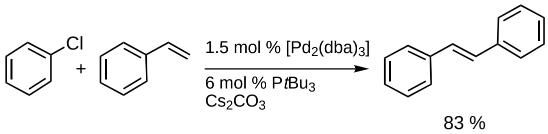
Take the Right Catalyst: Palladium-Catalyzed C−C, C−N, and C−O Bond Formation on Chloroarenes

Rainer Stürmer*

Chlorinated arenes are cheap to manufacture and therefore play a vital role as intermediates in the chemical industry. However, in contrast to their—much more expensive—brominated and iodinated counterparts, chloroarenes are quite unreactive in subsequent reactions. Classical functionalizations of the C−Cl bond in nonactivated arenes usually require harsh conditions, and side reactions may produce environmentally hazardous oxygenated chloroarenes. This leads to considerable problems in using these compounds as intermediates in the synthesis of more highly functionalized biologically active molecules, such as agrochemicals and pharmaceuticals.

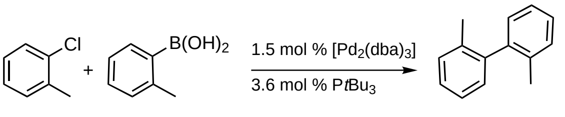
Due to recent developments in catalysis, former problems might be overcome: The groups of S. L. Buchwald, G. C. Fu, J. F. Hartwig, and others reported significant improvements in C−C, C−N, and C−O bond formation on chloroarenes. For all of these bond formations the right choice of catalyst is crucial for success. In other words: By ligand tuning, all three bond forming reactions can be realized through palladium catalysis. The following account focuses on recent work, since the subject has been already reviewed.[1]

Heck- and Suzuki-type couplings have been described by Fu et al.[2] The reaction of chlorobenzene and styrene in refluxing dioxane in the presence of $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) and the electron-rich, sterically hindered tri-*tert*-butylphosphane gives rise to *trans*-stilbene in 83% yield [Eq. (a)]. Besides the choice of the ligand—aryl phosphanes, tri-*n*-butylphosphane, and tricyclohexylphosphane show no conversion—the base is also crucial for success. Cesium carbonate gives the best results, although the cheaper potassium phosphate gives comparable yields. Under the same conditions the sterically more demanding 2-chlorotoluene is coupled in 70% yield. However, longer reaction times are necessary. Acceptor as well as donor substituents are tolerated under these conditions.



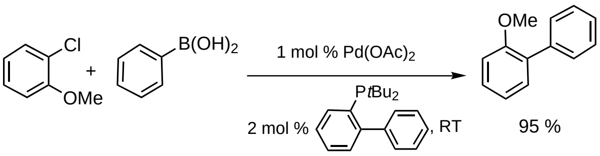
(a)

Tri-*tert*-butylphosphane is the ligand of choice in Suzuki couplings[3] as well: 2-Chlorotoluene reacts with 2-methylphenylboronic acid to provide 2,2′-disubstituted biphenyl in 87% yield [Eq. (b)]. Another contribution from Fu et al.[4] describes the Stille coupling of chloroarenes in which vinyl, allyl, phenyl, and even alkyl groups can be transferred in the presence of cesium fluoride.



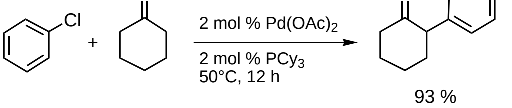
(b)

An improved variation of Suzuki couplings was recently described by Buchwald et al.[5] By use of 2-(di-*tert*-butylphosphanyl)biphenyl as ligand, palladium acetate and potassium carbonate facilitate couplings at room temperature [Eq. (c)]. Catalyst concentrations may be kept quite low (0.02 – 0.05 mol%).



(c)

In a similar context Hartwig et al.[6] published a screening method based on a fluorescence assay aimed at the rapid identification of efficient ligands in Heck-type couplings. Arylations of ketones and malonates with aryl chlorides [Eq. (d)] have been recently published by the same group.[7] Electron-rich phosphanes are used to secure good conversions.



