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Oxalic Diamides and *tert*-Butoxide: Two Types of Ligands Enabling Practical Access to Alkyl Aryl Ethers via Cu-Catalyzed Coupling Reaction

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ABSTRACT: A robust and practical protocol for preparing alkyl aryl ethers has been developed, which relies on using two types of ligands to promote Cu-catalyzed alkoxylation of (hetero)aryl halides. The reaction scope is very general for a variety of coupling partners, particularly for challenging secondary alcohols and (hetero)aryl chlorides. In case of coupling with aryl chlorides and bromides, two oxalic diamides serve as the powerful ligands. The *tert*-butoxide is first demonstrated as a ligand for Cu-catalyzed coupling reaction, leading to alkoxylation of aryl iodides complete at room temperature. Additionally, a number of carbohydrate derivatives are applicable for this coupling reaction, affording the corresponding carbohydrate-aryl ethers in 29-98% yields.

INTRODUCTION

Alkyl aryl ethers are common structural motifs in numerous natural products and synthetic molecules with various important functions.[1] In particular, they are ubiquitous in pharmaceuticals and account for a large part of the top-selling drugs, as selected examples present in Figure 1. Traditional approaches to such ethers often rely on using highly activated aryl halides (nucleophilic aromatic substitution),[2] alkylating agents that are carcinogenic in some cases (Williamson ether synthesis),[3] or relatively expensive azodicarboxylate esters and toxic phosphines (Mistunobu reaction),[4] which seriously limit their substrate scope and large-scale industrial applications. Thus, the development of more general and applicable methods for assembling alkyl aryl ethers has attracted continuous attention from both academia and industry.[1,5-9]

Over the past two decades, transition-metal catalyzed C-O coupling of readily available aryl halides with abundantly available alcohols has emerged as a useful and complementary approach to the existing methods.[1a,5] This method is even more attractive for industrial production because in most cases both reactants are cheaper and more environment-friendly than corresponding ones that are used in Williamson ether synthesis. In this regard, the reaction scope for Pd-catalyzed coupling has become more and more general upon extensive studies on ligand selection and condition optimization.[6] However, cost issue for both palladium and phosphine ligands and poor stability of related catalytic systems hampered their synthetic applicability (Scheme 1). To overcome this drawback, Stradiotto and coworkers recently developed a Ni-catalyzed coupling of aryl halides with alcohols.[7] Although several types of aryl electrophiles are applicable under their reaction conditions, this reaction still suffers from using expensive phosphine ligands and being inert to electron-rich aryl bromides and chlorides.[7] Prior to that, MacMillan group reported a Ni-catalyzed coupling reaction of aryl bromides with alcohols under the assistance of a photoredox catalyst.[8a] The reaction proceeded under the mild condition, but more expensive Ir-catalyst was required as the co-catalyst.

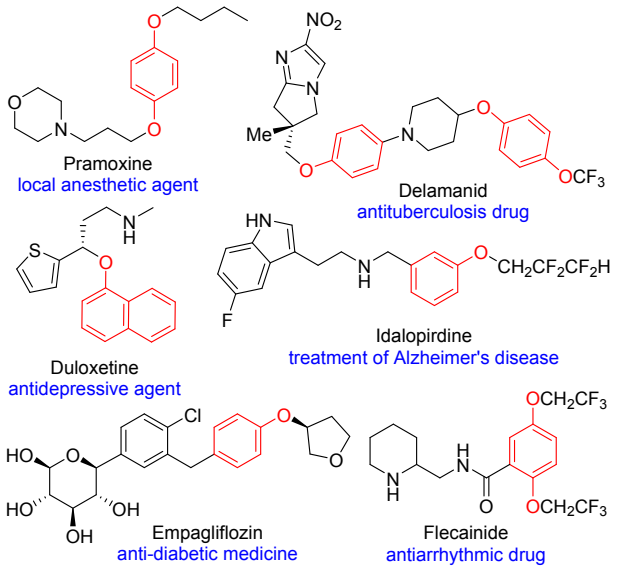


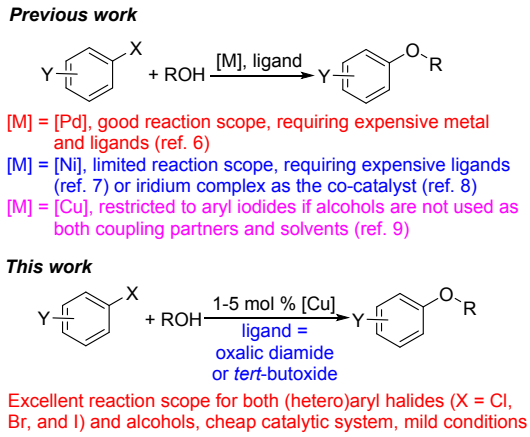
Figure 1. Selected Pharmaceuticals Containing the Alkyl Aryl Ether Core.

On the other hand, although Cu-catalyzed coupling reaction of aryl halides with alcohols is a more attractive approach in terms of its economical and operational benefits and is compared more favorable for reductive elimination than Pd and Ni,[8b] its substrate scope were largely restricted to aryl iodides.[9] When sterically-demanding or acyclic secondary alcohols were coupled with aryl iodides, harsh reaction conditions (140 °C) and stoichiometric amount of ligand were required to obtain the desired coupling products in good yields.[9a] For aryl bromides, using neat alcohols as both solvents and substrates and high temperatures (over 110 °C) are necessary to ensure a satisfactory conversion.[9h] Even under

these conditions, few secondary alcohols are suitable substrates. Moreover, no successful example employing comparatively cheap aryl chlorides has been reported to date.[9]

To address these challenges, we systematically examined a number of oxalic diamide ligands that have displayed excellent activity for promoting Cu-catalyzed arylation of other nucleophiles,[10] and discovered that under the assistance of two simple oxalic diamide ligands, Cu-catalyzed alkoxylation of unactivated aryl chlorides and bromides could be conducted at 60-100 °C. Only 2-3 equivalents of alcohol is needed to give a wide range of alkyl aryl ethers in good to excellent yields from both primary and secondary alcohols. Additionally, we revealed that *tert*-butoxide could serve as a ligand for Cu-catalyzed coupling, rendering the alkoxylation of aryl iodides to proceed at room temperature. Herein, we wish to describe our results.

