Angewandte
International Edition Chemie

Cross-Coupling

DOI: 10.1002/anie.201203460

C–O Cross-Coupling of Activated Aryl and Heteroaryl Halides with Aliphatic Alcohols**

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Aromatic ethers are ubiquitous structural motifs present in both natural and synthetic compounds including dozens of the 200 top-selling drugs on the market today (Figure 1).[1] Traditional methods for accessing this functionality, such as direct nucleophilic aromatic substitution (S_NAr) and Ullmann coupling, typically require reactive aryl halides or harsh reaction conditions and thus display limited substrate scope and functional-group compatability. As a result, over the past 15 years there has been a dramatic increase in the development of transition-metal-catalyzed C–O bond-forming reactions. In particular, advances in ligand design have resulted in improved methods for Pd-[2] and Cu-catalyzed[3] C–O coupling reactions of aliphatic alcohols with aryl halides. For example, Buchwald and co-workers recently reported bulky biarylphosphine ligands that show high activity with Pd for the coupling of a broad range of primary and secondary aliphatic alcohols and (hetero)aryl halides.[4]

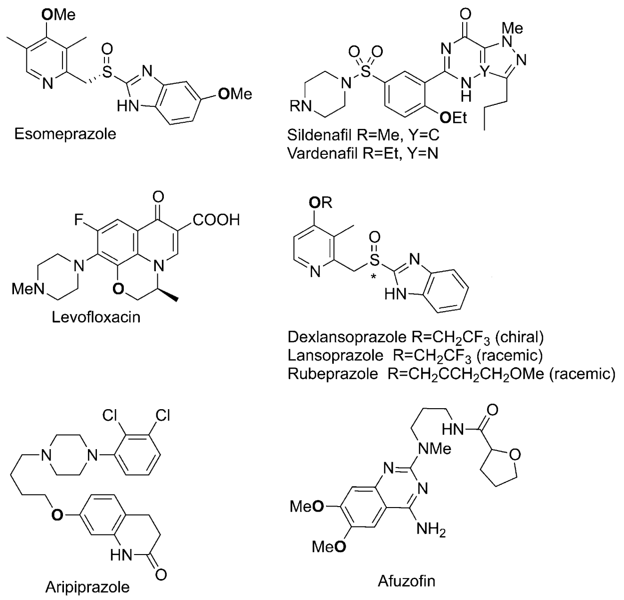

Figure 1. Selected pharmaceuticals containing aryl–alkyl ether units; the corresponding ether oxygen atoms are in bold.

Despite these advances, significant limitations remain with respect to generality, functional-group tolerance, alcohol stoichiometry, coupling partner scope, and catalyst availability. Herein, we describe a Pd/Josiphos catalyst system for the alkoxylation of activated aryl and heteroaryl halides with primary, secondary, and select tertiary alcohols. The catalyst system displays broad functional-group tolerance at both coupling partners, and provides a robust, complementary approach to existing methods.

Our interest in heteroaryl alkyl ethers for drug discovery led us to explore conditions for Pd-catalyzed CO coupling reactions that would allow general access to these systems. To survey the catalyst system that would display the broadest generality, a screen was performed for the coupling of three heteroaryl halides with alcohol **2a** (Figure 2).[5] While several ligands provided active catalysts for the coupling of **1b**,[6] only the Josiphos analogue CyPF-*t*Bu (Figure 3), utilized extensively by Hartwig and co-workers for C–N and C–S couplings,[7] displayed superior performance for the more challenging aryl halides **1a** and **1c**. A follow-up ligand screen with a total of 72 ferrocenyl-type phosphine ligands for the coupling of **1a** with **2a** confirmed CyPF-*t*Bu to provide the most active catalyst/ligand system.[5]

