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

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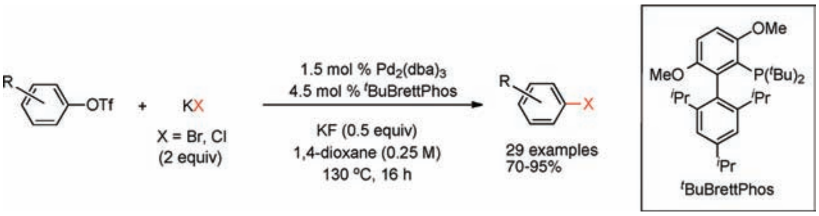
ABSTRACT



A facile Pd-catalyzed conversion of aryl and vinyl triflates to aryl and vinyl halides (bromides and chlorides) is described. This method allows convenient access to a variety of aryl, heteroaryl, and vinyl halides in good to excellent yields and with greatly simplified conditions relative to our previous report.

Aryl halides are present in a wide variety of biologically active molecules.[1] They are also important synthetic intermediates that are used for numerous transformations.[2] Traditional methods for producing aryl bromides and chlorides from phenols require either forcing reaction conditions[3] or multistep sequences.[4] Consequently, the development of general and efficient methods for the synthesis of aryl halides is of great importance. Aryl triflates, which serve as alternatives to aryl halides in many cross-coupling reactions,[5] are often referred to as pseudohalides. However, unlike aryl halides, aryl triflates cannot be used as precursors for the generation of free radicals[6] or organometallic reagents.[2] Thus, developing efficient methods for the conversion of readily available aryl triflates into aryl halides with wide functional group tolerance is of interest. Despite considerable effort,[7] to date only a few metal-catalyzed methods for the conversion of aryl and vinyl triflates to aryl and vinyl halides have been reported.[8] We recently disclosed the first example of a direct Pd-catalyzed conversion of aryl and vinyl triflates to bromides and chlorides.[8d] However, the reaction suffered from some limitations. In particular, the addition of ^{i}Bu$_3$Al (1.5 equiv) was required to sequester the formed KOTf that inhibited

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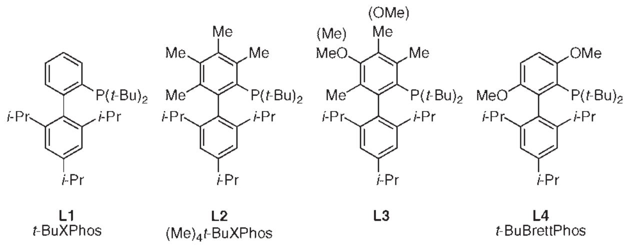
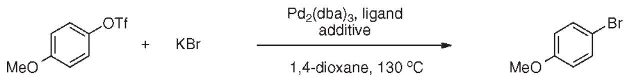


Figure 1. Biarylphosphine ligands.

Table 1. Evaluation of the Reaction Conditions[a]



entry	$Pd_2(dba)_3$ (mol %)	ligand (mol %)	additive (equiv)	conv (%)[b]	GC yield (%)[b]
1	2.5	**L1** (7.5)	none	42	41
2	2.5	**L1** (7.5)	KF (1.0)	86	61
3	2.5	**L1** (7.5)	KF (0.5)	84	59
4	2.5	**L2** (7.5)	KF (0.5)	89	71
5	2.5	**L3** (7.5)	KF (0.5)	89	68
6[c]	1.5	**L4** (4.5)	KF (0.5)	100	81
7[c]	1.5	**L4** (4.5)	none	74	67
8[c,d]	1.5	**L4** (4.5)	K_2CO_3 (1.0)	100	0
9[c,d]	1.5	**L4** (4.5)	$KHCO_3$ (1.0)	100	11
10[c,d]	1.5	**L4** (4.5)	KOAc (1.0)	96	66
11[c,d]	1.5	**L4** (4.5)	K_3PO_4 (1.0)	100	49
12[c,d]	1.5	**L4** (4.5)	KO^{t}Bu (1.0)	100	0