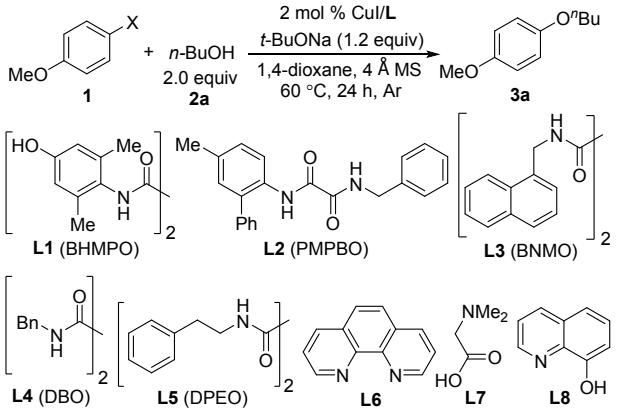
Scheme 1. Previous and Present Metal-Catalyzed Coupling Reactions of Aryl Halides with Alcohols



RESULTS AND DISCUSSION

Optimization of Reaction Conditions. As described in Table 1, we chose CuI-catalyzed coupling of 4-bromoanisole **1** and *n*-BuOH as a model reaction to explore optimal conditions. Initially, we checked two valuable ligands[10c,d] that were applied in Cu-catalyzed hydroxylation of aryl halides and diaryl ether formation, and found that **L1** or **L2** could make the coupling occur at 60 °C in the presence of *t*-BuONa and 4 Å molecule seives. However, only about 10-28% conversion was observed after 24 h (entries 1 and 2). After screening our oxalic diamide ligand library, we were pleased that the desired coupling product **3a** was obtained in 95% yield if *N*,*N*'-bis(naphthalen-1-ylmethyl)oxalamide (BNMO, **L3**) was used as a ligand (entry 3). Using a more conveniently available ligand, *N*,*N*'-dibenzyloxalamide (DBO, **L4**), the reaction also proceeded well, with only a slightly decreased yield (entry 4). The best result was observed with *N*,*N*'-diphenethyloxalamide (DPEO, **L5**) as the ligand (entry 5). Under the same conditions, previously reported ligands such as 1,10-phenanthroline (**L6**), *N*,*N*-dimethylglycine (**L7**) and quinolin-8-ol (**L8**) gave very poor conversions (entries 6-8). When the catalytic loading was reduced from 2 mol % to 1 mol %, there was no influence on the CuI/**L5**-catalyzed reaction (compare entries 5 and 10), although a slightly decreased yield was seen under the action of **L3** (compare entries 3 and 9). Noteworthy is that excellent yields were still observed without using argon (entry 11) and 4 Å MS (entry 12), which demonstrates the practicality of this reaction to some extent.

Table 1. Cu-Catalyzed Coupling of 4-Bromoanisole or 4-Chloroanisole with *n*-BuOH under the Assistance of Different Ligands[a,b]



Entry	Deviation from standard conditions	Yield (%)
1	X = Br, ligand = **L1**	10
2	X = Br, ligand = **L2**	28
3	X = Br, ligand = **L3**	95
4	X = Br, ligand = **L4**	81
5	X = Br, ligand = **L5**	99
6	X = Br, ligand = **L6**	7
7	X = Br, ligand = **L7**	7
8	X = Br, ligand = **L8**	4
9	X = Br, ligand = **L3**, 1 mol % CuI and ligand	85
10	X = Br, ligand = **L5**, 1 mol % CuI and ligand	99
11	X = Br, ligand = **L5**, without using argon	96
12	X = Br, ligand = **L5**, without using argon and 4 Å MS	90
13	X = Cl, **2a** (9.0 mmol), 10 mol % CuI, 10 mol % **L5**, *t*-BuONa (4.5 mmol), 100 °C	4
14	X = Cl, **2a** (9.0 mmol), 10 mol % $Cu(OAc)_2$, 10 mol % **L5**, *t*-BuONa (4.5 mmol), 100 °C	19
15	X = Cl, **2a** (9.0 mmol), 10 mol % $Cu(OAc)_2$, 10 mol % **L5**, *t*-BuOK (4.5 mmol), 100 °C	24
16	X = Cl, **2a** (9.0 mmol), 10 mol % $Cu(OAc)_2$, 10 mol % **L3**, *t*-BuOK (4.5 mmol), 100 °C	84
17	X = Cl, **2a** (9.0 mmol), 5 mol % $Cu(OAc)_2$, 10 mol % **L3**, *t*-BuOK (4.5 mmol), 100 °C	96
18	X = Cl, **2a** (9.0 mmol), 5 mol % $Cu(OAc)_2$, 10 mol % **L3**, *t*-BuONa (4.5 mmol), 100 °C	94
19	X = Cl, **2a** (9.0 mmol), 5 mol % $Cu(OAc)_2$, no ligand, *t*-BuONa (4.5 mmol), 100 °C	0

[a]Standard conditions: **1** (3.0 mmol), **2a** (6.0 mmol), 2 mol % CuI, 2 mol % ligand, *t*-BuONa (3.6 mmol), 1,4-dixoane (1.5 mL), 4 Å MS, 60 °C, 24 h, Ar. [b]The yield was determined by ^{1}H NMR analysis of crude products.

