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A General and Efficient Catalyst for Palladium-Catalyzed C−O Coupling Reactions of Aryl Halides with Primary Alcohols

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Abstract: An efficient procedure for palladium-catalyzed coupling reactions of (hetero)aryl bromides and chlorides with primary aliphatic alcohols has been developed. Key to the success is the synthesis and exploitation of the novel bulky di-1-adamantyl-substituted bipyrazolylphosphine ligand **L6**. Reaction of aryl halides including activated, nonactivated, and (hetero)aryl bromides as well as aryl chlorides with primary alcohols gave the corresponding alkyl aryl ethers in high yield. Noteworthy, functionalizations of primary alcohols in the presence of secondary and tertiary alcohols proceed with excellent regioselectivity.

Introduction

The synthesis of (hetero)aryl amines, anilines, (hetero)aryl ethers, and phenols via palladium- and copper-catalyzed cross-coupling methodologies has become an efficient and fundamental tool for advanced organic synthesis in both academic and industrial laboratories.[1] In addition to well established Buchwald−Hartwig amination reactions, in particular C−O bond forming reactions are interesting in organic synthesis due to the presence of these bonds in numerous natural products, biological compounds, pharmaceuticals, fragrances, cosmetics, and polymers.[2]

Traditionally, aryl ethers have been prepared by copper-mediated Ullmann coupling reactions of aryl bromides/iodides and phenols with the drawback of harsh reaction conditions and the need of a stoichiometric amount of metal.[3] Thus, the development of improved procedures, which allowed for the catalytic use of copper reagents and ligands initiated by Buchwald and co-workers and followed by many other groups during the past decade, was an important step forward.[4] Clearly, each of these protocols has its own virtues; however, limitations still exist with respect to substrate scope as well as an excess of alkoxides, undesirable solvents, etc. Thus, palladium-catalyzed intra- and intermolecular cross-coupling reactions of aryl halides with alcohols offer an interesting complementary method for the synthesis of aryl ethers under comparably mild conditions.[5] It is important to note that, in contrast to well-established palladium-catalyzed coupling reactions of tertiary alcohols and phenols,[6] only a few studies on the formation of alkyl aryl ethers with primary and secondary alcohols have been performed. On the other hand, aromatic ethers of aliphatic primary alcohols represent a structural motif in many naturally occurring and medicinal compounds (Scheme 1).

The general problem in the formation of these aromatic ethers is the competition of the desired reductive elimination to form

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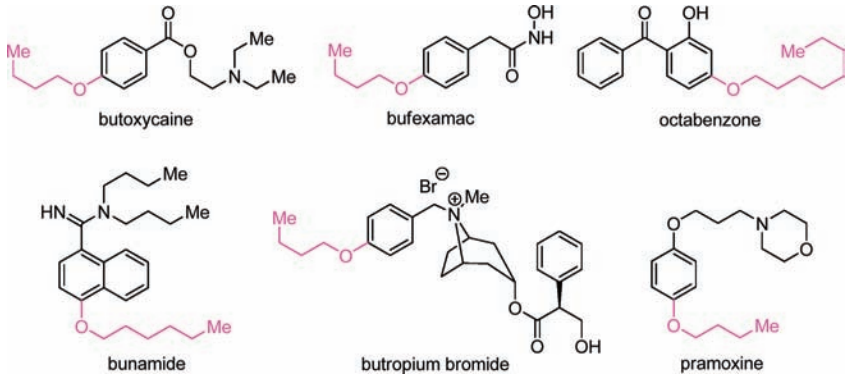
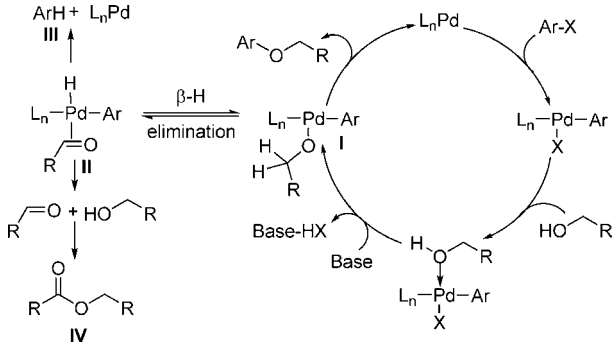
Scheme 1. Selected Examples of Biologically Important Aromatic Ethers of Primary Alcohols



Scheme 2. Coupling Reaction of Primary Alcohols and Aryl Halides: Product Formation and Side Reactions



the product and unwanted β-hydride elimination of the intermediate Ar−Pd−OCH_2R complex **I** (Scheme 2).