In a broader solvent screen using CyPF-*t*Bu, optimal results were obtained consistently with THF and toluene, although a number of solvents examined also gave moderate to high yields.[5] The Pd source [(allylPdCl)$_2$][5] provided the most active catalyst, followed by [Pd$_2$(dba)$_3$]. Under optimized conditions the coupling of heterocyclic halides **1a–c** with 2-phenylethyl alcohol (**2a**) on a 1 mmol scale using 1 mol% of CyPF-*t*Bu and 0.5 mol% of [(allylPdCl)$_2$] (3 equiv Cs_2CO_3, THF, 80°C, 20 h) proceeded with more than 99% conversion and provided the isolated product in yields of at least 90%.[8]

The surprisingly low reactivities observed with the RockPhos ligand (Figure 3)[4] in the initial screen prompted us to examine this catalyst in more detail (Table 1). The original publication noted that preformation of the catalyst was required for couplings of heteroaryl halide substrates, presumably because of competitive displacement of the phos-

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[**] We thank Prof. Stephen L. Buchwald and Michael Palucki for helpful discussions and Janine Noelle Brouillette for her contribution to the NMR structure elucidaton.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201203460.

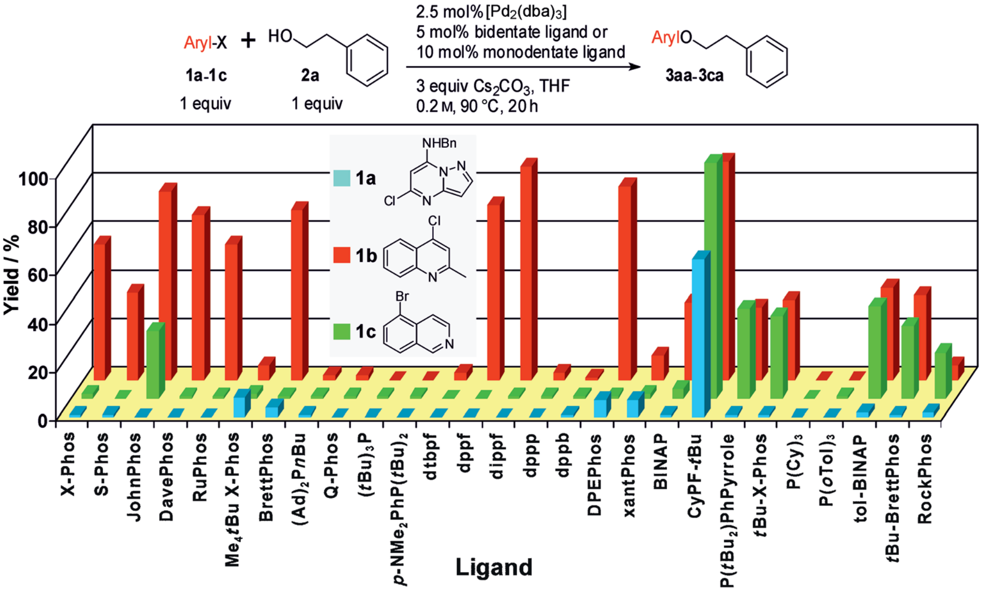


Figure 2. Initial ligand screen for the coupling of aryl halides **1a**–**1c** with alcohol **2a**. Reactions were performed using 0.02 mmol of each coupling partner in 0.1 mL of solvent. Assay yields are based on the aryl halide calculated from quantitative HPLC data. dba = dibenzylideneacetone. For ligand abbreviations see the Supporting Information.

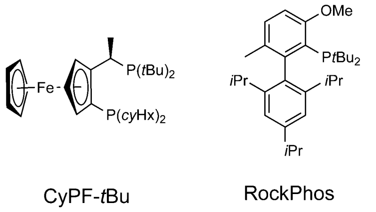
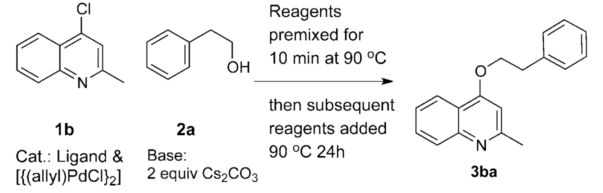


Figure 3. CyPF-*t*Bu and RockPhos ligands. *cy*Hx = cyclohexyl.