The excellent performance of CuI/**L5** catalytic system prompted us to challenge the coupling reaction with less reactive aryl chlorides. To our delight, the coupling of 4-

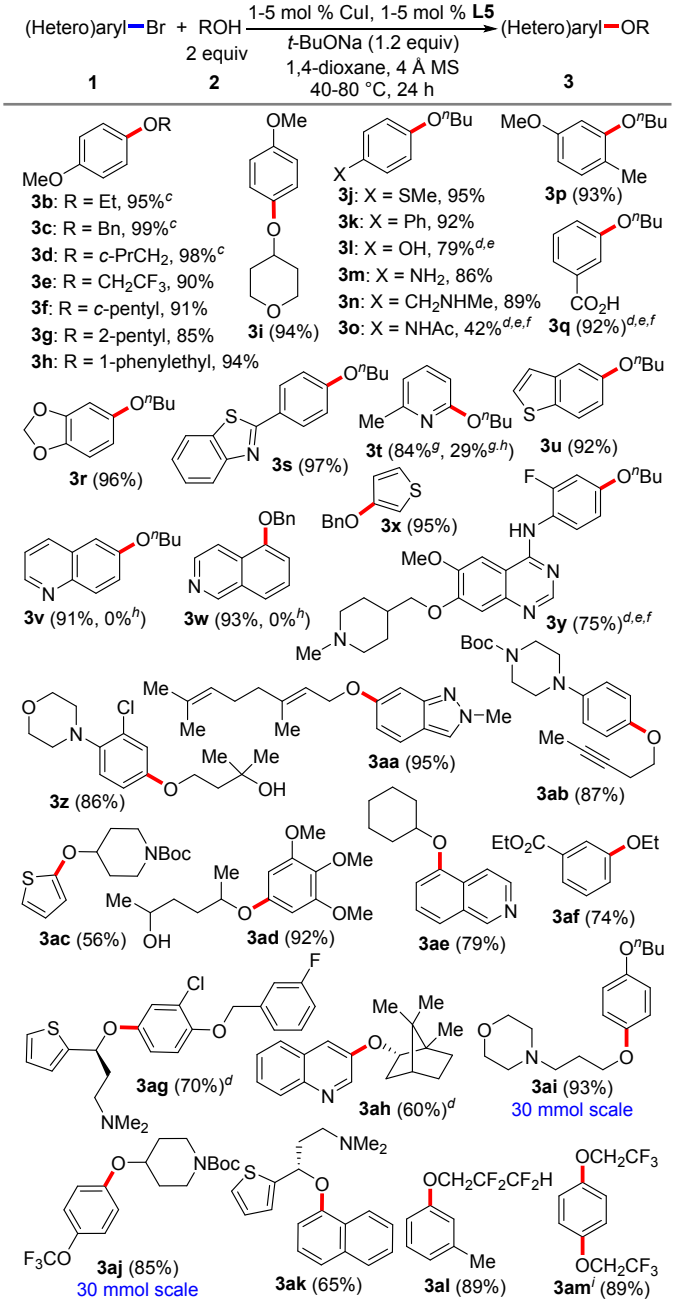
chloroanisole with *n*-BuOH gave 19% conversion when 10 mol % $Cu(OAc)_2$ and **L5** were utilized and the reaction temperature was increased to 100 °C (entry 14). In this case $Cu(OAc)_2$ gave a superior result (compare entries 13 and 14), presumably because of the improved catalytic capability of Cu(I) species generated in situ from Cu(II) salt. In addition, *t*-BuOK was found to be slightly better than *t*-BuONa (entry 15). Interestingly, **L3** turned to be much better than **L5** in this case, leading to the formation of **3a** in 84% yield (entry 16). Finally, fine tuning of the ratio of $Cu(OAc)_2$/**L3** from 1:1 to 1:2 provided 100% conversion and 96% yield with only 5 mol % catalyst loading (entry 17). Under the same conditions, *t*-BuONa also gave an excellent yield (entry 18). In addition, no detectable **3a** was formed in the absence of ligand, which further confirmed the vital role of **L3** (entry 19).

Substrate Scope for (Hetero)Aryl Bromides. With the optimized reaction conditions in hand, we first examined the coupling reactions of 4-bromoanisole with a variety of aliphatic alcohols (Table 2). With only 1-2 mol% catalyst loading, coupling products **3b-3e** were obtained in excellent yields from several primary alcohols, while secondary alcohols also worked well at elevated temperature (80 °C) to afford **3f-3i** in 85-94% yields. Next, the coupling of *n*-BuOH or BnOH with a series of (hetero)aryl bromides were tested. Impressively, their reactions all proceeded smoothly to provide **3j-3y** in moderate to excellent yields. Noteworthy is that an *ortho*-substituted aryl bromide (**3p**) was also applicable, which belongs to difficult substrates for some Cu-catalyzed coupling reactions.[5] When substrates bearing an acidic proton were used, increasing the amount of the base to 2.2 equiv is required to get satisfactory conversion (**3l**, **3o**, **3q** and **3y**). Simple nucleophilic aromatic substitution (S_NAr) was seen in case of some electron-poor heterocycles like 2-bromo-3-chloropyridine, 4-bromoquinoline and 2-bromoquinoxaline (data not shown). However, CuI/**L5** catalytic system is still helpful for coupling with 2-bromo-6-methylpyridine at a decreased temperature (**3t**) and coupling with 6-bromoquinoline (**3v**) and 5-bromoisoquinoline (**3w**). Furthermore, a number of more complex alkyl aryl ethers **3z-3am** were assembled by employing functionalized (hetero)aryl bromides and alcohols. Importantly, the present method is tolerant of many functional groups, such as hydroxyl (**3l**), amine (**3m**, **3n** and **3y**), amide (**3o**), carboxylic acid (**3q**), alkenyl (**3aa**), alkynyl (**3ab**), carbamate (**3ac** and **3aj**) and chloro (**3z**, **3ag**), as well as heterocycles such as thiophene (**3x**, **3ac**), quinolone (**3v**, **3ah**), isoquinoline (**3w, 3ae**), indazole (**3aa**), pyridine (**3t**), and quinazoline (**3y**).

Owing to use of strong bases, transesterification occurred when ethyl 3-bromobenzoate was coupled with *n*-BuOH, although its coupling with EtOH proceeded smoothly to afford **3af** in 74% yield. Thus, using carboxylic acid-embodied aryl bromides as alternative coupling partners is suggested to prepare ester-embodied aryl alkyl ethers (e.g. **3q**).