The chemoselectivity of the overall process depends strongly on relative rates of C−O bond-forming reductive elimination and β-hydride elimination. With most palladium alkoxy complexes β-hydride elimination proceeds faster compared to reductive elimination. Hence, alkoxides are known to be efficient hydride donors for reduction of aryl halides.[7] It is well-known that bulky nucleophilic phosphine ligands facilitate Pd-catalyzed reductive elimination at the expense of β-hydride elimination.[8] In this regard, this observation was successfully used by Buchwald and co-workers reported in 2001 for realization of the first example of Pd-catalyzed coupling of primary alcohols with aryl bromides and chlorides in the presence of bulky (2-(*N*,*N*-dimethylamino)-2′-di-*tert*-butylphosphinobinaphthyl.[9] Excellent results were obtained with aryl halides with electron-poor and one or two *ortho*-substituents, which facilitate the rate of reductive elimination. However, other aryl halides gave only poor to moderate yields. Later on in 2005, the Buchwald group introduced an improved, more tunable ligand system based on alkylated biaryls, which allowed for the coupling of primary and secondary, including allylic alcohols.[10] Here, the successful coupling was based on the ability to match the size of the ligand to that of the combination of substrates. However, elaborate synthesis of arylnaphthyl ligands, necessity to use a specific ligand for each group of aryl halides and alcohols, and the use of tri-*n*-butylamine as a solvent for arylation of secondary alcohols limit the general application of this methodology. Surprisingly, apart from Buchwald's biaryl phosphines, to date no other ligands have been successfully developed for palladium-catalyzed intermolecular coupling reactions of aliphatic alcohols.

In this paper we describe the application of air-stable easy-to-prepare bipyrazole phosphine ligand **L6** for general alkoxylation of aryl and heteroaryl bromides with primary and secondary alcohols.

Results and Discussion

For some years we have been interested in the development of palladium catalysts, which should be applicable for coupling reactions on both laboratory and industrial scale. In this respect, we have introduced in the past decade novel types of ligands such as di-1-adamantylalkylphosphines,[11] and especially 2-dialkylphosphino-*N*-arylindoles, pyrroles, and 2-dialkylphosphino-*N*-arylimidazoles.[12] Some of these ligands have been scaled up to kg-scale and commercialized.[13] Inspired by our recent work

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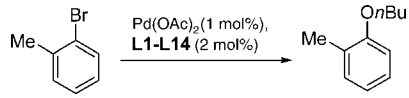
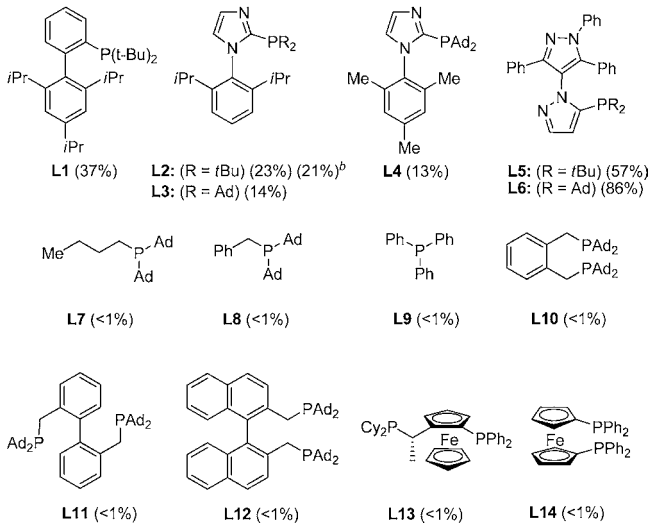
Table 1. Ligands Tested in the Pd-Catalyzed C−O Coupling of *o*-Bromotoluene with *n*BuOH[a]





[a] Reaction conditions: $Pd(OAc)_2$ (1 mol %), 2-bromotoluene (1.0 mmol), *n*BuOH (3.0 equiv), Cs_2CO_3 (1.5 equiv), toluene, 80 °C, 3−24 h, GC yield. [b] $Pd(dba)_2$.

on the reaction of aryl halides with hydroxide in the presence of sterically hindered 2-phosphino-*N*-arylimidazoles,[14] we decided to investigate these catalysts in coupling processes with aliphatic alcohols.