[a] Reaction conditions: ArOTf (0.5 mmol), KBr (1.0 mmol), KF, $Pd_2(dba)_3$ (2.5 mol %), ligand (7.5 mol %), 1,4-dioxane (0.5 mL), 130 °C, 12 h. [b] With decane as an internal standard. [c] Reaction conditions: ArOTf (0.5 mmol), KBr (1.0 mmol), additive, $Pd_2(dba)_3$ (1.5 mol %), **L4** (4.5 mol %), 1,4-dioxane (2 mL), 130 °C, 16 h. [d] The mass balance consists of product, starting material, and ArOAr byproduct.

further conversion. This necessitated the addition of 2-butanone (1.5 equiv) to generate the dialkylaluminum alkoxide *in situ* with ^{i}Bu$_3$Al to suppress the formation of undesired C–C cross-coupling[9] and reduction byproducts. Further, a phase-transfer catalyst (e.g., PEG3400) was required to increase the solubility of KBr. Overall, the complexity of the reaction conditions rendered this process less than ideal.

While seeking to develop a more general and practical method, we discovered that the utilization of KF as an additive significantly improved the reaction efficiency. Herein, we report an improved Pd-catalyzed conversion of aryl and vinyl triflates to bromides and chlorides using biarylphosphine ligands in the presence of KF.

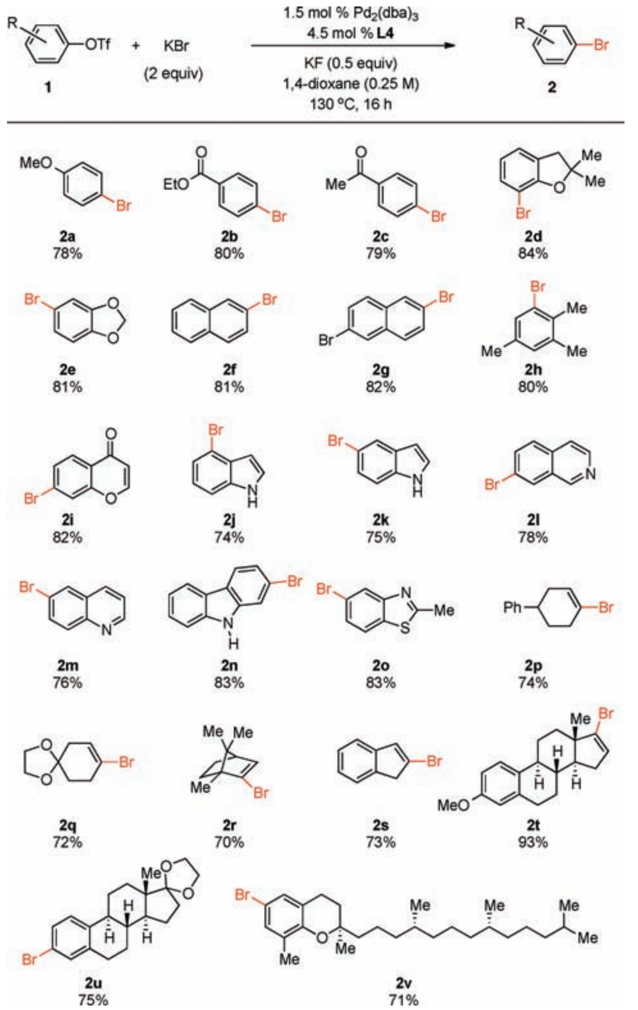


Figure 2. Pd-catalyzed conversion of triflates to bromides. Reaction conditions: ArOTf (1.0 mmol), $Pd_2(dba)_3$ (1.5 mol %), **L4** (4.5 mol %), KBr (2.0 mmol), KF (0.5 mmol), 1,4-dioxane (4 mL), 130 °C, 16 h. Isolated yields are based on an average of two runs.

