Published in final edited form as:
Org Lett. 2013 November 15; 15(22): . doi:10.1021/ol402904d.

Copper-Catalyzed Etherification of Arene C-H Bonds

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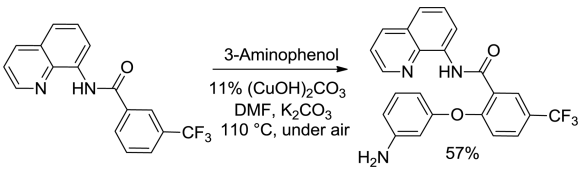
Abstract



A method for direct, auxiliary-assisted alkoxylation and phenoxylation of β-sp^2 C−H bonds of benzoic acid derivatives and γ-sp^2 C−H bonds of amine derivatives is reported. The reaction employs $(CuOH)_2CO_3$ catalyst, air as an oxidant, phenol or alcohol coupling partner, DMF, pyridine, or DMPU solvent, and K_2CO_3, tetramethylguanidine, or K_3PO_4 base at 90–130 °C.

Carbon-hydrogen bond functionalization methodology is perhaps the most direct way to introduce functionality into organic molecules. In the last decade, significant advances in C-H activation and functionalization have been realized.[1] However, relatively scarce second- and third row transition metals are most commonly used for these transformations. It would be beneficial if abundant first-row transition metals could replace their heavier analogues as catalysts for C-H bond functionalization.[2] Most examples of direct hydroxylation or etherification of sp^2 C-H bonds have been performed under palladium or ruthenium catalysis.[3] While copper-promoted oxygenation of sp^2 C-H bonds has been studied in context of evaluating mechanisms of oxidations by enzymes, catalytic applications of such reactions in synthetically relevant systems have been rare.[4] An early report by Reinaud showed that copper(II) mediates aromatic hydroxylation by trimethylamine *N*-oxide.[4a] More recently, Yu has shown that a number of nucleophiles, including water, can be coupled with 2-phenylpyridine by employing Cu(II) salts and oxygen oxidant.[4b] Subsequently, other groups have reported related copper-catalyzed sp^2 C-H bond functionalization reactions.[4] Martin has shown that copper-catalyzed hydroxylation of 2-phenylbenzoic acid is possible.[5a] This report is especially interesting since carboxylate functionality remains intact.[5b] We disclose here a general method for aminoquinoline and picolinamide-directed benzoic acid and amine derivative ortho-etherification by employing air as an oxidant.

In 2005, we introduced picolinic acid and 8-aminoquinoline auxiliaries for palladium-catalyzed C-H bond functionalization.[6] Subsequently, these auxiliaries have been used by a number of groups for palladium-, nickel-, iron-, and ruthenium-catalyzed sp^2 and sp^3 C-H bond functionalization.[7] Recently, we have developed aminoquinoline- and picolinamide-directed, copper-catalyzed sulfenylation, amination, and fluorination of arene and heteroarene C-H bonds.[8] The common feature of these reactions is the coupling of a

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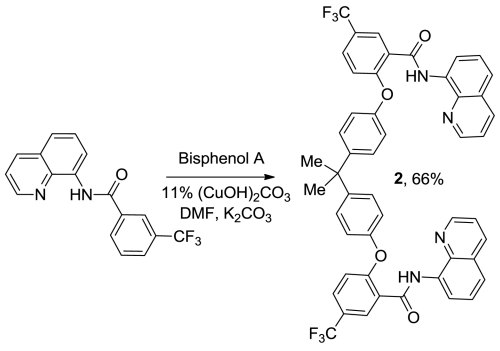
Supporting Information Available Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org..

nucleophile with a C-H bond. We speculated that copper-catalyzed etherification of sp^2 C-H bonds should be possible if aminoquinoline or picolinic acid directing groups are employed. Additionally, in an insightful mechanistic study of Cu(II)-mediated sp^2 C-H bond oxidation, Stahl has reported the methoxylation of *N*-(8-quinolinyl)benzamide by employing methanol solvent and 2 equiv of $Cu(OAc)_2$.[9a]