At the start of our work the reaction of *o*-bromotoluene with *n*BuOH was investigated as a model system in the presence of 1 mol % $Pd(OAc)_2$ and ligands **L1**−**L14** (Table 1). Unfortunately, in most cases dehalogenated toluene **III** and *n*-butyl butanoate **IV** were observed as main or side products. The formation of the latter ester is somewhat surprising but can be explained by dehydrogenation of the intermediate 1-butoxybutan-1-ol (Scheme 2). In this case the aryl halide acts as a stoichiometric oxidant. While such Pd-catalyzed reactions are rare, similar ruthenium-catalyzed processes are known.[15]

Both the commercially available Buchwald ligand **L1** and our imidazolylphosphine ligand **L2** gave mainly reductive dehalogenation and only low yields of the desired product (37 and 23%, respectively). Also little difference was observed on changing $Pd(OAc)_2$ to $Pd(dba)_2$. The results were even more disappointing with imidazolylphosphines **L3** and **L4** as well as with ligands **L7**−**L14**.

However, experiments performed in the presence of Singer's di-*tert*-butyl-substituted Bippyphos ligand **L5**[16] provided the best yield (57%) of the corresponding *n*-butyl aryl ether. Based on this promising result, we prepared the more bulky adamantyl-substituted analogue of **L5**. The straightforward synthesis of the new ligand **L6** is shown in Scheme 3. One-pot bromination of dibenzoyl methane with NBS followed by alkylation with pyrazole and condensation with phenylhydrazine resulted in the corresponding bipyrazolyl derivative in good yield. Subsequent lithiation and trapping of the intermediate with di-1-adamantylchlorophosphine afforded **L6** in excellent yield (86%). The structure of ligand **L6** is confirmed by ^1H, ^{13}C, ^{31}P NMR and mass spectra, and eventually by X-ray analysis (Scheme 3, ORTEP drawing of **L6**). Notably, **L6** is relatively air-stable and can be conveniently handled in air.

To our delight, the use of **L6** in the benchmark reaction resulted in the desired coupling product in 86% yield! Next, we investigated the influence of critical reaction parameters (palladium source, solvent system, base, and temperature) on the palladium-catalyzed coupling of *o*-bromotoluene with *n*-BuOH in the presence of **L6**. The source of palladium has no impact on the performance of the model reaction as $Pd(dba)_2$, $Pd_2(dba)_3$, $Pd(COD)(CH_2TMS)_2$, and $Pd(OAc)_2$ can be used interchangeably. Variation of the solvent (aromatics, amines, neat alcohol) confirmed that toluene was optimal for this reaction. Compared to K_2CO_3 and KOH, Cs_2CO_3 worked best for these reactions. While the reaction proceeded sluggishly at 65 °C, it is completed within 3 h at 80 °C in toluene.

With the optimized conditions in hand, we examined the reaction of several nonactivated aryl bromides and two aryl chlorides with *n*BuOH. As shown in Table 2, a series of alcohols such as 1-butanol, 1-hexanol, 1-octanol, 1-hexadecanol, and benzyl alcohol was reacted with *o*-bromotoluene. The corresponding tolyl alkyl ethers are obtained in 56−85% yield (Table 2, entries 1−5). Similarly, *o*-chlorotoluene yielded the desired product in 70% yield (Table 2, entry 6). Next, we examined the coupling of *m*- and *p*-bromotoluene whose reactions are not facilitated by the increased rate of reductive elimination from **I** due to *ortho*-substitution. However, both substrates are converted smoothly to the corresponding ethers in good yield (75 and 80%

