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An Improved Cu-Based Catalyst System for the Reactions of Alcohols with Aryl Halides

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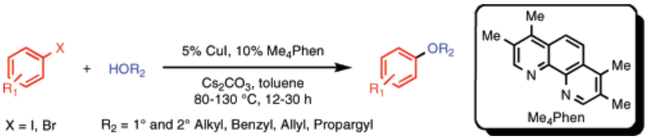

The use of 3,4,7,8-tetramethyl-1,10-phenanthroline (Me$_4$-Phen) as a ligand improves the Cu-catalyzed cross-coupling reactions of aryl iodides and bromides with primary and secondary aliphatic, benzylic, allylic, and propargylic alcohols. Most importantly, by employing this catalyst system, the need to use an excessive quantity of the alcohol coupling partner is alleviated. The relatively mild conditions, short reaction times, and moderately low catalyst loading allow for a wide array of functional groups to be tolerated on both the electrophilic and nucleophilic coupling partners.

In our continuing quest to improve metal-catalyzed C-heteroatom bond-forming reactions, we have developed several Pd- and Cu-based catalyst systems for the intermolecular coupling reactions of aliphatic alcohols with aryl halides to prepare alkyl aryl ethers.[1,2] Using Pd-based catalysts, the low yields observed in the coupling of certain substrates have been attributed to the slow rate of C−O reductive elimination relative to β-hydride elimination from the $L_nPd^{II}(Ar)(alkoxide)$ intermediate.[1a,b,3] In these cases, Cu-based catalyst systems can provide complementary reactivities, as the analogous intermediates derived from these catalysts do not readily undergo β-hydride elimination reactions.[4]

The substrate scopes and the overall utility of the traditional Cu-based methods for the synthesis of alkyl aryl ether are severely limited by (1) the use of superstoichiometric quantities of Cu, (2) high reaction temperatures, and (3) the use of strong alkoxide bases.[5] Currently, few generally applicable Cu-based catalyst systems, which facilitate the reaction under mild conditions, have been reported for the cross-coupling of aliphatic alcohols with aryl halides.[2,6,7]

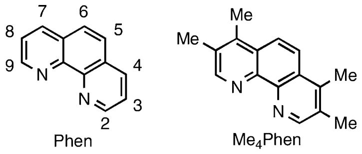

FIGURE 1. 1,10-Phenanthroline-based ligands for Cu-catalyzed C−O bond formation.

In 2002, we reported that 10 mol % of CuI in conjunction with 20 mol % of 1,10-phenanthroline (Phen, Figure 1) could facilitate C−O bond formation between aryl iodides and aliphatic alcohols under mild reaction conditions (Cs_2CO_3/110 °C/18−38 h); however, in most cases, the use of the alcohol as a solvent was required to achieve satisfactory yields, thus rendering the procedure impractical for the use of precious or highly functionalized alcohols.[2] In certain simple cases, toluene could be utilized as a solvent to reduce the quantity of alcohol required for the reactions. Recently developed catalysts systems that employ amino acids as ligands or KF/Al_2O_3 as the base have also failed to overcome the required use of excess quantities of alcohols for these reactions.[7] In addition, reactions of both secondary (2°) cyclic and acyclic alcohols provided the corresponding products in low yields due to incomplete conversion of the aryl iodides in reasonable time periods ($<$24 h).[2,7]

More recently, we reported that the use of a commercially available ligand, 3,4,7,8-tetramethyl-1,10-phenanthroline (Me$_4$-Phen, Figure 1), improved the Cu-catalyzed nucleophilic substitution reactions of aryl iodides and alkyl-substituted vinyl iodides with amino alcohols and allylic alcohols, respectively; however, the scope of the reaction was not investigated/explored beyond these selected substrates.[8,9] Herein, we report an in-depth account of the use of Me$_4$Phen in Cu-catalyzed C−O bond-forming reactions that presents the scope and limitations of this catalyst system.

