J|A|C|S
COMMUNICATIONS

Published on Web 09/21/2010

# Palladium-Catalyzed Conversion of Aryl and Vinyl Triflates to Bromides and Chlorides

Xiaoqiang Shen, Alan M. Hyde, and Stephen L. Buchwald*

*Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States*

Received August 18, 2010; E-mail: sbuchwal@mit.edu

***Abstract:*** The palladium-catalyzed conversion of aryl and vinyl triflates to aryl and vinyl halides (bromides and chlorides) has been developed using dialkylbiaryl phosphine ligands. A variety of aryl, heteroaryl, and vinyl halides can be prepared via this method in good to excellent yields.

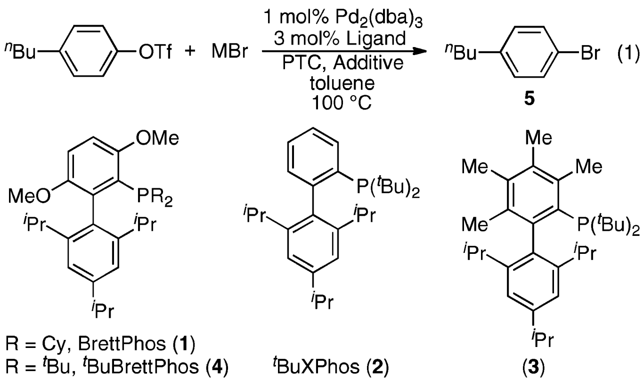
Aryl halides are ubiquitous synthetic intermediates in organic chemistry that are used for numerous transformations.[1] They are also present in a wide variety of natural products, pharmaceuticals, and agrochemicals.[2] Therefore, the development of general and regioselective methods for the preparation of functionalized aryl halides is of great importance. Sulfonate esters, often referred to as pseudo-halides, can be employed as alternatives to aryl halides in many cross-coupling reactions.[3] Such pseudo-halides, however, cannot be used as precursors for the generation of free radicals[4] or organometallic reagents.[1] Traditional methods for the synthesis of aryl halides (bromides or chlorides) from phenols require either forcing conditions[5] or multi-step procedures.[6] Herein, we report the first example of palladium-catalyzed direct conversion of readily available aryl sulfonate esters to aryl bromides and chlorides.

Although a catalytic method has not yet been reported, several mechanistically related metal-mediated carbon−halogen bond-forming processes have been published.[7] For example, the reductive elimination of aryl halides from Pt(IV),[8] Ni(III),[9] Pd(IV),[10] and Pd(III)[11] has been demonstrated. In addition, the reductive elimination of aryl halides from arylpalladium(II) halide complexes in the presence of a large excess of P(*t*-Bu)$_3$ has been reported.[12,13] A number of copper-[14] and nickel-mediated[15] halide exchange reactions have also been developed in which carbon−halogen reductive elimination processes are proposed to take place.

Despite these advances in aryl−halide bond formation, to the best of our knowledge, there are few examples of the catalytic conversion of an aryl sulfonate to an aryl halide,[16] including the ruthenium-catalyzed conversion of 2-naphthyl triflate to 2-bromonaphthalene[16b] and our recent report of the palladium-catalyzed conversion of aryl triflates to aryl fluorides.[17] This prompted us to query whether we could uncover a catalytic process to convert aryl triflates into corresponding aryl bromides and chlorides; the results are disclosed herein.

Catalysts based on dialkylbiaryl monophosphines **1**−**4**, which have been successfully utilized as ligands in numerous transformations,[17,18] were initially examined for the conversion of 4-*n*-butylphenyl triflate into 4-*n*-butylbromobenzene (**5**). In initial experiments, these reactions were carried out in the presence of 2.0 equiv of Bu$_4$NBr, 1 mol % Pd$_2$(dba)$_3$, and 3 mol % ligand in toluene at 100 °C. This set of conditions afforded only small amounts of aryl bromide products (1−6%, entries 1−4). Other bromide sources were tested, but the results were unimpressive, with KBr providing the highest yield (11%, entry 5). Since potassium bromide has a low solubility in toluene, we reasoned that the use of a phase-transfer catalyst (PTC) might be beneficial. Adding polyethylene glycols improved the yield to 32% (entry 6). All attempts to increase the yield of this reaction with more forcing conditions or higher catalyst loading failed. We were initially puzzled by this and wondered whether product inhibition was occurring. Therefore, we repeated the 4-*n*-butylphenyl triflate to 4-*n*-butylbromobenzene reaction (eq 1) in the presence of 1 equiv of potassium triflate and found that the reaction was completely inhibited (entry 7). This was surprising since the triflate anion is known to be a poor nucleophile.[19] In order to probe whether this result was due to the existence of an unfavorable equilibrium, **5** was heated under similar catalytic conditions with KOTf as the coupling partner. However, no conversion to aryl triflate was observed, ruling out this possibility. Our next efforts focused on the sequestration of KOTf as it was formed. After surveying a broad