Scheme 3. Synthesis of the New Biheteroaryl Ligand **L6**

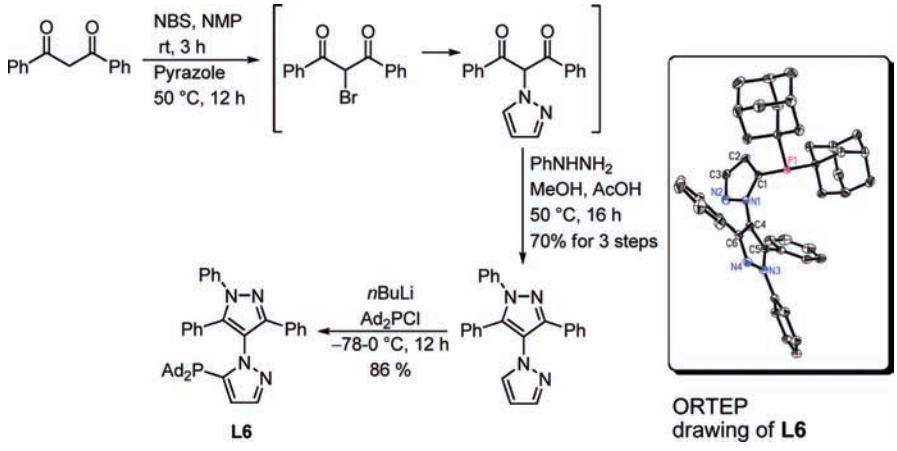
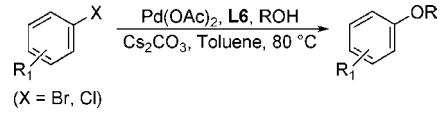
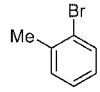
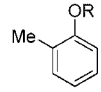
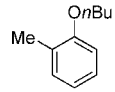
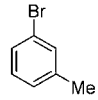
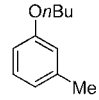
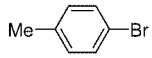
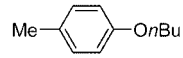
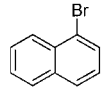
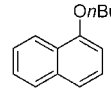
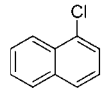
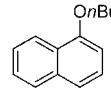
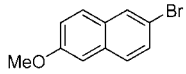
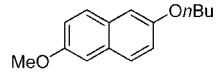
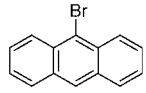
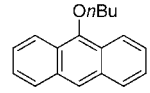
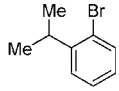
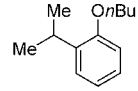
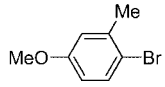
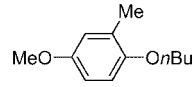
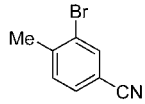
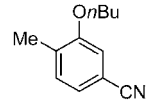
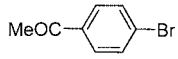
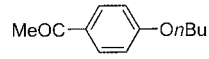
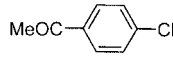
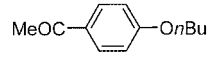
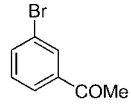
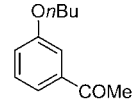
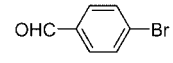
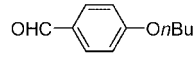
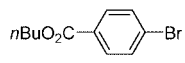
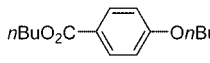


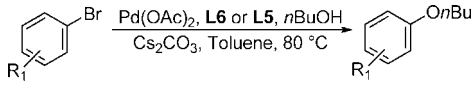
Table 2. Pd-Catalyzed Coupling Reactions of Aryl Halides with Primary Alcohols[a]

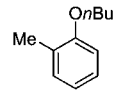
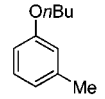
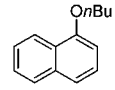
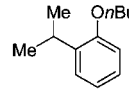
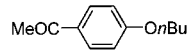


Entry	Aryl Halide	Product	Yield (%)[b]
1		 R = *n*Bu	85 (60)[c]
2		R = *n*Hex	81
3		R = *n*Oct	81
4		R = $nC_{16}H_{33}$	80
5		R = CH_2Ph	56
6			70[d]
7			75
8			80
9			87
10			74[e]
11			76
12			82
13			73
14			62
15			69
16			96
17			67
18			76
19			86
20			77

[a] Reaction conditions: $Pd(OAc)_2$ (1 mol %), **L6** (2 mol %), aryl halide (1.0 equiv), *n*BuOH (3.0 equiv), Cs_2CO_3 (1.5 equiv), toluene, 80 °C, 3−6 h. [b] Isolated yield. [c] 65 °C, 10 h. [d] 10% of the starting material was recovered, 12 h. [e] 10% of the starting material was recovered, 9 h.

