NH$_3$ and KOH Couplings

DOI: 10.1002/anie.200605071

Palladium-Catalyzed Coupling of Ammonia and Hydroxide with Aryl Halides: The Direct Synthesis of Primary Anilines and Phenols

Michael C. Willis*

Keywords:
amination · arenes · etherification · homogeneous catalysis · palladium

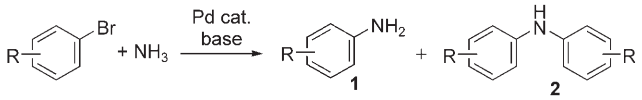
The last decade has seen the palladium-catalyzed C−N and C−O bond-forming cross-coupling reactions of aryl halides emerge as tremendously powerful synthetic tools.[1] Both processes have reached a level of sophistication that allows a wide range of coupling partners to be combined efficiently. For example, amination reactions employing nucleophiles as diverse as primary and secondary amines, amides, carbamates, anilines, azoles, ureas, and hydrazones are all known. Although more limited in scope, etherification reactions incorporating primary, secondary, and tertiary alcohols, phenols, and silanols have all been described. Both processes are effective with a number of different arene components, and couplings to traditionally challenging aryl chloride substrates are now commonplace. The advances in catalyst design that have allowed reactions of such broad scope to be realized have also been responsible for the low catalyst loadings and mild reaction conditions that can be achieved. Despite the increasing complexity of the molecules that can be fashioned using these methods, it is the use of what are conceptually the simplest N- and O-based nucleophilic coupling partners—ammonia and water—that has remained a significant challenge.

Ammonia is one of the basic feedstocks of chemistry, and its low cost and wide availability make it an extremely attractive source of nitrogen for synthesis.[2] The use of ammonia as a coupling partner in palladium-catalyzed amination reactions would allow the direct synthesis of valuable primary anilines from simple aryl halide substrates. The considerable appeal of this transformation has resulted in the development of many coupling partners that are the synthetic equivalent of ammonia; allyl,[3] benzyl,[1] and silyl amines,[4] imines,[5] and amides[1] have all been employed for this purpose. Despite the success of these systems, the need to incorporate a deprotection step in the overall transformation, and in some cases the high cost of the reagent, detracts from their utility.

Using ammonia directly in these reactions is complicated by several issues: ammonia is an excellent ligand for many metals and will often bind to the metal in preference to the ligands needed to form active catalyst systems; the stability of amido–metal complexes also makes the key reductive elimination, leading to C−N bond formation, a difficult process; and, finally, if a successful amination with ammonia could be achieved, the product of the reaction, a primary amine such as **1**, is very likely to be an excellent coupling partner itself, leading to the formation of di- and triaryl amines (Scheme 1).[6]

The use of water as a nucleophile in palladium-catalyzed etherification reactions is attractive in the same way as the ammonia chemistry and would lead to the direct preparation of phenols from aryl halides. The difficulties of realizing such a reaction mirror those of the ammonia-based transformation, with the formation of diaryl ethers posing a significant problem. Indirect methods of achieving this conversion, employing tertiary alcohols and silanols as the coupling partners, have been reported.[7] The groups of Hartwig and Buchwald have recently shown the considerable challenges in using ammonia and water as coupling partners can be overcome by ligand design.

The Hartwig group has shown that selective coupling reactions between aryl halides and ammonia can be achieved if catalysts incorporating the bulky ferrocene-based ligand **A** are employed (Scheme 2).[8] For example, the reaction between unhindered aryl bromide **3** and ammonia (80 psi) at 90 °C using 1 mol % of [**A**PdCl$_2$] and the strong base NaO*t*-Bu delivered aniline **4** in 86 % yield. Importantly, only a few percent of the diaryl amine was observed (17:1 ratio of mono-/dicoupled material). The second example in Scheme 2 shows that the process is also able to tolerate signifi-



Scheme 1. Formation of the desired aniline **1** and the unwanted diarylated product **2**.

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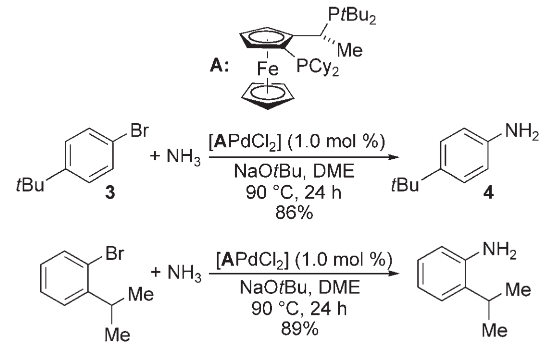
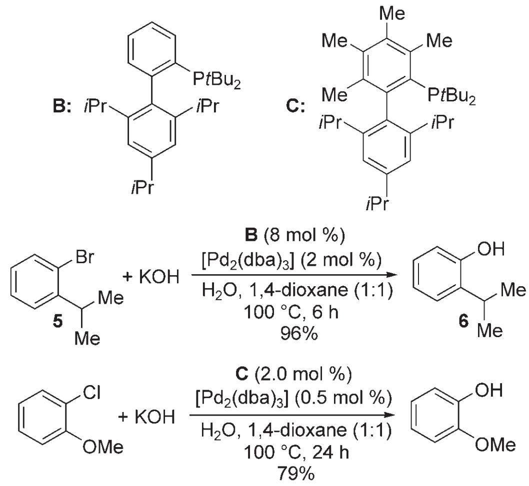
[*] Dr. M. C. Willis
Department of Chemistry
University of Oxford
Chemical Research Laboratory
Mansfield Road, Oxford, OX1 3TA (UK)
Fax: (+44) 1865-285-002
E-mail: michael.willis@chem.ox.ac.uk



Scheme 2. Successful ammonia monoarylation reactions. Cy = cyclohexyl, DME = dimethoxyethane.



