A General and Long-Lived Catalyst for the Palladium-Catalyzed Coupling of Aryl Halides with Thiols
Manuel A. Fernández-Rodríguez, Qilong Shen, and John F. Hartwig*
Department of Chemistry, Yale University, PO Box 208107 New Haven, Connecticut 06520-8107
Received November 25, 2005; E-mail: john.hartwig@yale.edu
Published on Web 01/31/2006

Palladium-catalyzed coupling has become a principal method of forming aromatic carbon–heteratom bonds. Among this class of reactions, the synthesis of arylamines and aryl ethers from aryl halides has experienced significant development. However, parallel studies to develop the synthesis of aryl sulfides have been less fruitful. Migita first reported the coupling of iodo and bromoarenes with thiols using Pd(Ph3)4 as catalyst, and many ligands have now been tested for this reaction. However, the published reactions occur with low turnover numbers (TON ≤ 50), encompass chloroarenes containing only nitrile and ester functionality, and do not include any reactions of aryl tosylates. These drawbacks have limited the use of this reaction to prepare sulfides with biological activity or sulfides that lead to biologically active compounds.

The limitations of these reactions could result from the notorious sensitivity of late metal catalysts to substrates containing reactive sulfur functionality. Although palladium thiolates form easily and slow reductive elimination, thus, a more reactive catalyst for the coupling of aryl halides with thiols are likely to be limited by displacement of dative ligands by thiolates to form anionic thiolate complexes or by the formation of bridging thiolate complexes that undergo slow reductive elimination. Thus, a more reactive catalyst for the coupling of thiolates might contain a bisphosphine that binds the metal strongly enough to prevent formation of anionic or bridging thiolate complexes, while simultaneously promoting oxidative addition and reductive elimination.

With these requirements in mind, we considered that the restricted backbone conformation, steric hindrance, and strong electron donation of the Josiphos ligand, CyPF-t-Bu (1 in Table 1), could create practical catalysts for the coupling of thiols with aryl chlorides and tosylates. We show here that complexes generated from this ligand couple a broad range of thiols with aryl halides and sulfonates, and that reactions conducted with the Josiphos ligand occur with turnover numbers and tolerance of functional groups that far surpass those of previous catalysts. This catalyst also allows diarylsulfides to be prepared from two different bromoarenes and a hydrogen sulfide surrogate.

We initially assessed catalyst activity by conducting the coupling of the electron-rich 4-chloroanisole with 1-octanethiol. These studies showed that 0.1 mol % of equimolar amounts of Pd(OAc)2 and ligand in DME (1,2-dimethoxyethane) at 110 °C provided high yield in less than 4 h (Table 1, entry 1). Reactions of alkylthiols with weaker carbones or phosphate bases occurred to low conversions and formed large amounts of dialkyl disulfide. Reactions in other solvents or at lower temperatures also either occurred to lower conversions, required longer reaction times, or both. The coupling of aromatic thiols under the same conditions produced undesired symmetrical sulfides in a 5–10% combined yield, but reactions of aromatic thiols with KOBu as base and Pd(dba)2 as precursor in toluene formed the aryl sulfide in high yield with only traces of side products (Table 1, entry 2). Reactions under the standard conditions, but without catalyst, formed mostly disulfides and less than 5% of the desired aryl sulfides.

Reactions of a series of aryl chlorides and thiols were evaluated under these conditions, and the results are summarized in Table 1. Primary, secondary, and tertiary aliphatic thiols and aromatic thiols were successfully coupled with activated and nonactivated aryl chlorides. Excellent yields in short reaction times were obtained using 1 or 2 orders of magnitude less catalyst than had been used in previous couplings to form aryl sulfides (8500 turnovers, entry 4). Even the more sterically demanding substrates coupled in high yield using catalyst loadings in the range of 0.25–1 mol % (entries 16–19). Reactions at lower temperatures (70 °C) simply required increasing the amount of catalyst to 2–3 mol % and increasing reaction times to 24 h (entries 6, 9, and 13).

This coupling of chloroarenes with thiols is tolerant of a wide range of common functional groups (Table 1, entries 20–30).
Chloroarenes bearing a nitrile, ketone, amide, and carboxylic acid, as well as unprotected amino and aromatic or aliphatic hydroxyl groups, coupled under the standard conditions to form the corresponding aryl sulfide in good to excellent yields. Moreover, reactions of aryl chlorides with ester or aldehyde groups that are incompatible with nucleophilic alkoxide bases occurred in high yield.

For example, reactions of chloroarenes bearing a nitrile, ketone, amide, and carboxylic acid, probed the scope of the reactions of other aryl halides and sulfonates (Table 2). As shown in eq 1, the coupling of benzenethiol with the aryl tosylate did not occur (entry 16).

In summary, we have described a general, highly efficient and functional-group-tolerant catalyst system for the coupling of aryl halides and triflates with thiols that typically occur with TONs that are 2 or 3 orders of magnitude higher than those of related couplings by previous catalysts. The results of these studies are consistent with the hypothesis that ligand 1 overcomes the tendency of thiolates to inactivate previous catalysts by displacement of the dative ligand. Studies of the mechanism of this coupling process will be the subject of future work.

Acknowledgment. We thank the NIH-NIGMS (GM-55382) for support of this work. M.F.-R. thanks the Ministerio de Educación y Ciencia for a MEC Fulbright fellowship.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds and complete ref 16. This material is available free of charge via the Internet at http://pubs.acs.org.

References

6. Although nickel- and copper-catalyzed couplings of thiols with aryl halides have been reported, these processes require either high temperatures or high catalyst loadings, (a) Nickel-catalyzed: Cristiani, H. J.; Chabaud, B.; Chene, A.; Christol, H. Synthesis 1981, 1892–1894. (b) For a review on copper-catalyzed, see: Ley, S. V.; Thomas, A. W. Angew. Chem., Int. Ed. 2003, 42, 5400–5449. (c) For a recent report of the coupling of bromobenzene with benzzenethiol catalyzed by Cu(N)-dimethylglycine (20 mol %), see: Deng, W.; Zou, Y.; Wang, Y.-F.; Liu, L.; Guo, Q.-X. Synlett 2004, 1254–1258.
21. See Supporting Information. Equivalent results were obtained with racemic and commercially available enantiomeric ligand.