We examined the conversion of 4-methoxyphenyl triflate into 4-bromoanisole, using Pd catalysts based on different biarylphosphine ligands in the presence and absence of different additives (Figure 1).[10] We initially examined a catalyst based on *t*-BuXPhos (**L1**). Utilizing dioxane as the solvent, this catalyst provided the desired 4-bromoanisole in 41% yield (42% conversion, Table 1, entry 1) after 12 h at 130 °C. A marked increase in conversion and yield was found when KF (1.0 equiv) was employed as an additive. Reducing the amount of KF to 0.5 equiv produced the same result. An examination of alternative ligands revealed that the utilization of *t*-BuBrettPhos (**L4**) in conjunction with 1.5 mol % of $Pd_2(dba)_3$ significantly improved the reaction efficiency, affording the desired product in 81% yield. Again, KF played a crucial role in producing the desired product, as the conversion and yield dropped to 74% and 67%,

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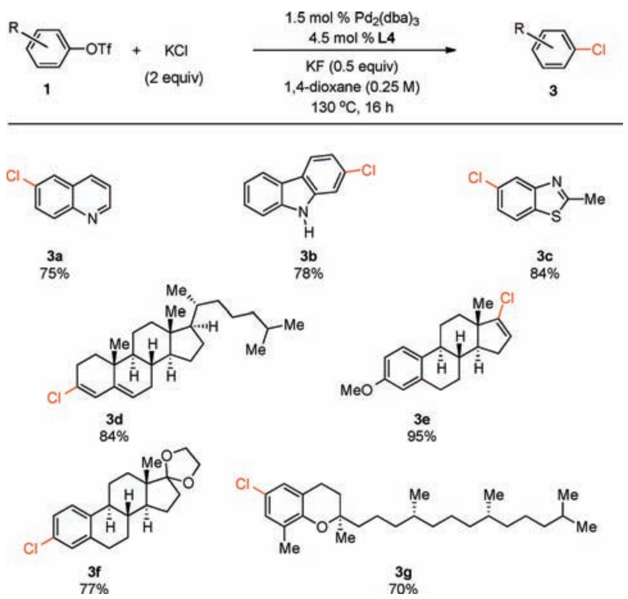

Figure 3. Pd-catalyzed conversion of triflates to chlorides. Reaction conditions: ArOTf (1.0 mmol), $Pd_2(dba)_3$ (1.5 mol %), **L4** (4.5 mol %), KCl (2.0 mmol), KF (0.5 mmol), 1,4-dioxane (4 mL), 130 °C, 16 h. Isolated yields are based on an average of two runs.

respectively, in the absence of KF. Notably, employing other additives provided either no product or a lower yield (Table 1, entries 8 to 12).

With optimized conditions in hand, we set out to explore the substrate scope for the conversion of triflates to bromides (Figure 2). We found that electron-rich and electron-deficient aryl triflates, as well as heteroaryl triflates such as indoles, quinolines, isoquinolines, carbazoles, and benzothiazoles, could be efficiently converted into the corresponding aryl bromides in good to excellent yields. It should be noted that ketone groups and ester groups, which were problematic in our previous method, are well tolerated. In addition, the free N−H groups of indole and carbazole are compatible with these conditions. Vinyl triflates are also efficiently converted to the corresponding vinyl bromides in good to excellent yields under the same reaction conditions.

We next examined the conversion of triflates to chlorides. It was found that conditions similar to those described above were also applicable to the conversion of triflates to chlorides when KCl was employed as the chloride source. As shown in Figure 3, a variety of aryl triflates, heteroaryl triflates, and vinyl triflates underwent chlorination smoothly, affording the corresponding chlorides in good to excellent yields.

In summary, we have developed a facile Pd-catalyzed conversion of aryl and vinyl triflates into aryl and vinyl halides (bromides and chlorides). This method affords convenient access to a variety of aryl, heteroaryl, and vinyl halides in good to excellent yields from a wide range of readily available triflates. Key to the success of this method is the addition of KF. At present, we are unsure of the mechanism by which the inclusion of KF improves upon our previous method.

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