Table 1: Exploring the order of addition for different ligands.[a]



		Yield [%]	
	Premixed reagents	RockPhos	CyPF-*t*Bu
1	Cat.	22	99
2	Cat., **1b**, Cs_2CO_3	58	> 99
3	Cat., **2a**, Cs_2CO_3	26	> 99
4	Cat., **1b**, **2a**	4	> 99
5	Cat., **1b**, **2a**, Cs_2CO_3	0	99
6	Cat., **1b**, Cs_2CO_3	56[b]	–
7	Cat., **1b**, Cs_2CO_3, 4 Å M.S.	98[b]	–

[a] Assay yields based on aryl halide calculated from quantitative HPLC data. Reaction conditions: $[\mathbf{1b}]_0 = [\mathbf{2a}]_0 = 0.2$ M, 0.5 mol% $[(allylPdCl)_2]$, 2 equiv Cs_2CO_3, 90 °C, 24 h. RockPhos or *t*Bu-BrettPhos/Pd = 1.5:1.0; CyPF-*t*Bu/Pd = 1:1. [b] $[\mathbf{1b}]_0 = 0.5$ M, 2 equiv **2a**.

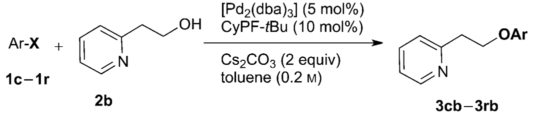
phine ligand by the heterocycle.[4] After examining a number of variations on catalyst preformation and orders of addition, we found that heating the palladium source, ligand, heteroaryl chloride, and 4 Å molecular sieves in toluene at 90 °C for 10 min prior to the introduction of the alcohol was required to achieve high conversion and yield (Table 1, entry 7). In contrast, the CyPF-*t*Bu/Pd catalyst system did not require catalyst preformation and was not sensitive to the order of addition of reagents (Table 1). This increased robustness of the CyPF-*t*Bu/Pd system in the presence of heterocyclic substrates is attributed to the bidentate nature of the ligand[7a] and was further illustrated by comparing the performance of RockPhos and CyPF-*t*Bu in the coupling of the heterocyclic alcohol **2b** with the heterocyclic aryl halides **1c** and **1d**: under the optimized conditions the RockPhos-derived catalyst gave yields of 30 % and 70 %, respectively, with significant by-product formation, while CyPF-*t*Bu gave full conversion and more than 99 % yield.[5]

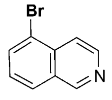
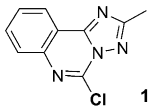
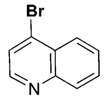
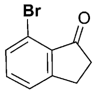
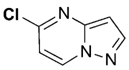
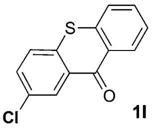
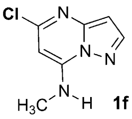
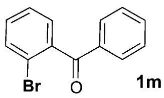
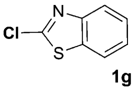
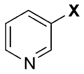
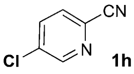
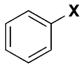
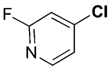
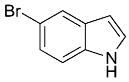
The scope of the (hetero)aryl halide component of the reaction using **2b** as a representative alcohol was explored. We were pleased to find that the optimized reaction conditions were tolerant of a wide variety of electron-deficient aromatic and heteroaromatic systems.[9] In all cases, only one equivalent of alcohol was used, and minimal background reactions were observed. This is highlighted by the selective functionalization of 2-fluoro-4-chloropyridine (Table 2, entry 7) which provided only the product of reaction at chlorine under the optimized reaction conditions. Additionally, no C–N coupling reactions were observed for amine-bearing substrates **1a** and **1f**.