***Table 1.*** Evaluation of Reaction Conditions for Bromination[a]

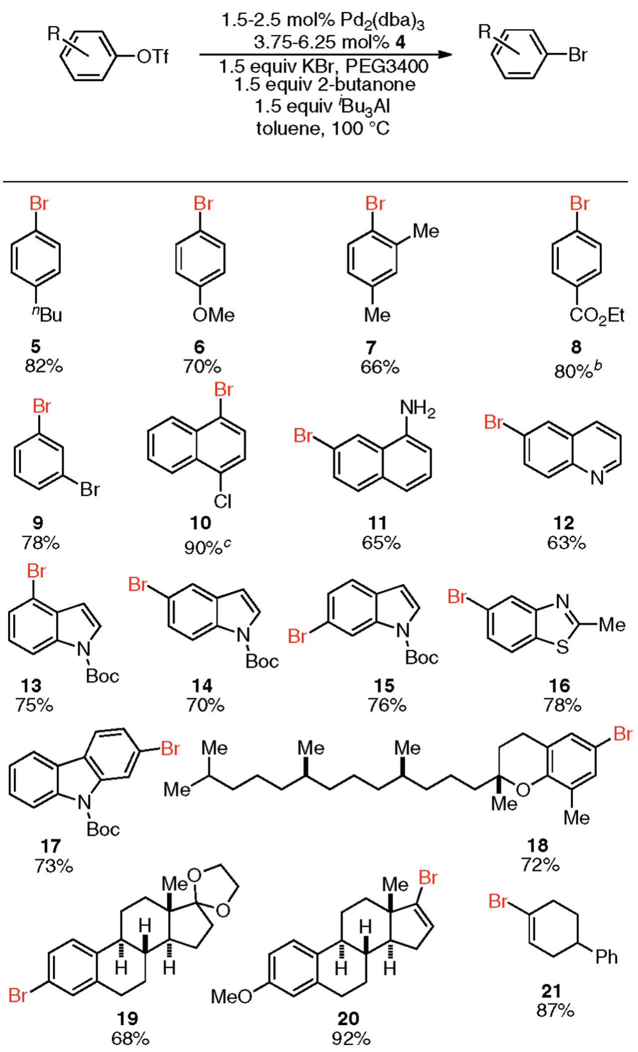


| entry | MBr | ligand | PTC | additive | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | Bu$_4$NBr | **1** | | | 1[c] |
| 2 | Bu$_4$NBr | **2** | | | 2[c] |
| 3 | Bu$_4$NBr | **3** | | | 3[c] |
| 4 | Bu$_4$NBr | **4** | | | 6[c] |
| 5 | KBr | **4** | | | 11[c] |
| 6 | KBr | **4** | PEG | | 32[c] |
| 7 | KBr | **4** | PEG | KOTf[d] | 1[c] |
| 8 | KBr | **4** | PEG | Et$_3$B | 50[c] |
| 9 | KBr | **4** | PEG | $^i$Bu$_2$AlF | 54[e] |
| 10 | KBr | **4** | PEG | $^i$Bu$_3$Al | 41[e] |
| 11 | KBr | **4** | PEG | ($^i$PrO)$_3$Al | 1[c] |
| 12 | KBr | **4** | PEG | $^i$Pr$_3$Al[f] | 25[g] |
| 13 | KBr | **4** | PEG | $^i$Bu$_3$Al/2-butanone[h] | 92 |

[a] Reaction conditions: 0.25 mmol of aryl triflate, 2.0 equiv of MBr, 1.5 equiv of additive, 50 mg of PEG3400 [poly(ethylene glycol), $M_n \approx$ 3400], 1.0 mL of toluene. [b] Yields determined by GC analysis with an internal standard of dodecane. [c] The remaining material was the 4-*n*-butylphenyl triflate. [d] 1.0 equiv of KOTf. [e] The remaining material was the 1-*n*-butyl-4-*i*-butylbenzene. [f] Triisopropylaluminum diethyl etherate as additive. [g] The remaining material was the *n*-butylbenzene. [h] 1.5 equiv of *i*-Bu$_3$Al and 2-butanone as additives.