Table 3. Comparison of Ligands **L6** and **L5**[a]



Entry	Product	Ligand	Time (h)	Yield (%)
1		**L5**	3	57
		L6	3	85
2		**L5**	8	52
		L6	5	75
3		**L5**	18	67[b]
		L6	3	87
4		**L5**	15	57
		L6	3	73
5		**L5**	10	83
		L6	3	96

[a] Reaction conditions: $Pd(OAc)_2$ (1 mol %), **L6** (2 mol %), aryl halide (1.0 equiv), *n*BuOH (3.0 equiv), Cs_2CO_3 (1.5 equiv), toluene, 80 °C. [b] 5% of the starting material was recovered.

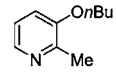
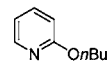
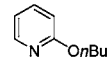
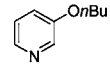
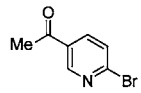
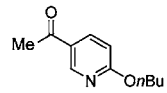
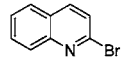
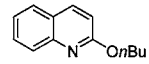
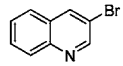
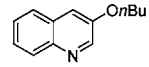
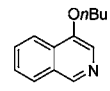
respectively, Table 2, entries 7 and 8). Likewise, 1-bromo- and 1-chloronaphthalene as well as 9-bromoanthracene gave the aryl alkyl ethers in 74−87% yield (Table 2, entries 9, 10, and 12). Reactions of methoxy-substituted 2-bromo-6-methoxynapthalene and 4-bromo-3-methylanisole are achieved in 76 and 62% yield, respectively (Table 2, entries 11 and 14). On the other hand substrates with electron-withdrawing substituents, e.g. CN, COMe, CO_2nBu, and CHO, are also coupled successfully in moderate to excellent yields (Table 2, entry 15−20).

Then, we compared the performance of ligand **L6** and the commercially available ligand **L5** in the coupling of various aryl bromides with *n*-butanol (Table 3). In all cases the novel ligand **L6** gave considerably higher yields of coupling products (Table 3, entry 1−5).

To the best of our knowledge, only one example of the coupling of (hetero)aryl halides with primary alcohols has been reported.[8a] Hence, we were interested in the performance of our catalytic system with (hetero)aryl halides. Notably, aliphatic ethers of pyridine and quinoline are a common scaffold found in current drugs.[17] Thus, we were pleased to find that 2- and 3-bromopyridine, 2-chloropyridine, 2- and 3-bromoquinoline, and 4-bromoisoquinoline are readily transformed with *n*-butanol into the corresponding products (Table 4, entries 1−8). Apart from 3-bromopyridine, 3-bromoquinoline, and 4-bromoisoquinoline, all substrates were converted to the *n*-butyl ethers in excellent yield.

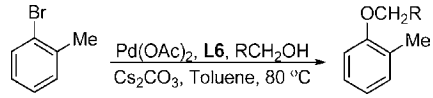
Next, we examined the selective functionalization of primary aliphatic alcohols in the presence of secondary and tertiary alcohols. For example, 1,3-butanediol has both a primary and secondary hydroxyl group, which obviously competes for the synthesis of the respective alkyl aryl ethers. To our delight conversion of 1,3-butanediol proceeded with complete regioselectivity (99%) for the primary alcohol to give the ether in 69% yield (Table 5, entry 1). Similarly, 3-methylbutane-1,3-diol with primary and tertiary hydroxyl groups gave the ether of the primary alcohol in 71% yield with excellent selectivity (>99%). The regioselectivity of these couplings are confirmed by GC-

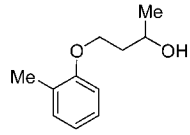
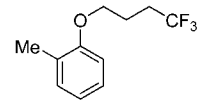
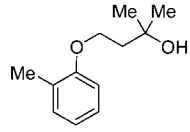
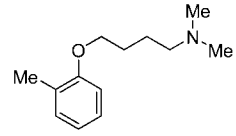
Table 4. Palladium-Catalyzed Coupling Reactions of Heteroaryl Halides with Primary Alcohols[a]

Entry	Heteroaryl Halides	Product	Yield (%)[b]
1			90
2			98
3			80[c]
4			58
5			93
6			96
7			57
8			31

[a] Reaction conditions: $Pd(OAc)_2$ (1 mol %), **L6** (2 mol %), heteroaryl halide (1 mmol), Cs_2CO_3 (1.5 equiv), *n*BuOH (3.0 equiv), toluene, 80 °C, 3−6 h. [b] Isolated yield. [c] 5−10% of the straring material was recovered, 7 h.