A variety of 1,10-phenanthroline-substituted ligands were tested in the reaction of 4-iodoanisole with *n*-hexanol using the following catalyst system: 5 mol % CuI/10 mol % ligand/Cs_2CO_3/toluene/80 °C/12 h (Table 1). The data presented suggest that the presence of methyl and phenyl substituents in positions 3−5 of the phenanthroline backbone increase the activity of the catalyst (entries 1−7). More specifically, the catalytic activity of the methyl-substituted ligands increases as a function of the number of methyl substituents present on the Phen core: Phen $<$ 4-MePhen $\sim$ 5-MePhen $<$ 4,7-Me$_2$Phen $<$ 5,6-Me$_2$P-hen $<$ Me$_4$-Phen. Two hypotheses to explain the high activity of the catalyst systems, which employ methyl-substituted Phen ligands, are (1) the alkyl substituents might increase the solubility of the metal catalyst in a nonpolar organic solvent, thus raising

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(4) For reviews including Cu-catalyzed C−O bond formation, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 2337. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

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(8) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978.

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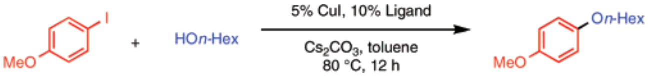
TABLE 1. Cu-Catalyzed Reaction of 4-Iodoanisole with *n*-Hexanol Using 1,10-Phenanthroline-Derived Ligands[a]



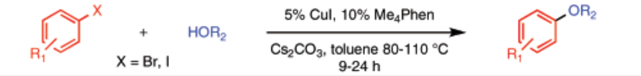
entry	ligand	conversion (%)	yield (%)
1	1,10-phenanthroline (Phen)	50	44
2	4-Me-Phen	56	54
3	5-Me-Phen	55	51
4	4,7-Me_2-Phen	68	57
5	5,6-Me_2-Phen	64	54
6	3,4,7,8-Me_4-Phen	82	79
7	4,7-Ph_2-Phen	63	64
8	neocuproine	10	0
9	4,7-$(MeO)_2$-Phen	83	66
10	4,7-$(NMe)_2$-Phen	37	19
11	4,7-Cl_2-Phen	35	33

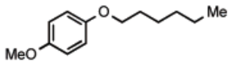
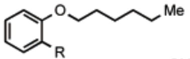
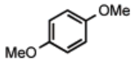
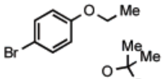
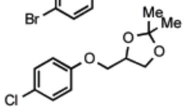
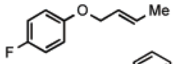
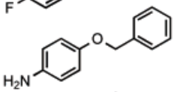
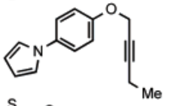
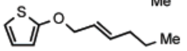
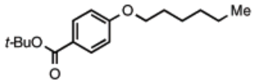
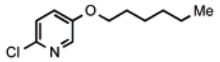
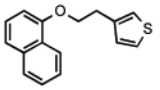
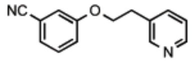
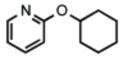
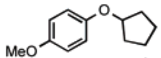
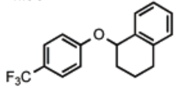
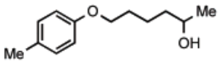
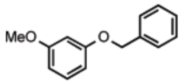
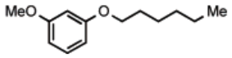
[a] Reaction conditions: 1.0 mmol of 4-iodoanisole, 1.5 mmol of *n*-hexanol, 0.050 mmol of CuI, 0.10 mmol of ligand, 1.5 mmol of Cs_2CO_3, and 0.5 mL of toluene under Ar atmosphere at 80 °C for 12 h. Corrected conversion and yield data were calculated from GC analyses of the crude reaction mixtures using dodecane as an internal standard.

the effective concentration of catalyst in solution, and/or (2) the presence of the alkyl substituents on the ligand increases the σ-donating ability of the nitrogen atoms[10] and accelerates the rate-limiting aryl halide activation step. Neocuproine (2,9-dimethyl-Phen) is not a good ligand for this transformation and reinforces the notion that Cu-catalyzed C-heteroatom bond-forming reactions are extremely sensitive to steric hindrance.[4] When 4,7-$(MeO)_2$Phen is employed as a ligand for this transformation, 1,4-dimethoxybenzene is produced as a byproduct (~15% GC yield), presumably due to nucleophilic displacement of the methoxy groups of the ligand by *n*-hexanol, followed by cross-coupling of the resulting methoxide nucleophile with the aryl iodide (entry 9). Interestingly, the combined yield of methoxy- and *n*-hexyloxy-substituted products (~81%) when employing the dimethoxy-substituted ligand is comparable to the yield of product observed when Me_4Phen is used (79%), suggesting that these two catalyst systems facilitate C−O bond formation at comparable rates. Other 4,7-bis-heteroatom-substituted-Phen derivatives provide relatively inactive catalysts (entries 10, 11).