Reaction of 8-aminoquinoline 3-trifluoromethyl-benzamide **1** was investigated with respect to Cu catalyst, oxidant, and base (Table 1). The conditions developed for arene amination[8b] resulted in low yield of coupling product (entry 1). Replacing Ag_2CO_3 with K_2CO_3 was beneficial (entry 2), and the reaction could be run under an atmosphere of oxygen for additional increase of yield (entry 3). Interestingly, omission of NMO oxidant and running the reaction under air in an open flask was successful (entry 4). Furthermore, yield could be increased if reaction time was decreased from 12 to 6 hours (entry 5). Thus, the optimal reaction conditions involve 1 equiv of phenol, K_2CO_3 base, 11 % (22% based on Cu) of $(CuOH)_2CO_3$ catalyst, DMF solvent, 110 °C, and air as oxidant.

The reaction scope with respect to phenols is presented in Table 2 and Equation 1. Reactions were run on a 0.5 mmol scale. Electron-rich (entries 1, 8, 9) and electronpoor (entries 3–6) phenols are reactive. The reactions tolerate most functional groups, such as thioether (entry 2), bromide (entry 4), chloride (entries 7 and 8), amino (entry 9) and even iodide (entry 5). Ester functionality is also tolerated (entry 6). *ortho*-Substituted phenols are reactive (entry 8). Interestingly, bisphenol A can be used and double arylation product **2** was isolated in 66% yield (eq 1). The yields range from good to excellent, and reaction times are 2–8 hours. A 3.2 mmol scale reaction of **1** with 4-*t*-butylphenol afforded 73% isolated yield of product (entry 1).

Reaction scope with respect to aliphatic alcohols is presented in Table 3. Optimal base for alkoxylation is tetramethylguanidine (TMG), and the best results were obtained by employing 5 equiv of alcohol in pyridine solvent. Air was used as an oxidant. Simple primary alkyl alcohols such as cyclopropylmethanol afford good yields of the product (entry 1). Trifluoromethanol (entry 2) and allyl alcohol (entry 3) are reactive and coupling products were isolated in 73 and 71% yields. More complex structures such as carbitol (entry 4), cinchonine (entry 5), and ethyl lactate (entry 6) gave products in fair to excellent yields. The latter examples show that aliphatic esters, amines, esters, and polyethers are tolerated in the reaction. Reaction with trifluoroethanol was carried out in closed vessel pressurized with O_2 due to volatility of the alcohol.

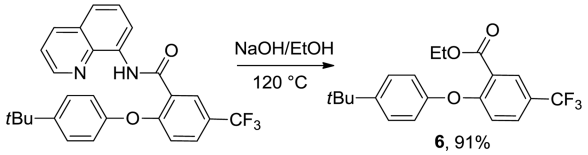


(1)

The reaction scope with respect to aminoquinoline benzamides is presented in Table 4. Cyano- (entry 1), trifluoromethyl- (entry 2), nitro- (entry 3), and methoxysubstituted (entries

4 and 5) amides are reactive and monosubstitution products are obtained in moderate to good yields. Heterocyclic amides are compatible with the reaction conditions (entires 7 and 8). In contrast with aminoquinoline benzamide amination where diamination products were not observed,[8b] bis-phenoxylation is possible by employing higher phenol/amide rations and DMPU solvent (entry 8). The disubstitution product was obtained in 47% yield.

Picolinamide can also serve as a directing group (Scheme 1). Thus, α,α-dimethylbenzylamine picolinamide can be phenoxylated in moderate yield at 110 °C by employing $(CuOH)_2CO_3$ catalyst, K_3PO_4 base, and DMF solvent. 1-Naphthylamine picolinamide phenoxylation occurs at 8-position and the product was isolated in 70% (0.5 mmol scale reaction) or 73% yield (5 mmol scale reaction). The reactions can be scaled up at least tenfold without loss of yield. The directing group can be removed by base hydrolysis affording 8-aryloxynaphthylamine **5** in high yield. Aminoquinoline auxiliary can be removed as well (eq 2).



