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2-(Trimethylsilyl)ethanol as a new alcohol equivalent for copper-catalyzed coupling of aryl iodides

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ABSTRACT

2-(Trimethylsilyl)ethanol as a new alcohol equivalent has been employed for copper-catalyzed coupling of aryl iodides. Using mild reaction conditions, it has been observed that substituted phenols and phenols with sensitive functional groups can be readily prepared.

Aryl ethers and phenols are very important structural motifs of numerous biologically active natural products and important pharmaceutical compounds and polymers in the material science industries and consequently, much research has been focused on their synthesis.[1–3] Available methods for the synthesis of aryl ethers and phenols via direct nucleophilic or Cu(I)-catalyzed substitution of an aryl halide with an alcohol typically require high reaction temperatures and/or a large excess of the alcohol and are limited in substrate scope.[4–6] The need to employ HMPA, DMSO, or DMF as solvent further diminishes the applicability of these methods, particularly for large-scale processes.

The formation of carbon-heteroatom bonds by transition metal catalyzed cross-coupling methodology has been the subject of significant interest during the past few years.[7] Although the majority of efforts has focused on C–N bond forming processes, techniques for the formation of aromatic C–O bonds have also been reported.[8–10] Buchwald and Hartwig groups as well as others, have shown that tertiary alcohols, silanols, and phenols, all lacking β-hydrogen groups, can be efficiently coupled with aryl chlorides and bromides.[10] The copper-mediated Ullmann ether synthesis is a classical method for the synthesis of aryl alkyl ethers.[11] The synthetic scope of this reaction, however, is reduced as a result of the harsh reaction conditions. This C–O bond forming process requires strong bases such as alkoxides or sodium hydride. Other severe drawbacks include the following requirements: (a) a large amount of the alkoxide, (b) high temperatures, (c) highly polar aprotic solvents, and (d) stoichiometric quantities of the copper salt.[12]

Aromatic carbon–oxygen bond formation under a mild condition is a difficult transformation. For reactions of inactivated aryl halides, direct, uncatalyzed substitutions and copper-mediated couplings typically require temperatures of 120 °C or higher.[13–15] Diazotization and displacement with oxygen nucleophiles is generally limited to synthesis of phenol and uses stoichiometric amounts of copper in its mildest form.[16] One of the conventional methods for the reactions of inactivated aryl halides to phenols via boronic acid formation followed by peroxide treatment is well known.[17] Since the general methods for the preparation of aryl boric acids do not lend themselves to a direct synthesis of hydroxyphenylboric acids, it was necessary to introduce the phenolic hydroxyl by indirect methods. The direct hydroxylation of aryl halides has been a major challenge in coupling chemistry. Buchwald and co-workers achieved this goal for the first time, by applying their bulky, monodentate ligands which facilitate C–O reductive elimination.[18] Chen and co-workers reported the palladium-catalyzed hydroxylation of highly activated aryl bromides in the presence of P(t-Bu)$_3$.[19] Recently, iron-catalyzed method for the conversion of inactivated aryl halides to phenol has been

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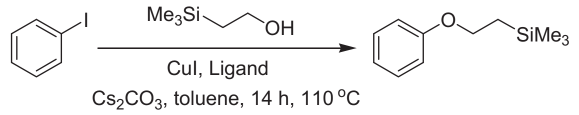
Table 1
Screening of ligands for Cu-catalyzed C–O coupling[a]



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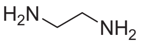
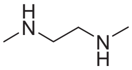
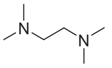
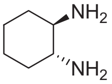
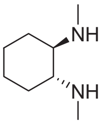
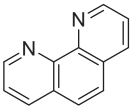
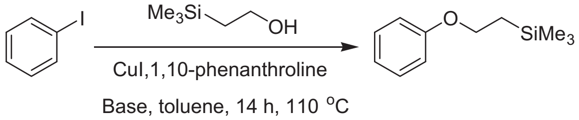
1		0
2		0
3		0
4		0
5		22
6		96

[a] Reaction conditions: Aryl iodide (1 mmol), 2-trimethylsilyl alcohol (3 mmol), CuI (10 mol %), ligand (20 mol %), Cs_2CO_3 (2.0 mmol), toluene (0.5 ml), Schlenk tube, 110 °C, 14 h.