Using symmetric diols could give mono-arylation product **3ad** exclusively, while regioselective coupling at less hindered site was observed in case of an asymmetric alcohol (**3z**). Indeed, the present coupling reaction is quite sensitive to steric bulk of alcohol substrates, as evident from the facts that increasing catalytic loading to 5 mol% was required for some bulky secondary alcohols (**3ag** and **3ah**) and tertiary alcohols were not applicable.

Table 2. CuI/DPEO-Catalyzed Coupling Reaction of (Hetero)Aryl Bromides with Aliphatic Alcohols[a,b]

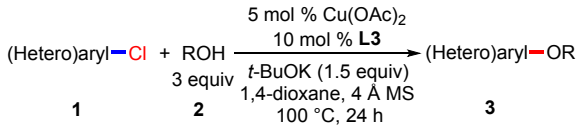


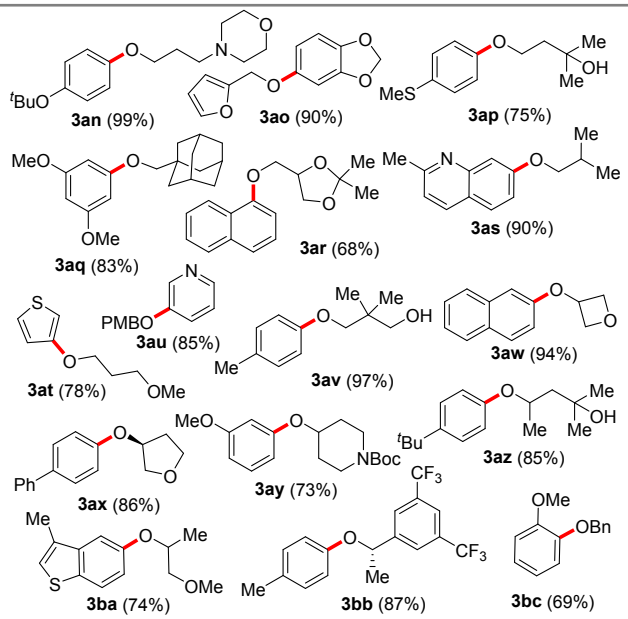
[a]Reaction conditions: **1** (5.0 mmol), **2** (10.0 mmol), 2 mol % CuI, 2 mol % **L5**, *t*-BuONa (6.0 mmol), 1,4-dioxane (2.5 mL), 4 Å MS, 60 °C (primary alcohol) or 80 °C (secondary alcohol), 24 h. [b]Isolated yield. [c]1 mol % CuI and **L5**. [d]5 mol % CuI and **L5**. [e]*t*-BuONa (2.2 equiv) and 1,4-dioxane (5 mL) were used. [f]80 °C. [g]40 °C. [h]Without addition of CuI and **L5**. [i]CF_3CH_2OH (3.0 equiv), *t*-BuONa (2.2 equiv), 80 °C.

Application in the Synthesis of Pharmaceuticals. The synthetic usage of this reaction was demonstrated by direct assembly of some drugs (as indicated in Figure 1) and their

synthetic intermediates. For example, **3ai** (pramoxine) and **3aj** could be obtained in a multi-gram scale by coupling with the corresponding aryl bromides. The former one is a traditional local anesthetic agent,[11] while latter one is a common building block for manufacturing delamanid[12] that was approved for the treatment of tuberculosis in 2014. The previous method for preparing **3aj** relied on Mistunobu reaction,[12a] which should be inferior to the present one because using azodicarboxylate ester and phosphine reagents resulted in the formation of large amount of waste materials. Furthermore, our coupling method was also suitable for synthesis of **3ak**, a key intermediate for preparing the antidepressant duloxetine.[13] Multiple fluorinated alkyl aryl ether **3al** is an intermediate for synthesizing serotonin 6 (5-HT_6) receptor antagonist idalopirdine, currently in phase III clinical trials for the treatment of Alzheimer's disease. Previously, this compound was prepared through Williamson ether synthesis, which required pre-activation of $CHF_2CF_2CH_2OH$ with tosyl chloride.[14] In our hand, direct coupling with $CHF_2CF_2CH_2OH$ gave **3al** in 89% yield. Another fluorinated alkyl aryl ether **3am**, a potential intermediate for preparing antiarrhythmic drug flecainide, was obtained in 89% yield through coupling with CF_3CH_2OH.[15]

Table 3. $Cu(OAc)_2$/BNMO-Catalyzed Coupling Reaction of (Hetero)Aryl Chlorides with Aliphatic Alcohols[a,b]