(2)

In conclusion, we have developed a method for direct, auxiliary-assisted alkoxylation and phenoxylation of β-sp^2 C−H bonds of benzoic acid derivatives and γ-sp^2 C−H bonds of amine derivatives. The reaction employs $Cu_2(OH)_2CO_3$ catalyst, air as an oxidant, phenol or alcohol coupling partner, DMF, pyridine, or DMPU solvent, and K_2CO_3, tetramethylguanidine, or K_3PO_4 base at 90–130 °C. The method is advantageous compared to the existing sp^2 C-H bond etherification procedures due to utilization of inexpensive copper basic carbonate (malachite) catalyst and a removable directing group. The method shows high generality and functional group tolerance, with ester, amine, nitro, nitrile, and halogen functionalities compatible with the reaction conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the Welch Foundation (Grant No. E-1571), NIGMS (Grant No.R01GM077635), and Camille and Henry Dreyfus Foundation for supporting this research.

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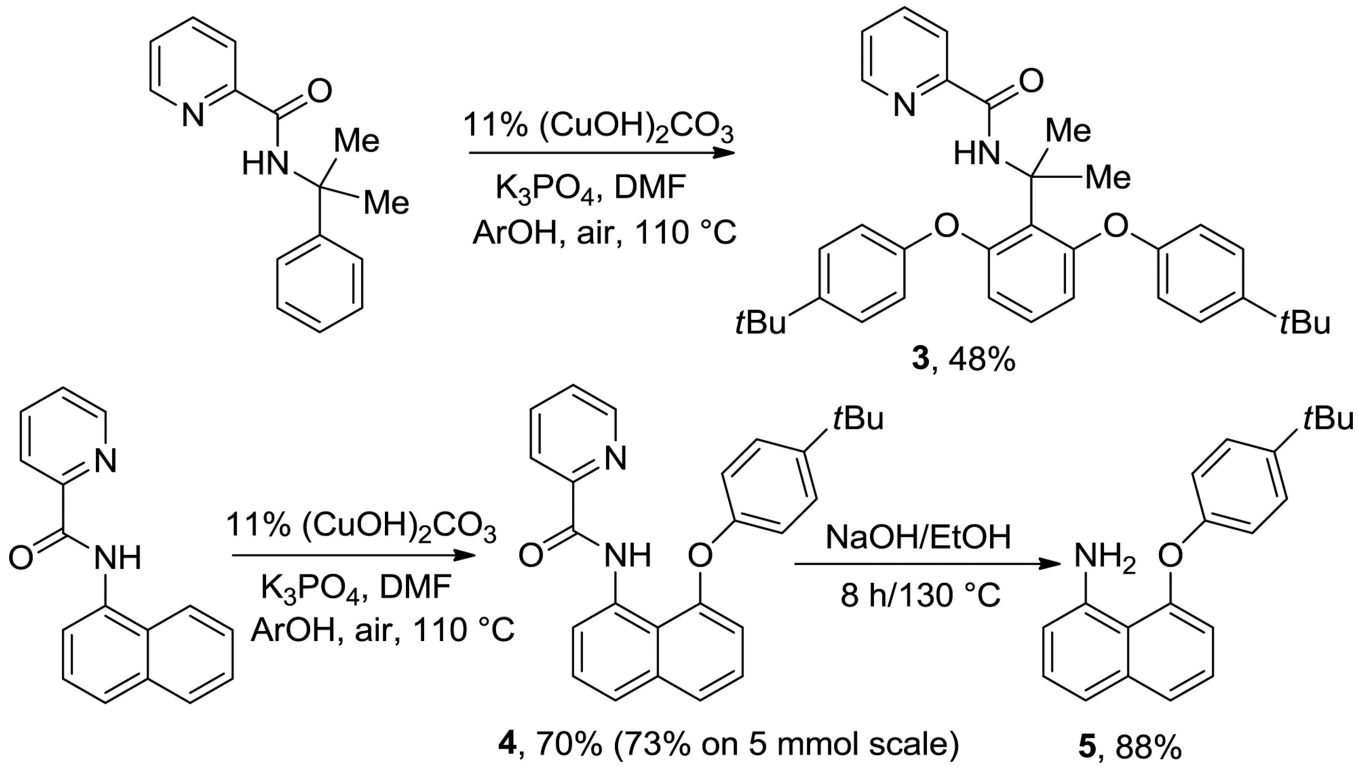
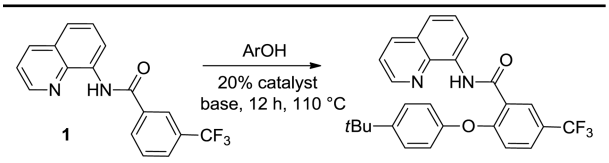