10.1021/ja107481a

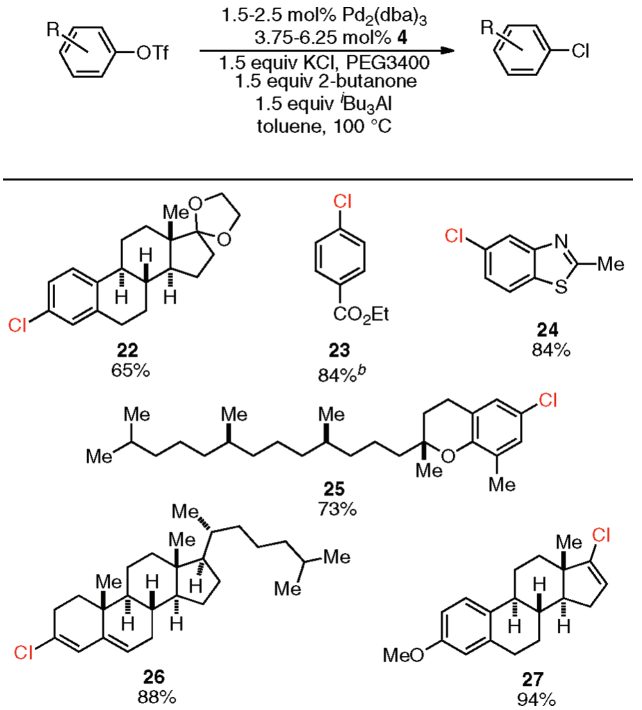
***Table 2.*** Palladium-Catalyzed Conversion of Triflates to Bromides[a]



---

[a] Reaction conditions: 1.0 mmol of triflate, 1.5−2.5 mol % of Pd$_2$(dba)$_3$, 3.75−6.25 mol % of **4** (**4**:Pd = 1.25:1), 1.5 mmol of KBr, 1.5 mmol of 2-butanone, 1.5 mL of $i$-Bu$_3$Al (1 M solution in toluene), 120 mg of PEG3400, 6.0−8.0 mL of toluene, 20−24 h. Isolated yields (average of two runs). [b] 1.25 equiv of $i$-Bu$_3$Al and EtOH as additives; contains ∼5% of ethyl 4-$i$-butylbenzoate. [c] Contains 1,4-dichloronaphthalene and 1,4-dibromonaphthalene (4−10% total).

***Table 3.*** Palladium-Catalyzed Conversion of Triflates to Chlorides[a]



---

[a] Reaction conditions: 1.0 mmol of triflate, 1.5−2.5 mol % of Pd$_2$(dba)$_3$, 3.75−6.25 mol % of **4** (**4**:Pd = 1.25:1), 1.5 mmol of KCl, 1.5 mmol of 2-butanone, 1.5 mL of $i$-Bu$_3$Al (1 M solution in toluene), 120 mg of PEG3400, 6.0−8.0 mL of toluene, 20−24 h. Isolated yields (average of two runs). [b] 1.25 equiv of $i$-Bu$_3$Al and EtOH as additives; contains ∼5% of ethyl 4-$i$-butylbenzoate.

range of Lewis acids, we found that the yield of the reaction could be increased to 50% when Et$_3$B was used as additive (entry 8). Full conversions were observed when commercially available $i$-Bu$_2$AlF or $i$-Bu$_3$Al was used; however, about 50−60% of the C−C coupling product, 1-$n$-butyl-4-$i$-butylbenzene, was formed in both cases (entries 9 and 10).[20] The use of the bulkier $i$-Pr$_3$Al additive prevented the formation of the C−C coupling product, although the desired aryl bromide was only formed in 25% yield, with the reduction product, $n$-butylbenzene, now formed in 75% yield (entry 12). Fortunately, in situ formation of dialkylaluminum alkoxides by the addition of ketones or alcohols suppressed both C−C coupling and reduction byproducts; the yield was increased to 92% when 2-butanone was used (entry 13).

With the optimal conditions for this new transformation in hand, we next explored the reaction scope (Table 2). Both electron-poor and electron-rich aryl triflates are suitable substrates and provide aryl bromides in good yield. Significantly, heteroaryl triflates, such as quinolines, indoles, carbazoles, and benzothiazoles, can be efficiently converted to the corresponding aryl bromides. Ester groups were well tolerated but can, in some cases, undergo unwanted transesterification. With 4-trifluoromethylsulfonyl ethylbenzoate as substrate, this undesired side reaction could be avoided by using EtOH as an additive in place of 2-butanone (Table 2, compound **8**). Aromatic amines are also tolerated in these transformations, as exemplified by the formation of 7-bromo-1-naphthylamine in moderate yield from the corresponding triflate (Table 2, compound **11**). In this case, the 2-butanone imine was initially formed, which was then cleaved after workup and flash chromatography. The bromination of 3-bromophenyl triflate and 4-chloro-1-naphthyl triflate demonstrates that polyhalogenated products may be efficiently formed. Vinyl triflates are also effective substrates for the bromination reaction. For example, a vinyl triflate derived from estrone is easily converted to the corresponding vinyl bromide in 92% yield (Table 2, compound **20**).