[b] Isolated yield.

Table 2
Screening of base for Cu-catalyzed C–O coupling[a]



Entry	Base	Yield[b] (%)
1	Et_3N	0
2	K_2CO_3	68
3	Na_2CO_3	0
4	K_3PO_4	88
5	Pyridine	0
6	Cs_2CO_3	96

[a] Reaction conditions: Aryl iodide (1 mmol), 2-trimethylsilyl alcohol (3 mmol), CuI (10 mol %), 1,10-phenanthroline (20 mol %), base (2.0 mmol), toluene (0.5 ml), Schlenk tube, 110 °C, 14 h.

[b] Isolated yield.

Table 3
2-(Trimethylsilyl)ethanol as oxygen surrogate in the copper-catalyzed coupling of aryl and heterocyclic iodide[a]

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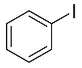
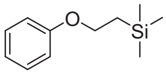
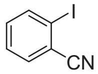
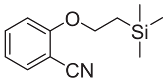
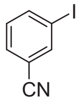
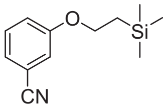
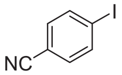
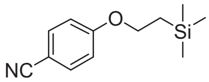
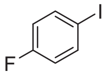
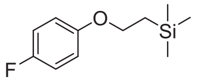
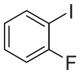
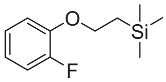
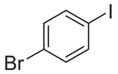
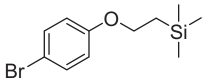
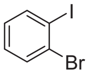
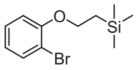
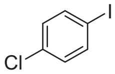
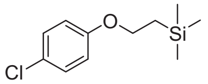
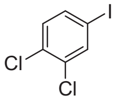
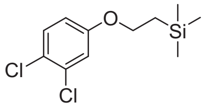
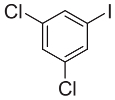
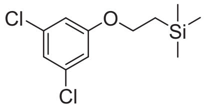
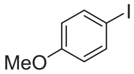
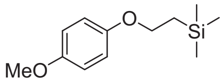
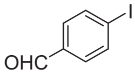
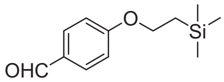
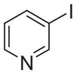
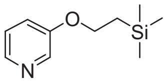
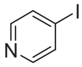
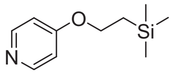
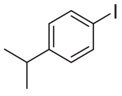
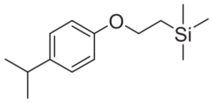
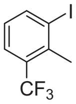
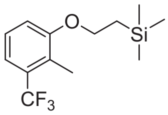
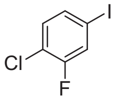
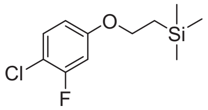
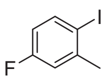
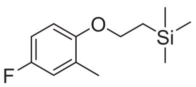
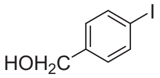
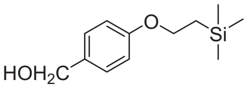
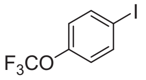
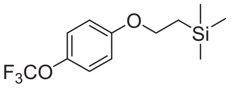
1			96 (93)
2			86 (91)
3			92 (90)
4			91 (94)
5			95 (89)
6			89 (87)
7			94 (96)
8			85 (91)
9			94 (88)
10			80 (83)
11			88 (87)
12			93 (90)
13			90 (81)
14			92 (93)
15			91 (95)
16			81 (88)
17			88 (78)
18			83 (82)

(*continued on next page*)

developed with water as the solvent at 180–200 °C.[20] Although the economic attractiveness of copper has led to remarkable progress in the development of copper-catalyzed coupling reaction,[21] the copper-mediated hydroxylation of aryl halides with hydroxide salts (e.g., KOH and NaOH) as nucleophiles to directly form phenols under mild conditions is limited.[22]