Scheme 1.
Picolinic Acid Directing Group

Table 1

Screening of Reaction Conditions[a]



entry	catalyst	base	oxidant	yield, %
1[b]	$Cu(OAc)_2$	Ag_2CO_3	NMO	21
2[c]	$Cu(OAc)_2$	K_2CO_3	NMO	64
3[c,d]	$Cu(OAc)_2$	K_2CO_3	NMO/O_2	67
4[e]	$(CuOH)_2CO_3$	K_2CO_3	air	68
5[e,f]	$(CuOH)_2CO_3$	K_2CO_3	air	88

[a] Amide (0.1 mmol), phenol (0.1 mmol), catalyst (0.02 mmol), base (0.2 mmol). Yields determined by NMR of crude reaction mixtures.

[b] NMO (*N*-methylmorpholine oxide) 0.2 mmol, NMP solvent.

[c] NMO 0.2 mmol, DMF solvent.

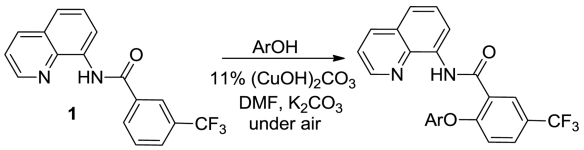
[d] Under 1 atm of O_2.

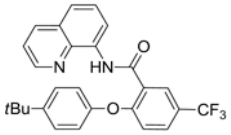
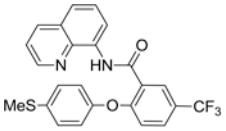
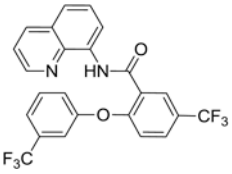
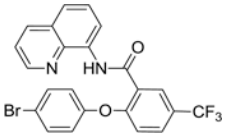
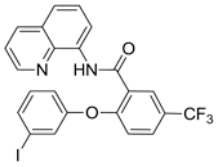
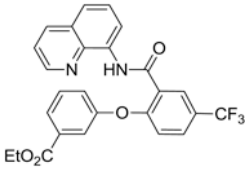
[e] Reaction open to air, 11 mol % catalyst (22% Cu).

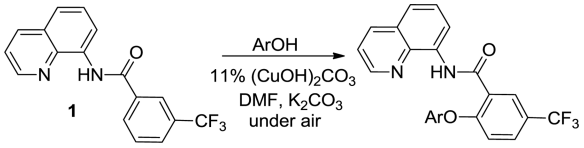
[f] Isolated yield, reaction time − 6 h.

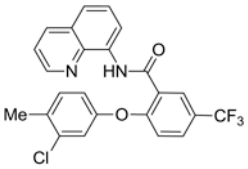
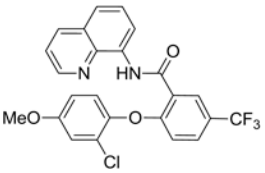
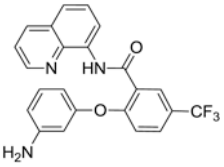
Table 2

Reaction Scope with Respect to Phenols[a]



entry	phenol	product	yield, %
1	4-*t*Bu-phenol		88 73[b]
2	4-SMe-phenol		75
3	3-CF_3-phenol		55
4	4-Br-phenol		78
5	3-I-phenol		56
6	3-CO_2Me-phenol		84



entry	phenol	product	yield, %
7	3-Cl-4-Me-phenol		77
8	2-Cl-4-MeO-phenol		78
9[c]	3-amino-phenol		57

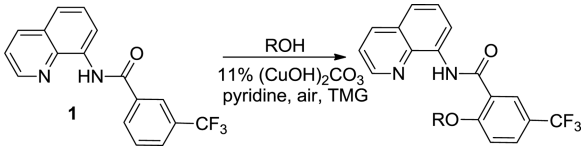
[a] Scale: 0.5 mmol; time: 2–8 h; 1/1 amide/phenol ratio, 110 °C, 11% catalyst = 22 mol % Cu. Please see Supporting Information for details.