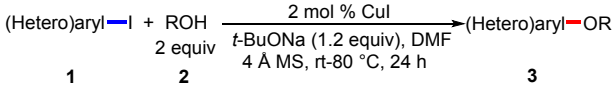


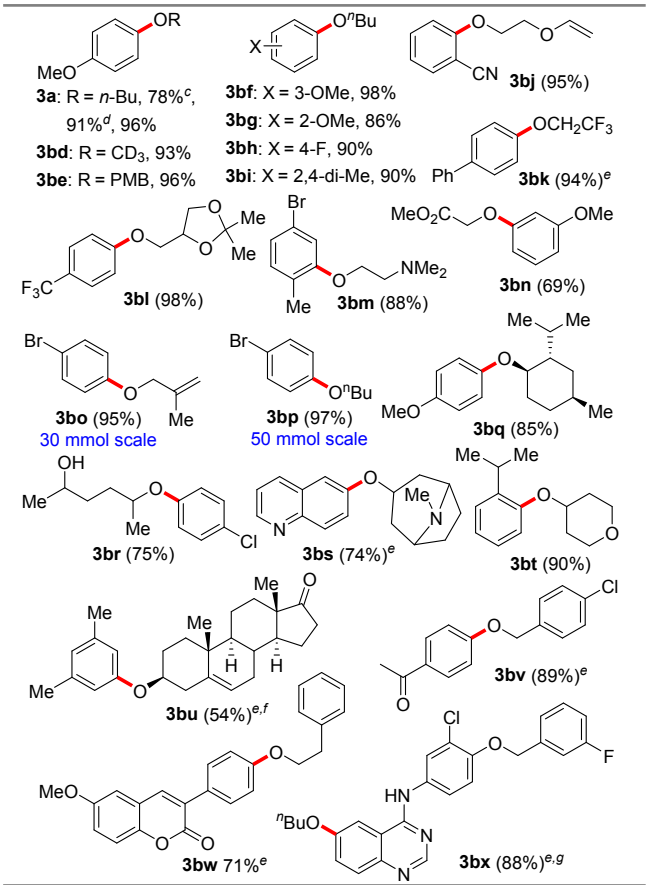


[a]Reaction conditions: **1** (5.0 mmol), **2** (15.0 mmol), 5 mol % $Cu(OAc)_2$, 10 mol % L**3**, *t*-BuOK (7.5 mmol), 1,4-dioxane (2.5 mL), 4 Å MS, 100 °C, 24 h. [b]Isolated yield.

Substrate Scope for (Hetero)Aryl Chlorides. We next explored the scope and limitations of the coupling reaction with (hetero)aryl chlorides. As summarized in Table 3, both primary and secondary alcohols could couple with electron-rich (hetero)aryl chlorides, affording desired products **3an-3aq**, **3at 3av**, and **3ay-3bb** in good to excellent yields. It is notable that some of these transformations were difficult to be achieved by the existing Pd or Ni-catalyzed methods.[1a,6-8] Additionally, electron-poor (hetero)aryl chlorides were applicable, providing the corresponding coupling products **3as** and **3au** in 85-90% yields. However, when sterically hindered 2-chloroanisole was used, **3bc** was isolated in a relatively low yield.

Table 4. CuI-Catalyzed Coupling Reaction of Aryl Iodides with Aliphatic Alcohols[a,b]





[a]Reaction conditions: **1** (5.0 mmol), **2** (10.0 mmol), 2 mol % CuI, *t*-BuONa (6.0 mmol), DMF (2.5 mL), 4 Å MS, rt (primary alcohol) or 60 °C (secondary alcohol), 24 h. [b]Isolated yield. [c]2 mol % **L5**. [d]1,4-dioxane. [e]5 mol % CuI. [f]80 °C, DMF (5.0 mL). [g]*t*-BuONa (2.2 equiv), DMF (5 mL), 60 °C.

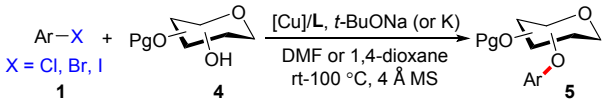
Substrate Scope for (Hetero)aryl Iodides. In view of the above encouraging results, we speculated that the coupling with more reactive aryl iodides might be conducted at milder conditions. As expected, CuI/**L5**-catalyzed coupling of 4-iodoanisole with *n*-BuOH took place at room temperature to afford **3a** in 78% yield (Table 4). Interestingly, removal of **L5** led to the formation of **3a** in an increased yield (91%), while switching solvent from 1,4-dioxane to DMF improved the reaction yield slightly. Thus, we concluded that using 2 mol % CuI as the catalyst, *t*-BuONa as the base, DMF as the solvent

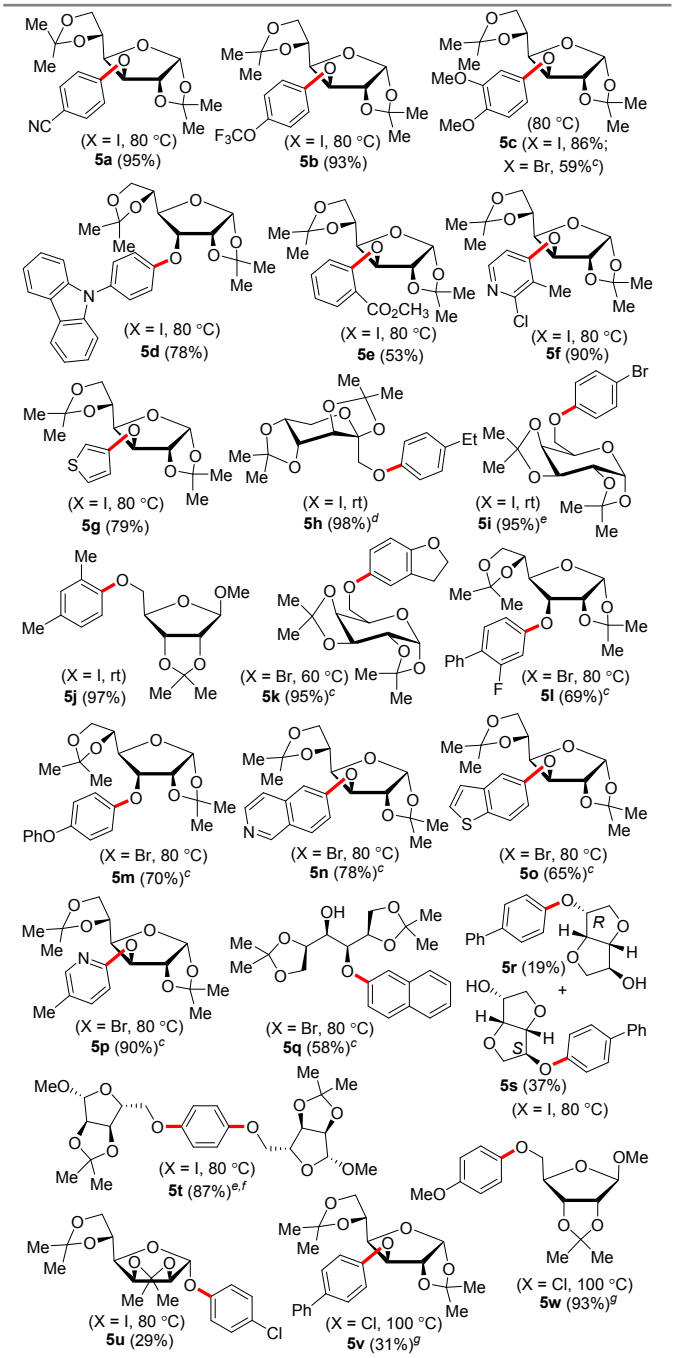
and 4 Å molecular sieve as the additive could give the best result. Under these optimized conditions a number of (hetero)aryl iodides and alcohols were examined. A series of *para*-, *meta*- and *ortho*-substituted aryl iodides coupled with primary alcohols to provide **3bd-3bp** in 69-98% yields. Excellent chemoselectivity between aryl bromides and iodides was seen in the formation of **3bm**, **3bo** and **3bp**. When secondary alcohols were employed, elevated temperature (60 °C) was necessary to get satisfactory yields in most case (**3bq-3bt**). Some sterically bulky substrates could be successfully transformed into the desired products (**3bq**, **3bt**). Noteworthy is that highly functionalized dehydroepiandrosterone (**3bu**) was also workable, implying that the present method has great potential in the total synthesis and modifications of natural products. Additionally, we examined some base-sensitive substrates, and were glad that ketone-, lactone- and 4-aminoquinazoline-embodied aryl iodides worked well to provide the corresponding aryl alkyl ethers **3bv-3bx** in good yields.