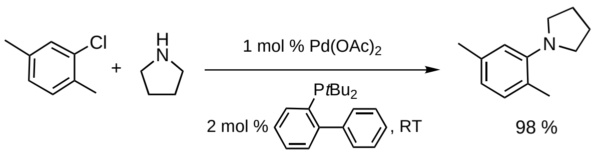
(d)

2-(Di-*tert*-butylphosphanyl)biphenyl has been used by Buchwald et al.[5] as the most efficient ligand in the palladium-catalyzed amination of aryl chlorides. 2-Chloro-4-

---

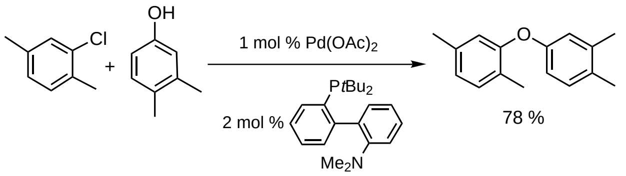
[*] Dr. R. Stürmer
BASF AG, Hauptlaboratorium, ZHF/D, A30
67056 Ludwigshafen (Germany)
Fax: (+49) 621-60-20440
E-mail: rainer.stuermer@basf-ag.de

methyltoluene can be aminated with pyrrolidine in 98 % yield using sodium *tert*-butoxide [Eq. (e)]. These reactions went to completion at room temperature within 15–20 h; donor and acceptor substituents are tolerated.

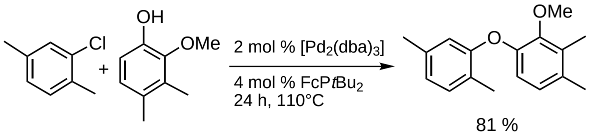


(e)

Palladium-catalyzed C$-$O bond forming reactions were performed by Buchwald et al.[8] with 2-dimethylamino-2′-di-(*tert*-butylphosphanyl)biphenyl as ligand. 3,4-Dimethylphenol can be arylated smoothly with 2-chloro-4-methyltoluene in the presence of sodium hydride [Eq. (f)]. Hartwig et al.[9] developed a novel ferrocene-based dialkylphosphane ligand for this arylation: 2-Methoxy-3,4-dimethylphenol is arylated with 2-chloro-*p*-xylene in 81 % yield [Eq. (g)].



(f)



(g)

For quite a long time chloroarenes were considered as too unreactive for catalysis. However, significant improvements in various coupling reactions of chloroarenes by the use of electron-rich phosphanes have rendered this statement as no longer valid. The use of these cheap intermediates as coupling partners in the synthesis of more highly functionalized molecules of industrial relevance is now within reach. Since some of these ligands are commercially available already, it is probably only a question of time until we see the first industrial applications of these improved procedures.

Recent work from Lipshutz et al.[10] even shows the replacement of the rather expensive palladium with nickel, at least in C$-$C bond formations. Chloroarenes are coupled with organozink compounds under nickel(0) catalysis.[11]

German version: *Angew. Chem.* **1999**, *111*, 3509–3510

Keywords: aminations · cross-coupling · homogeneous catalysis · palladium

---

[1] a) M. Beller, T. H. Riermeier in *Transition Metals for Organic Synthesis, Vol. 1* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, pp. 184–193; M. Beller, T. H. Riermeier, G. Stark in *Transition Metals for Organic Synthesis, Vol. 1* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, pp. 208–236; b) J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2154–2177; *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; c) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125–146.

[2] A. F. Littke, G. C. Fu, *J. Org. Chem.* **1999**, *64*, 10–11.

[3] A. F. Littke, G. C. Fu, *Angew. Chem.* **1998**, *110*, 3586–3587; *Angew. Chem. Int. Ed.* **1998**, *37*, 3387–3388.

[4] A. F. Littke, G. C. Fu, *Angew. Chem.* **1999**, *111*, 2568–2570; *Angew. Chem. Int. Ed.* **1999**, *38*, 2411–2413

[5] a) J. P. Wolfe, S. L. Buchwald, *Angew. Chem.* **1999**, *111*, 2570–2573; *Angew. Chem. Int. Ed.* **1999**, *38*, 2413–2416; b) R. A. Singer, S. L. Buchwald, *Tetrahedron Lett.* **1999**, *40*, 1095–1098.

[6] K. H. Shaugnessy, P. Kim, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 2123–2132.

[7] M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478.

[8] A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378.

[9] G. Mann, C. Incarvito, A. L. Rheingold, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225.

[10] B. H. Lipshutz, P. A. Blomgren, *J. Am. Chem. Soc.* **1999**, *121*, 5819–5820.

[11] Note added in proof (received October 6, 1999): Nolan et al. (C. Zhang, J. Huang, M. L. Trudell, S. P. Nolan, *J. Org. Chem.* **1999**, *64*, 3804–3805) introduced a phosphane-free catalyst formed from $[Pd_2(dba)_3]$ and in situ generated Arduengo-Herrmann carbene ligand for Suzuki couplings. With cesium carbonate as base, excellent results with various chloroarenes are achieved.