Using the optimized reaction conditions, a wide variety of substrates containing useful functional groups can be successfully cross-coupled (Table 2). The reaction of our model substrates (*n*-hexanol with 4-iodoanisole) proceeds in excellent yield at temperatures as low as 80 °C using 5% catalyst (entry 1). At 110 °C using 2% and 5% catalyst loading, this same reaction proceeds in 24 and 12 h, respectively (entries 2, 3). The catalyst system is tolerant of ortho-substituents on the aryl halide (entries 4−6), as well as both electron-donating and withdrawing substituents on the aromatic ring. Aryl iodides can be selectively cross-coupled in the presence of aryl bromides, chlorides, and fluorides (entries 8−10). Low-boiling point alcohols, as well as allyl, propargyl, and benzyl alcohols, furnish the corresponding aryl ethers in good to excellent yields (entries 7, 8, 10−13). The latter example provides ready access to the corresponding phenols, as the resulting aryl benzyl ether can be readily cleaved.[11] Remarkably, the catalyst system can selectively cross-couple alcohols in the presence of an unprotected aniline (entry 11) or aliphatic amines.[9] Although the Cu-

TABLE 2. CuI/Me_4Phen-Catalyzed Cross-Coupling Reactions of Alcohols with Aryl Iodides and Bromides[a]



entry	product	X =	temperature (°C)	time (h)	yield (%)
1		I	80	20	87[b]
2		I	110	24	99[b,c]
3		I	110	12	95[b]
4	 R = Me	I	110	24	83
5	OMe	I	110	30	94
6	Cl	I	110	24	80
7		I	80	20	82
8		I	80	24	72[d]
9		I	80	16	75
10		I	80	20	74
11		I	80	16	81
12		I	80	20	92
13		I	80	16	59
14		I	80	24	92[e]
15		I	80	16	86
16		I	110	24	95
17		I	80	24	78[f]
18		I	110	24	85[f]
19		I	110	24	88
20		I	110	24	75
21		I	80	24	73[g]
22		Br	110	24	94[h]
23		Br	130	24	77[i]

[a] Reaction conditions: 1.0 mmol of ArX, 1.5 of mmol alcohol, 0.050 of mmol CuI (5%), 0.10 mmol of Me_4Phen (10%), 1.5 mmol of Cs_2CO_3, and 0.50 mL of toluene under an Ar atmosphere. The isolated yields reported are averages of two or more runs of material judged to be >95% pure by ^{1}H NMR and/or elemental analysis. [b] GC yield reported. [c] 2% CuI, 4% Me_4Phen. [d] GC analysis: 14:1 mixture of I- to Br-substituted products which were separated by column chromatography. [e] Inseparable 7:1 mixture of depicted product and *n*-hexyl 4-(hexyloxy)benzoate. [f] 200 mg of 4 Å mol sieves added to reaction mixture. [g] One regioisomer detected by GCMS and ^{1}H NMR. [h] 10% CuI, 20% Me_4Phen. [i] 130 °C, 0.50 mL of *n*-hexanol used as solvent.

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[10] pK_a in H_2O: +H-Me_4Phen = 6.31, +H-Phen, = 4.86. Schilt, A. A.; Smith, G. F. *J. Phys. Chem.* **1956**, *60*, 1546.

catalyzed reaction of ethyl 4-iodobenzoate with *n*-hexanol provides a complex mixture of transesterified and cross-coupled products, the formation of the transesterified product can be drastically reduced by employing the *tert*-butyl ester (entry 14). Heterocyclic compounds can be employed either as the electrophilic or nucleophilic reactant (entries 12, 13, 15−18). Products containing water-sensitive functional groups can be provided in good yields by adding activated molecular sieves to the reaction mixtures. (entries 17, 18).