Despite these developments, there are very limited reports of selective hydroxylation methods being developed where one halogen group (I or Br) can be hydroxylated exclusively in the presence of other halo group. Phenols are often quite polar and their purification can be challenging. Furthermore, the relative acidity and nucleophilicity of phenols make them incompatible with many reactions. For these reasons, we sought to synthesize protected

Table 3 (*continued*)

Entry	Substrate	Product	Yield[b] (%)
19			92 (79)
20			76 (88)
21			78 (72)

[a] Reaction conditions: Aryl iodide (1 mmol), 2-trimethylsilyl alcohol (3 mmol), CuI (10 mol %), 1,10-phenanthroline (20 mol %), Cs_2CO_3 (2.0 mmol), toluene (0.5 ml), Schlenk tube, 110 °C, 14 h.

[b] Isolated yield is given. Yield given in bracket is for the deprotected product.

phenols that would be tolerant of a variety of reaction conditions. To meet these needs, a stable alcohol surrogate is required for the hydroxylation and it is also important that the resulting ether compound with alcohol surrogate to be stable during further transformations. Moreover, we also sought to avoid harsh conditions and strong basic hydroxide salts (e.g., KOH and NaOH) as nucleophiles and DMSO or DMF as solvent. So, it was a natural extension for us to investigate the copper-catalyzed coupling of aliphatic alcohols with aryl halides.[23]

During the past few years, some significant modifications have been made. In 2002, Buchwald's group first reported that using 10 mol % of CuI in conjunction with 20 mol % of 1,10-phenanthroline could make C–O bond formation between aryl iodides and aliphatic alcohols successfully under mild reaction conditions (Cs_2CO_3/120 °C/18–38 h).[24] We have introduced trimethylsilyl ethanol as primary aliphatic alcohol for ether formation which can be easily deprotected by using fluoride source.[25]

In the primary screening experiments, a series of ligands were examined in the reaction of iodobenzene and trimethylsilyl ethanol using the following catalyst system: 10 mol % CuI/20 mol % ligand/Cs_2CO_3/110 °C/14 h and toluene as solvent. The results of screening experiments were presented in Table 1. From the results, it was apparent that 1,10-phenanthroline showed the best activity. Further experiments were performed to examine the influence of base on the conversion and the selectivity. A set of bases were examined in the reaction of iodobenzene and trimethylsilyl ethanol, under the following reaction conditions: 10 mol % CuI/20 mol % 1,10-phenanthroline/110 °C/14 h and toluene as solvent. The results of screening experiments were presented in Table 2. From the results, it was apparent that in case of K_3PO_4 and Cs_2CO_3 as base the starting material was nearly transformed completely to the desired product after 14 h. Herein we report that the catalyst system consisting of copper(I) iodide, 1,10-phenanthroline, and cesium carbonate is an efficient method for the synthesis of a variety of phenols within 14 h at 110 °C.[26]

The reactions can be carried out under air without exclusion of moisture.[27] To determine the scope of the catalytic system; the present protocol was applied in reactions of a range of commercially available aryl iodides and trimethylsilyl ethanol. As shown in Table 3, the coupling of trimethylsilyl ethanol with different aryl iodides was successful, leading to the desired products in good yields. Herein, we report a simple, inexpensive, and effective catalytic system for the synthesis of phenols under mild reaction conditions. A variety of functional groups are compatible with these reaction conditions. We could also utilize the intrinsic reactivity of aryl halides to selectively couple the –I group when –Br or –Cl existed in the aromatic ring (Table 3, entries 7–11). The mild reaction conditions and increased scope relative to conventional ones would render this protocol attractive to synthetic chemists. Further studies on the scope of the reactions of trimethylsilyl ethanol with different aryl bromides and chlorides are in progress.

Acknowledgments

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Supplementary data

Supplementary data (experimental and analytical data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.023.

References and notes

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