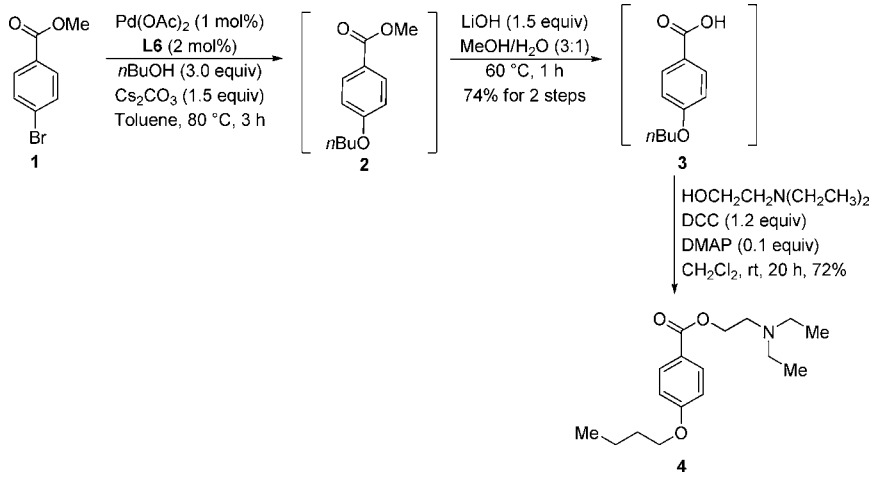
Table 5. Selective Pd-Catalyzed Arylation of Functionalized Alcohols[a]



Entry	Product	Yield (%)[b]	Entry	Product	Yield (%)[b]
1		69[c]	3		93
2		71	4		74

[a] Reaction conditions: $Pd(OAc)_2$ (1 mol %), **L6** (2 mol %), 2-bromotoluene (1 mmol), Cs_2CO_3 (1.5 equiv), alcohol (3.0 equiv), toluene, 80 °C, 3 h. [b] Isolated yield. [c] 18 h.

Scheme 4. Synthesis of Butoxycaine **4**



MS studies of the reaction mixture. Product characterization is confirmed by 2D NMR correlation techniques. In addition, other functionalized alcohols such as 4,4,4-trifluoro-1-butanol and *N*,*N*-dimethylbutanol afforded the coupling products under standard conditions in good yields (74−93%).

Finally, we envisioned a short application of our methodology for the synthesis of butoxycaine **4**, which represents a local anesthetic drug.[18] Straightforward palladium-catalyzed C−O bond formation of methyl 4-bromobenzoate **1** proceeded in the presence of $Pd(OAc)_2$ (1 mol %), **L6** (2 mol %), and Cs_2CO_3 (1.5 equiv) with *n*BuOH (3.0 equiv) at 80 °C in 3 h to produce **2** with a trace amount of the trans-esterified butyl ester (20:1 ratio, based on GC). Without purification **2** was subjected to alkaline hydrolysis (LiOH) to give **3** in 74% yield over two steps. Subsequent DCC coupling with 2-(diethylamino)ethanol provided the current drug butoxycaine **4** in 72% yield (Scheme 4).

In conclusion, we describe the synthesis of the novel sterically hindered, air-stable bispyrazolylphosphine ligand **L6** and its application in the palladium-catalyzed synthesis of alkyl aryl ethers. (Hetero)aryl alkyl ethers are obtained in moderate to excellent yields from activated, nonactivated, and (hetero)aryl substrates with primary alcohols. Furthermore, we have demonstrated for the first time the regioselective C−O bond-forming arylation of primary

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alcohols in the presence of secondary and tertiary alcohols. Our catalyst system tolerates a variety of functional groups including amines. The presented protocol is complementary to the two known catalyst systems of Buchwald and co-workers and allows for interesting applications in organic synthesis.

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Supporting Information Available: Detailed experimental procedures and characterization of products. The material is available free of charge via the Internet at http://pubs.acs.org.

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