The Cu-catalyzed cross-coupling reactions of secondary alcohols with aryl halides are particularly important reactions, due to the increased propensity for 2° alcohols to undergo β-hydride elimination using Pd-based catalyst systems.[1] Further, the complementary uncatalyzed Williamson reactions of 2° alkyl halides with poorly nucleophilic phenols typically provide low yields of the aryl alkyl ether products.[12] The CuI/Me_4Phen-catalyzed reactions of 2° cyclic alcohols with aryl iodides are generally slower than the respective primary (1°) alcohol counterparts (entries 18−20), requiring higher reaction temperatures (110 °C compared to 80 °C). However, the reactions of secondary acyclic alcohols (e.g., isopropyl alcohol and 3-pentanol) with simple aryl iodides are unsuccessful, unless the reactions are run in neat alcohol. This difference in reactivity can be exploited to selectively cross-couple a 1° alcohol in the presence of a 2° alcohol (entry 21). We speculate that this selectivity difference occurs due to the poor coordinating ability of the 2° alcohol relative to the 1° alcohol.

The cross-coupling reactions of aryl bromides are less successful than their iodide counterparts. At a 10% catalyst loading, the reaction of benzyl alcohol with 3-bromoanisole proceeds smoothly (entry 22). However, the Cu-catalyzed reactions of other aliphatic alcohols are more challenging for this catalyst system. An aryl bromide can be successfully cross-coupled in neat *n*-hexanol at an elevated temperature (130 °C, entry 23). However, the reactions of both 2° cyclic and acyclic alcohols do not proceed to full conversion under these and more rigorous conditions. These data suggest that the efficacy of Cu-catalyzed cross-coupling reactions of various alcohols with aryl halides follows the trend benzylic $>$ 1° alkyl $>$ 2° cyclic alkyl $>$ 2° acyclic alkyl. We suspect that the efficiency of reactions that employ benzylic alcohols is due, in large part, to their enhanced acidity relative to other aliphatic alcohols.[13]

In summary, we have explored the utility of Me_4Phen as a ligand in the Cu-catalyzed cross-coupling reactions of aryl iodides and bromides with alcohols. With this protocol, the cross-coupling reactions of aryl iodides with alcohols can be run under mild conditions without the required use of excess quantities of nucleophile in the reaction. This catalyst system complements Pd-based catalyst systems, as well as traditional Williamson reactions, and nucleophilic substitution reactions of activated aryl halides for the preparation of alkyl aryl ethers. We believe that chemists in both academic and industrial laboratories will find this improved catalyst system useful in their work.

Experimental Section

General Procedure for the Cu-Catalyzed Cross-Coupling of Alcohols with Aryl Halides. An oven-dried screw-cap test tube was charged with CuI (9.5 mg, 0.050 mmol), Me_4Phen (24 mg, 0.10 mmol), aryl halide (1.0 mmol, if solid), Cs_2CO_3 (490 mg, 1.5 mmol), and a magnetic stir bar. The reaction vessel was fitted with a rubber septum. The test tube was evacuated and back-filled with dry argon. Aryl halide (1.0 mmol, if liquid) and toluene (0.50 mL) were then added by syringe. The rubber septum was removed and the reaction tube was quickly sealed with a Teflon-lined septum. The vessel was immersed in a preheated oil bath and stirred vigorously until TLC and/or GC analysis of the crude reaction mixture indicated that the aryl halide had been completely consumed. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (15 mL), filtered through a plug of silica gel, and further eluted with additional ethyl acetate (30 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (hexane/ethyl acetate) to provide the desired product.

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

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[12] Smith, M. B.; March J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,* 5th ed.; John Wiley & Sons, Inc.: New York, 2001; p 477.

[13] pK_a in DMSO: BnOH = 26.9, EtOH = 29.8. (a) Bordewll, F. G.; Liu, W. Z. *J. Am. Chem. Soc.* **1996**, *118*, 8777. (b) Olmstead, W. N.; Margolin, Z.; Bordwell, F. B. *J. Org. Chem.* **1980**, *45*, 3295.