In contrast to electron-deficient aromatic and heteroaromatic halides, electron-neutral aryl halides typically reacted with low conversion (Table 2, entries 12–14). Since CyPF-*t*Bu/Pd is known to be reactive for C–N and C–S couplings of unactivated aryl chlorides,[7] it is unlikely that sluggish oxidative addition explains our observation. Rather, it is possible that either alcohol displacement of the halide in the Pd–(aryl halide) complex, or the subsequent reductive elimination of the C–O bond to form the product ether are disfavored at this highly hindered, electron-rich metal center.[10]

The reaction exhibited excellent functional-group tolerance for structurally diverse alcohols in couplings with **1c** (Table 3). Unexpectedly, an alkyne was concurrently transformed to the 1,3-diene **3ci**, presumably by means of 1,2-aryloxy migration (Table 3, entry 8).[11] Complete regioselectivity was observed for primary over secondary over tertiary alcohols (Table 3, entries 6 and 14).[12]

Table 2: Aryl halide scope.[a]



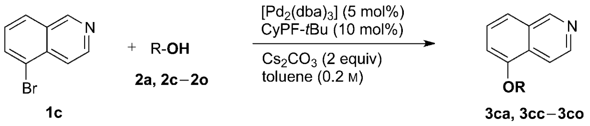
	Ar–X	Yield temp. time		Ar–X	Yield temp. time
1	 **1c**	86% 80°C 16 h	8	 **1j**	66% 140°C 1 h
2	 **1d**	82% 80°C 16 h	9	 **1k**	55% 140°C 1 h
3	 **1e**	82% 80°C 2 h	10	 **1l**	58% 80°C 16 h
4	 **1f**	49% 80°C 16 h	11	 **1m**	70% 140°C 1 h
5	 **1g**	67% 80°C 2 h	12	 **1n**: X=Cl **1o**: X=Br	< 5% 120°C 16 h
6	 **1h**	56% 140°C 1 h	13	 **1p**: X=Cl **1q**: X=Br	< 5% 120°C 16 h
7	 **1i**	60% 140°C 1 h	14	 **1r**	< 5% 120°C 16 h

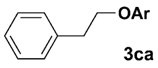
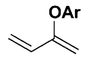
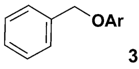
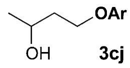
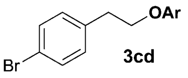
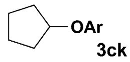
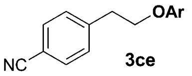
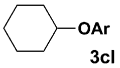
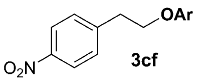
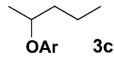
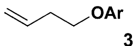
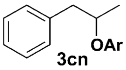
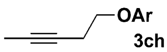
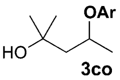
[a] Reaction conditions: CyPF-*t*Bu (10 mol%), [Pd$_2$(dba)$_3$] (5 mol%), Cs$_2$CO$_3$ (2 equiv), toluene (0.2 M).

Furthermore, tertiary alcohols were found to couple successfully (Table 4), although the more sterically demanding alcohol **2r** failed to give significant conversion to product. The use of [(allylPdCl)$_2$] rather than [Pd$_2$(dba)$_3$] as well as higher reaction temperatures was found neccessary for efficient couplings with these more challenging substrates. To the best of our knowledge, this is the first example of a general intermolecular Pd-catalyzed C–O cross-coupling reaction tolerant of primary, secondary, and tertiary alcohols employing a relatively mild base.

In conclusion, a robust and general Pd/Josiphos catalyst system has been identified for the alkoxylation of activated heretoaryl halides with primary, secondary, and select tertiary alcohols without the need for an excess of either coupling partner. The commercial availability of the Josiphos CyPF-*t*Bu ligand, excellent regioselectivity, absence of a required catalyst preformation step, insensitivity to the order of reagent addition, and broad functional-group tolerance make this protocol a robust, complementary approach to existing methods for C–O bond formation.

