of the system. Instead, they deliberately chose the sterically hindered aryl pivalates as carbon electrophiles which would undergo hydrolytic decomposition to a lesser extent. Because the aryl boroxines proved to be unreactive under these conditions, the boronic acid component was used in excess.

The optimized protocol can be applied to an appreciable number of variously substituted naphthyl, phenyl, and vinyl pivalates in combination with a series of boronic acids. Selected examples are shown in Scheme 4. The pivalates are all rather electron-rich, whereas both electron-rich and electron-poor boronic acid derivatives were successfully converted. Higher temperatures are required for the conversion of electron-deficient boronic acids, which suggests that—in contrast to the analogous reaction of aryl methyl ethers—the insertion into the C(aryl)−O bond is not the rate-determining step here.[9] Even though not many functional groups appear to be tolerated, it is notable that aryl methyl ethers remain unchanged under the reaction conditions.

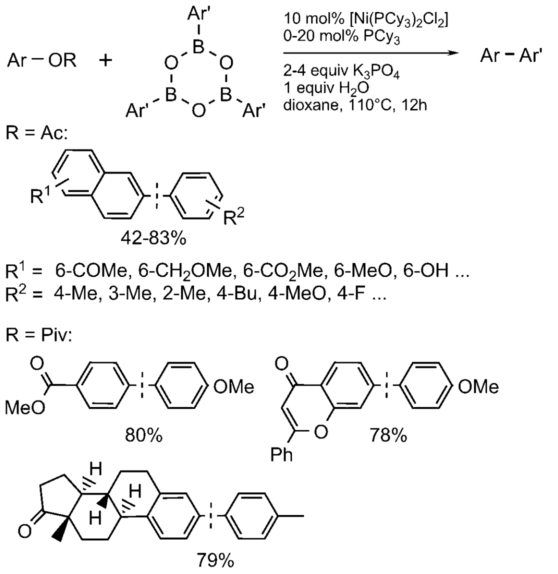
Shi et al. suppressed the hydrolysis of the phenyl esters by employing preformed aryl boroxines instead of boronic acids while adding defined amounts of water to the dioxane solvent.[18] One equivalent relative to the ester proved to be the optimum. Under these controlled conditions, a number of aryl esters, including 2-naphthyl acetate, benzoate, and pivalate, were successfully coupled with triphenyl boroxine. Good yields were also achieved in the conversion of diversely functionalized 2-naphthyl acetates, which seems to imply that the transformation is limited more by the electronic properties of the aryl electrophile than by the presence of functional groups (Scheme 5). After conversion into their pivalates, an even larger variety of phenols can be converted, among them even the electron-poor 4-acetyl phenol. This is a remarkable



Scheme 3. Mechanism of the new biaryl synthesis according to Shi et al.



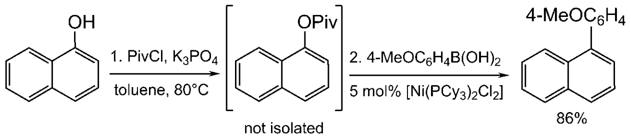
Scheme 4. Cross-coupling of aryl pivalates with arylboronic acids according to Garg et al. The aryl residues originating from the boronic acids are placed on the right-hand side of the structures.



Scheme 5. Cross-coupling of aryl carboxylates with aryl boroxines according to Shi et al. The aryl residues originating from the boronic acids are placed on the right-hand side of the structures.

example because electron-withdrawing substituents increase the acidity of the phenol and thus further assist the competing insertion into the C(acyl)–O bond.

In follow-up experiments, Garg et al. were able to show that the esterification of the phenols with pivalyl chloride and their catalytic cross-coupling can be combined into a one-pot procedure (Scheme 6). This underlines the practicality of the new process and its attractiveness for synthetic applications.



Scheme 6. One-pot procedure for the esterification and cross-coupling of phenol derivatives.

In conclusion, these first publications raise expectations that the cross-coupling of aryl carboxylates by C(aryl)–O activation will become a serious alternative to the analogous transformation of aryl sulfonates and aryl halides. With the results provided by their follow-up study on the cross-coupling of zinc compounds, Shi et al. demonstrate that this reaction type is not limited to boronic acids. Crucial for a broad application of this new methodology would be for future catalyst systems to succeed in minimizing the dependence of both coupling partners on steric and electronic factors, as well as in enhancing the functional group tolerance.

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