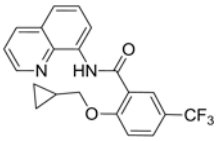
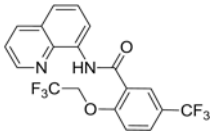
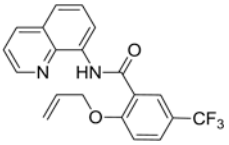
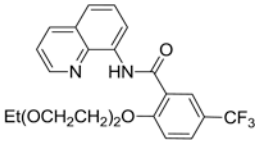
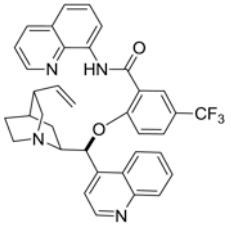
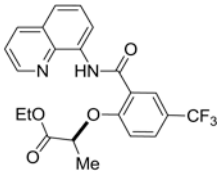
[b] Scale: 3.2 mmol, 5.5 mol % $(CuOH)_2CO_3$.

[c] Amide/phenol ratio: 1/2.

Table 3

Reaction Scope with Respect to Aliphatic Alcohols[a]



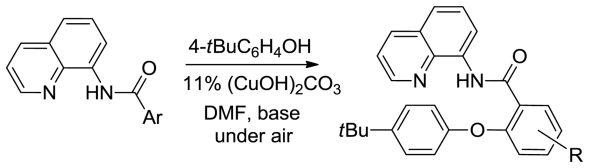
entry	alcohol	product	yield, %
1	cyclopropyl-methanol		75
2[b]	$HOCH_2CF_3$		73
3	allyl alcohol		71
4	carbitol		72
5	cinchonine		85
6	ethyl lactate		39

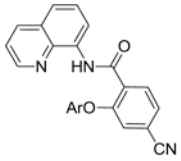
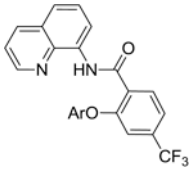
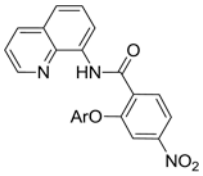
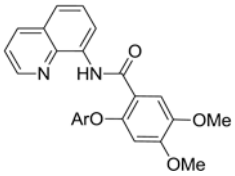
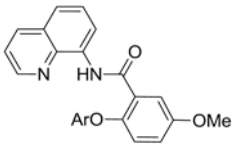
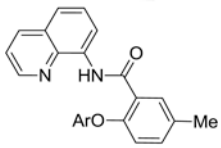
[a] Scale: 0.5 mmol; time: 2–8 h; 1/5 amide/alcohol ratio, 110 °C, 11% catalyst = 22 mol % Cu. Please see Supporting Information for details.

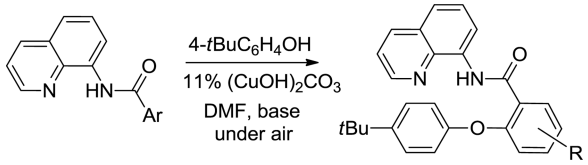
[b] Closed vessel pressurized with O_2.

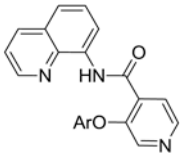
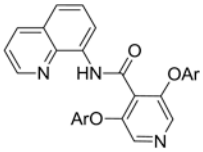
Table 4

Reaction Scope with Respect to Amides



entry	Ar	product	yield, %
1	4-CNC_6H_4		55
2	4-$CF_3C_6H_4$		74
3	4-$NO_2C_6H_4$		59
4	3,4-$(OMe)_2C_6H_4$		57
5	3-$MeOC_6H_4$		54
6	3-MeC_6H_4		60



entry	Ar	product	yield, %
7	4-C_5H_4N		51
8[b]	4-C_5H_4N		47

[a] Scale: 0.5 mmol; time: 2–8 h; 1/1 amide/alcohol ratio, 90–110 °C, 11% catalyst = 22 mol % Cu. Please see Supporting Information for details.

[b] Amide/alcohol ratio: 1/3, DMPU solvent.