Application in the Preparation of Carbohydrate-Derived Aryl Ethers. Carbohydrates not only serve as a common source of energy in living organisms, but also play essential roles in many biological processes.[16] Decoration of carbohydrates with various functional groups can broaden the chemical space and biological profiles, which has great importance for glycobiology research. Particularly, introduction of pharmaceutically interesting (hetero)aryl groups to the hydroxyl groups on sugar backbone is a valuable strategy to improve the pharmacodynamics and pharmacokinetic properties of sugar-derived compounds in medicinal chemistry.[17] However, *O*-arylation of the hydroxyl groups on carbohydrates is a challenging task, especially for sterically hindered secondary hydroxyl groups. Generally, such carbohydrate-aryl ethers could be constructed by alteration of the hydroxyl groups into good leaving groups and subsequent nucleophilic substitution with phenols, which usually led to inversion of the corresponding C-stereochemistry.[18] Another promising approach is through a nucleophilic aromatic substitution reaction with highly activated aryl fluorides, which is limited by availability of activated electrophiles.[19] To solve these problems, several metal-catalyzed coupling methods have been recently attempted. Olofsson and coworkers discovered that efficient *O*-arylation of carbohydrates could be achieved using electrophilic diaryliodonium salts.[20a] Taylor and Niu groups independently found that site-selective *O*-arylation of carbohydrate derivatives took place using arylboronic acids[21] or diaryliodonium reagents[20b] as the electrophiles under the catalysis of suitable copper salts. Whereas remarkable progress has been made, the direct *O*-arylation of the hydroxyl groups on sugar scaffolds using abundant but less reactive aryl halides as arylating reagents has been rarely explored.[8a] Moreover, *O*-arylation with more medicinally important heterocycles remains elusive.[20b] In view of our success in the C-O cross couplings of aryl halides with both primary and secondary alcohols, we next attempted to apply our copper-catalyzed method to assemble more difficult carbohydrate-aryl ethers.

To exploit the potential of our established method in the synthesis of such ethers, the O3-unprotected glucofuranose and D-allofuranose were selected as model substrates considering their low price and poor reactivity (sterically congested hydroxyl group). To our delight, these two alcohols could couple with both electron-deficient (**5a**) and electron-rich (**5b-5d**) aryl iodides to afford the corresponding aryl ethers in 78-95% yields by conducting the reaction at 80 °C in the presence *t*-BuONa and 4 Å molecular sieve with 5 mol % CuI as the catalyst (Table 5).

Table 5. Synthesis of Carbohydrate-Aryl Ethers[a,b]





[a]Reaction conditions: **1** (5.0 mmol), **4** (10.0 mmol), 5 mol % CuI, *t*-BuONa (6.0 mmol), DMF (2.5 mL), 4 Å MS, 24 h.

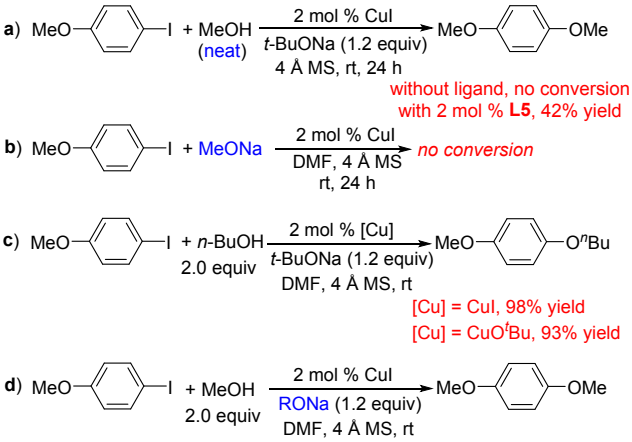
[b]Isolated yield. [c]5 mol % **L5**, 1,4-dioxane (2.5 mL). [d]2 mol % CuI. [e]DMF (5.0 mL). [f]**4** (3.0 equiv), *t*-BuONa (2.2 equiv). [g]**4** (15.0 mmol), 5 mol % $Cu(OAc)_2$, 10 mol % **L3**, *t*-BuOK (7.5 mmol), 1,4-dioxane (2.5 mL).

Two sterically hindered *ortho*-substituted (hetero)aryl iodides also worked well, leading to the formation **5e** and **5f** in good yields. More importantly, heterocycles such as pyridine and thiophene-embodied carbohydrate-aryl ethers (**5f** and **5g**) could be obtained in high yields, which were difficult to be assembled via previously reported methods.[20,21] Other commercially available carbohydrate alcohols derived from D-fructose (**5h**), D-galactopyranose (**5i**), D-ribofuranose (**5j**), could be easily arylated with different aryl iodides under the catalysis of 2-5 mol % CuI. Noteworthy is that the coupling reactions with these carbohydrate primary alcohols proceeded smoothly at room temperature to afford the coupling products in nearly quantitative yields.