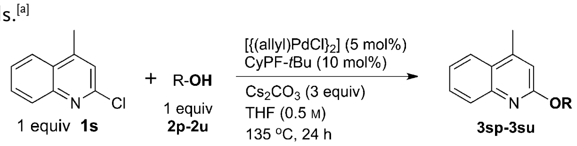
Table 3: C–O cross-coupling of 5-bromoquinoline with structurally diverse alcohols.[a]

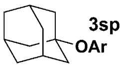
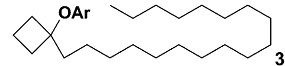
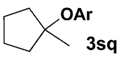
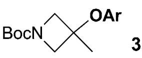
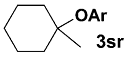
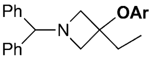


	R-OAr	Yield temp. time		R-OAr	Yield temp. time
1	 **3ca**	84% 80°C 20 h	8	 **3ci**	72%[b] 140°C 6 h
2	 **3cc**	75% 100°C 20 h	9	 **3cj**	87% 80°C 20 h
3	 **3cd**	74% 100°C 20 h	10	 **3ck**	90% 140°C 6 h
4	 **3ce**	75% 100°C 20 h	11	 **3cl**	88% 140°C 6 h
5	 **3cf**	72% 100°C 20 h	12	 **3cm**	86% 100°C 20 h
6	 **3cg**	77% 100°C 20 h	13	 **3cn**	83% 140°C 6 h
7	 **3ch**	86% 100°C 20 h	14	 **3co**	81% 140°C 6 h

[a] Reaction conditions: CyPF-*t*Bu (10 mol%), [Pd$_2$(dba)$_3$] (5 mol%), Cs$_2$CO$_3$ (2 equiv), toluene (0.2 M). [b] Alcohol starting material was but-2-yn-1-ol.

Table 4: C–O coupling of 2-chloro-4-methylquinoline with tertiary alcohols.[a]



	R-OAr	Yield		R-OAr	Yield
1	 **3sp**	72%	4	 **3ss**	77%
2	 **3sq**	58%[b]	5	 **3st**	83%
3	 **3sr**	< 5%[c]	6	 **3su**	85%

[a] Yield of isolated product after chromatographic purification.
[b] Product is hydrolytically unstable. [c] No isolation attempted.

Received: May 4, 2012
Revised: June 1, 2012

Keywords: C–O cross-coupling · heterocycles · homogeneous catalysis · palladium · synthetic methods

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[1] D. J. Mack, M. L. Weinrich, E. Vitaku, J. T. Njaroarson, http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster.

[2] S. Enthaler, A. Company, *Chem. Soc. Rev.* **2011**, *40*, 4912–4924.

[3] a) J. Niu, P. Guo, J. Kang, Z. Li, J. Zu, K. Hu, *J. Org. Chem.* **2009**, *74*, 5075–5078; b) R. A. Altman, A. Shafir, A. Choi, P. A. Lichtor, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 284–286.

[4] X. Wu, B. Forrs, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 10117–10121; *Angew. Chem. Int. Ed.* **2011**, *50*, 9943–9947.

[5] See the Supporting Information for further details.

[6] Similar results were obtained using K_3PO_4 as the base in toluene.

[7] a) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544; b) M. A. Fernádez-Rodríguez, J. F. Hartwig, *Chem. Eur. J.* **2010**, *16*, 2355–2359.

[8] Substrates **1a–c** showed no appreciable product formation with phenylethyl alcohol (**2a**) in toluene or THF in the absence of Pd catalysis (S_NAr conditions), and only very sluggish conversion with the formation of byproducts in DMF, DMAc, and DMSO at 80–140 °C.

[9] Because of its widespread availability, shelf stability, and ease of handling, $[Pd_2(dba)_3]$ was chosen as the Pd source for studies aimed at demonstrating the synthetic scope of this catalyst system.

[10] a) G. Mann, C. Incarvito, A. L. Rheingold, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225; b) G. Mann, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110; c) R. A. Widenhoefer, S. L. Buchwald, G. Mann, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, *120*, 6504–6511.

[11] G. Li, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 3740. The structure of the product was determined by 2D NMR correlation techniques.

[12] Regioselectivity was confirmed by 2D NMR correlation techniques.