As highlighted in Table 3, aryl and vinyl triflates can also be converted to aryl and vinyl chlorides under similar reaction conditions using KCl as the chloride source in good to excellent yields.[21]

In conclusion, a new method for the direct conversion of aryl and vinyl triflates to aryl and vinyl halides has been achieved using palladium catalysis. The use of sterically hindered dialkylbiaryl monophosphines is key for success in achieving this new transformation.

**Acknowledgment.** Generous financial support from the National Institutes of Health (GM46059) is gratefully acknowledged.

**Supporting Information Available:** Procedural and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) For general reviews on halogen−metal exchange, see: (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (b) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.

(2) (a) Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141. (b) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335.

(3) For a selected review, see: Ritter, K. *Synthesis* **1993**, 735.

(4) Bunnett, J. F. *Acc. Chem. Res.* **1992**, *25*, 2.

(5) (a) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964. (b) Bay, E.; Bak, D. A.; Timony, P. E.; Leone-Bay, A. *J. Org. Chem.* **1990**, *55*, 3415.

(6) (a) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277. (b) Thompson, A. L. S.; Kabalka, G. W.; Akula, M. R.; Huffman, J. W. *Synthesis* **2005**, 547. (c) Kang, H.; Facchetti, A.; Stern, C. L.; Rheingold, A. L.; Kassel, W. S.; Marks, T. J. *Org. Lett.* **2005**, *7*, 3721. (d) Grunewald, G. L.; Seim, M. R.; Regier, R. C.; Criscione, K. R. *Bioorg. Med. Chem.* **2007**, *15*, 1298.

(7) For general reviews on metal-mediated carbon-halogen bond formation, see: (a) Vigalok, A. *Chem.−Eur. J.* **2008**, *14*, 5102. (b) Sheppard, T. D. *Org. Biomol. Chem.* **2009**, *7*, 1043.

(8) (a) Yahav-Levi, A.; Goldberg, I.; Vigalok, A. *J. Am. Chem. Soc.* **2006**, *128*, 8710. (b) Yahav-Levi, A.; Goldberg, I.; Vigalok, A.; Vedernikov, A. N. *Chem. Commun.* **2010**, *46*, 3324.

(9) Higgs, A. T.; Zinn, P. J.; Simmons, S. J.; Sanford, M. S. *Organometallics* **2009**, *28*, 6142.

(10) (a) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (b) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. (c) Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796. (d) Arnold, P. L.; Sanford, M. S.; Pearson, S. M. *J. Am. Chem. Soc.* **2009**, *131*, 13912.

(11) Power, D. C.; Ritter, T. *Nature Chem.* **2009**, *1*, 302.

(12) (a) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232 (b) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13944.

(13) An example of reversible oxidative addition of palladium into 2-bromoindoles has appeared: Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416.

(14) (a) Bacon, R. G. R.; Hill, H. A. O. *J. Chem. Soc.* **1964**, 1097. (b) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844.

(15) (a) Takagi, K.; Hayama, N.; Okamoto, T. *Chem. Lett.* **1978**, *7*, 191. (b) Tsou, T. T.; Kochi, J. K. *J. Org. Chem.* **1980**, *45*, 1930. (c) Arvela, R. K.; Leadbetter, N. E. *Synlett* **2003**, 1145.

(16) For the Ni-catalyzed conversion of pyranyl triflates to pyranyl bromides, see: (a) Milne, J. E.; Jarowicki, K.; Kocienski, P. J. *Synlett* **2002**, 607. For the Ru-catalyzed conversion of alkenyl triflates to alkenyl halides, see: (b) Shirakawa, E.; Imazaki, Y.; Hayashi, T. *Chem. Commun.* **2009**, 5088.

(17) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.

(18) (a) Cho, E.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679. (b) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. (c) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001. (d) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *128*, 10694. (e) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (f) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

(19) (a) Lawrance, G. A. *Chem. Rev.* **1986**, *86*, 17. (b) Howells, R. D.; McCown, J. D. *Chem. Rev.* **1977**, *77*, 69.

(20) For examples of Pd-catalyzed cross-coupling of organoaluminum reagents, see: (a) Babu, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729. (b) Hirota, K.; Isobe, Y.; Maki, Y. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2513.

(21) About 5% of 1-*n*-butyl-4-iodobenzene was formed when 4-*n*-butylphenyl triflate was subjected to similar catalytic conditions using KI as the iodide source.

JA107481A