Next, the arylation of carbohydrate alcohols with less reactive aryl bromides was investigated. Under the catalysis of CuI and DPEO, several aryl bromides bearing either electron-donating or electron-withdrawing groups (**5k**-**5m** and **5q**), and heteroaryl bromides (**5n**-**5p**), could successfully couple with a series of carbohydrate derivatives, although the yields were slightly decreased. When carbohydrate derived diols were used, selective monoarylation could be realized. For example, arylation of isopropylidene D-mannose with 2-bromo-naphthalene gave monoarylated product **5q** exclusively; monoarylation of isosorbide (a sustainable dianhydro-D-glucose diol) with 4-iodo-1,1'-biphenyl afforded **5r** and **5s** in 19% and 37% yields, respectively. Although the combined yield was only moderate, such high selectivity for monoarylated products was unachievable via previous methods.[20a] Another notable element is that diiodobenzene could simultaneously couple with 2 equivalents of D-ribofuranose alcohol to provide **5t** in 87% yield. Additionally, arylation of O1-unprotected D-mannose was possible. However, the yield for formation of **5u** was only 29%, indicating that coupling with the lactol moiety is still challenging.[20,21] Furthermore, aryl chlorides were also workable substrates as aforementioned in the coupling with sugar-derived alcohols, providing the desired carbohydrate-aryl ethers (**5v** and **5w**) in 31-93% yields with 3 equivalents of alcohols and elevated temperature (100 °C).

Mechanistic Studies. The coupling of aryl iodides with aliphatic alcohols proceeded smoothly at room temperature in the absence of additional ligands, which attracted our attention to conducting mechanistic investigation. When CuI was removed from the reaction mixture, or replaced with other transition metal such as $Pd(OAc)_2$ and AgOAc, no desired coupling product could be determined, indicating the critical role of Cu catalyst. Addition of TEMPO to the reaction mixture, or carrying out the reaction under no light condition, also did not impede its transformation. The coupling reaction of *n*-BuOH with 1-(allyloxy)-2-iodobenzene, a frequently used radical probe, gave the exclusive intermolecular C-O coupling product, further demonstrating that this C-O bond formation might not proceed through a free radical mechanism.

During our studies of the coupling between 4-iodoanisole and methanol, we observed that no coupling occurred if replacing solvent from DMF to MeOH, while adding 2 mol % **L5** still gave the coupling product in 42% yield (Figure 2a). Another control experiment showed that directly changing *t*-BuONa with sodium methoxide led to no conversion (Figure 2b). These results indicated that *tert*-butoxide should not only serve as a base, but also play a role as catalytic species. It has been reported that the cuprous *tert*-butoxide formed in these reactions was highly stable while the corresponding Cu(I) primary alkoxides decomposed rapidly at room temperature.[21] Accordingly, we postulated that *tert*-butoxide might behave as a ligand to stablize the Cu catalyst in the present reaction. To support our speculation, we preapared the CuO^tBu according to the known procedure,[22] and then ckecked its catalytic ability. As expected, almost same results were observed when either CuO^tBu or CuI was employed as the catalyst (Figure 2c). Next, we examined the steric effect of several freshly prepared tertiary alkoxides on reaction rate (Figure 2d). As anticipated, the reaction of 4-iodoanisole with MeOH was significantly accelerated with the steric hindrance of the tertiary alkoxide increased. When tertiary alkoxide **6e** was used, the reaction rate was dramatically improved, and the yield reached to 84% after 1 h. Additionally, coupling of 4-iodoanisole with secondary alcohol *i*-PrOH at room teperature gave only 42% conversion after 24 h if *t*-BuONa was used. Switching the base to **6e** could significantly improve the result (Figure 2e). These results implied that the bulkier tertiary alkoxides as the ligands could facilate some of the elemental steps in catalytic cycles.



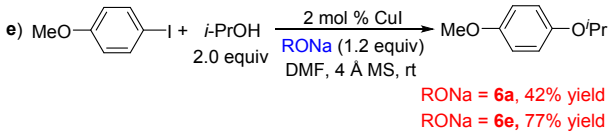
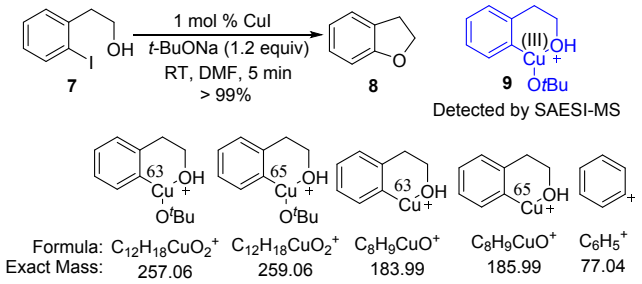
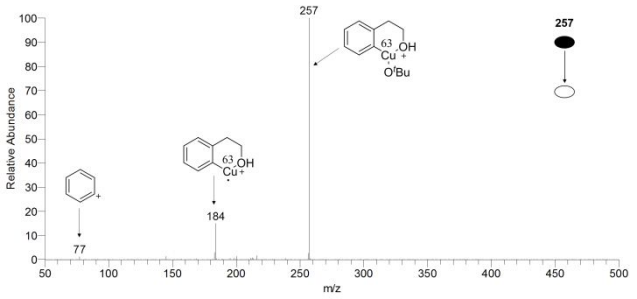


Figure 2. Mechanistic studies on coupling of aryl iodides with aliphatic alcohols.