Scheme 3. Successful hydroxide monoarylation reactions. dba = *trans,trans*-dibenzylideneacetone.

cantly hindered aryl bromide substrates. The authors also established that aryl chlorides and iodides are good coupling partners for the reaction.

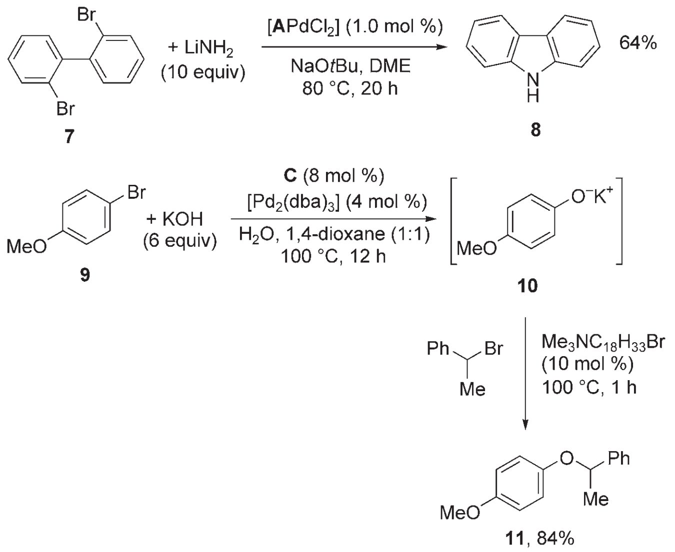
As the use of gaseous ammonia may not be practical in all settings, the authors have shown that solid lithium amide can also be conveniently used in these coupling reactions. The selectivity for mono- over diarylation was sometimes lower in these modified reactions but still synthetically useful, 8:1 to >50:1, with the more hindered aryl halide substrates being most selective. The major factor in the success of these reactions is the hindered, tightly bound chelated intermediates generated from the use of the sterically demanding diphosphine ligand.

The Buchwald group has developed a series of bulky electron-rich monophosphines that generate efficient catalysts for the coupling reactions between aryl halides and phenols.[9] They have very recently shown that these ligands are effective for the coupling of potassium hydroxide with aryl halides.[10] For example, the use of a catalyst featuring the sterically demanding biphenyl ligand **B** allowed the conversion of aryl bromide **5** to phenol **6** in 96% yield after 6 h (Scheme 3). The reactions were conducted in 1:1 water/dioxane at 100 °C. As the second example in Scheme 3 illustrates, the process was amenable to aryl chloride substrates. The latter example featured the bulkier ligand **C**, which was found to generate more stable catalysts and thus allow lower catalyst loadings. The reductive-elimination step of the mechanism, responsible for C–O bond formation, was identified as the key step of the process. By matching the ligand, either **B** or **C**, with the substrate under investigation, the authors were able to effectively convert a wide range of aryl bromides and chlorides to their corresponding phenol derivatives.

Although the ability to halt both the ammonia and hydroxide coupling reactions at the monoarylation stage was one of the chief difficulties to be overcome, the capacity to utilize these monoarylation products directly in controlled and synthetically useful second transformations presents many exciting possibilities for reaction development. Both groups have already seized this opportunity. The Hartwig group has demonstrated that the use of dibromobiphenyl substrate **7** allows the direct formation of carbazole **8** in 64% yield by way of a tandem amination process (Scheme 4).

The Buchwald group has developed a tandem process based on an initial hydroxide coupling, followed by the alkylation with an alkyl halide. In the overall transformation an aryl halide is converted to an alkyl aryl ether. For example, reaction of aryl halide **9** with potassium hydroxide leads to phenoxide intermediate **10**. Introduction of a secondary alkyl halide in combination with the phase-transfer catalyst cetyltrimethylammonium bromide, then provides alkyl aryl ether **11** in an overall yield of 84%. This new approach to alkyl aryl ether synthesis avoids the problem of unwanted β-hydride elimination often encountered with secondary alcohols in palladium-catalyzed etherification reactions of aryl halides. A second cascade sequence based on an initial hydroxide coupling was also developed. Coupling of potassium hydroxide with (2-chloroaryl)alkynes delivered phenol intermediates that cyclized under the reaction conditions to generate benzofuran products.

These recent developments by the Hartwig and Buchwald groups have provided solutions to two of the longest standing challenges in palladium-catalyzed heteroatom-coupling processes. Besides providing the direct methods to achieve these conceptually simple transformations, both groups have also demonstrated the potential utility of these new reactions in the construction of reaction cascades. The success of both processes stems from the use of ligand systems designed to address specific mechanistic issues identified to be reactivity limiting. Although palladium-cat-



Scheme 4. N- and O-based cascade processes.

alyzed C–S bond-forming reactions of aryl halides are less developed than the corresponding C–N and C–O variants, recent efforts in this area have seen considerable progress,[11] and indirect methods to achieve the transformation equivalent to hydrogen sulfide couplings have appeared.[12] Is a direct coupling of H_2S on the way?

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