Furthermore, we studied the reaction course of intramolecular C-O coupling reaction of 2-(2-iodophenyl)-ethan-1-ol **7** with solvent-assisted electrospray ionization tandem mass spectrometry (SAESI-MS/MS) technology, and determined a protonated copper intermediate with one coordination with *tert*-butoxide, which was assigned to be the copper (III) intermediate **9** as supported by SAESI-MS/MS data illustrated in Figure 3. The important intermediate was detected as the complex **9** at *m/z* 257($[C_{12}H_{18}{}^{63}CuO_2]^+$), *m/z* 259($[C_{12}H_{18}{}^{65}CuO_2]^+$). In the MS/MS process, $[C_{12}H_{18}{}^{63}CuO_2]^+$ at *m/z* 257 gave two main product ions: $[C_8H_9{}^{63}CuO]^{+\bullet}$ at *m/z* 184 and Ph^+ at *m/z* 77; while $[C_{12}H_{18}{}^{65}CuO_2]^+$ at *m/z* 259 also gave two similar main product ions: $[C_8H_9{}^{65}CuO]^{+\bullet}$ at *m/z* 186 and Ph^+ at *m/z* 77.



(a) SAESI-MS/MS spectrum of the ion at m/z 257



(b) SAESI-MS/MS spectrum of the ion at m/z 259

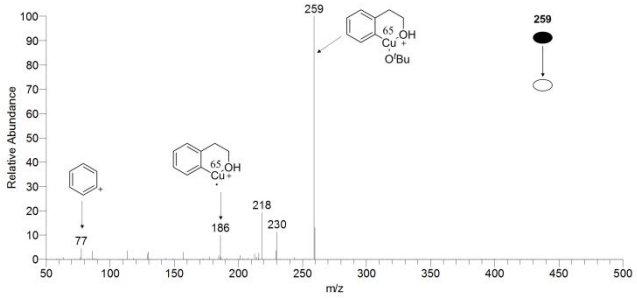


Figure 3. SAESI-MS/MS experiment on the intramolecular C-O coupling reaction of 2-(2-iodophenyl)ethan-1-ol **7**.

These findings further demonstrated the possible role of *tert*-butoxide in the C-O coupling reactions of aryl iodides with aliphatic alocohols. Accordingly, we proposed a possible mechanism as depicted in Figure 4.[23] The cuprous *tert*-butoxide **A** formed in situ might undergo oxidative addition to an aryl iodide to give Cu(III) complex **B**, which was coordinated with an alcohol to afford complex **C**. Upon base treatment, the intermediate **C** could be converted into Cu(III) complex **D**, which would deliver the desired alkyl aryl ether and regenerate the catalyst **A** after reductive elimination. For coupling with aryl bromides and chlorides, the complex **A** might not be reactive enough to initiate a catalytic cycle, and therefore oxamido bridged copper(I) complex **E** might form in the presence of an oxalic diamide ligand, which would serve as the active catalytic species to initate a similar catalytic cycle (through intermediates **F**, **G** and **H**) to afford the coupling product.

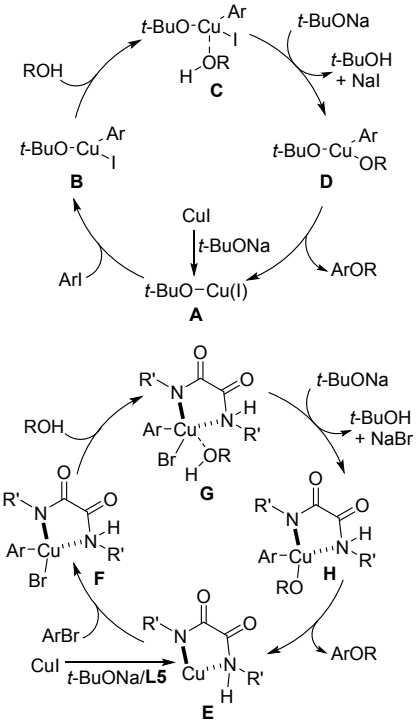


Figure 4. Two possible mechanisms for cross-coupling reactions of (hetero)aryl halides with aliphatic alcohols.

CONCLUSION

In summary, we have provided a general and mild synthetic method for assembly of alkyl aryl ethers via ligand-promoted Cu-catalyzed coupling of (hetero)aryl halides and alcohols. The present catalytic systems have overcome many existing problems in C-O cross-coupling and employ less expensive and conveniently available copper salts and ligands, and can be used for coupling of a wide range of (hetero)aryl halides and alcohols. The usage of our method has been demonstrated by direct installation of various pharmaceuticals and medicinally interesting carbohydrate-aryl ethers. The discovery of *tert*-butoxide as a valuable ligand in Cu-catalyzed coupling reaction may not only stimulate the ligand design, but also help understand its mechanistic process.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications websites at DOI: 10.1021/jacs.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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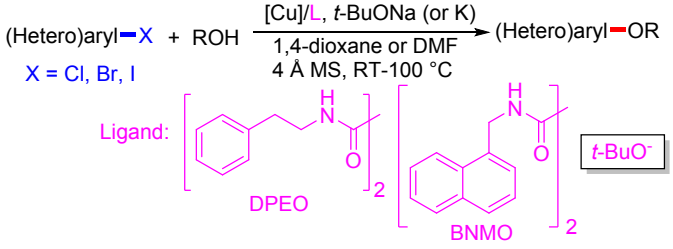
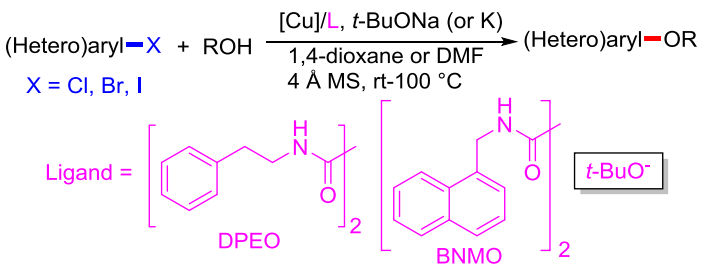

(Hetero)aryl–X + ROH
X = Cl, Br, I
[Cu]/L, t-BuONa (or K)
1,4-dioxane or DMF
4 Å MS, RT-100 °C
(Hetero)aryl–OR
Ligand:
DPEO
BNMO
t-BuO⁻

TOC


(Hetero)aryl–X + ROH
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