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Copper-Mediated Etherification of Arenes with Alkoxysilanes Directed by (2-Aminophenyl)pyrazole Group

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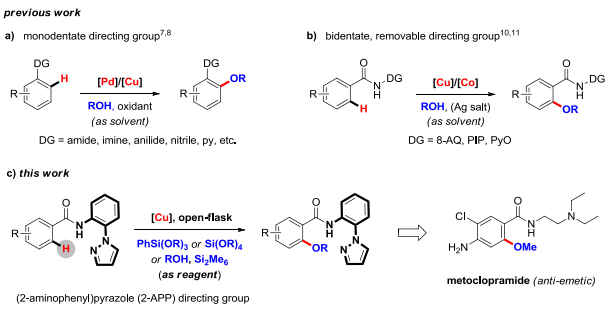
An efficient copper-mediated etherification of inert C–H bonds of (hetero)arenes with *reagent-amount* of alkoxysilanes and alkanols has been developed using (2-aminophenyl)pyrazole (2-APP) as a removable directing group. The reaction is scalable, rapidly proceeds under an open atmosphere, and tolerates diverse functional groups to provide alkyl aryl ethers in high yields (up to 87%). As an application, the formal synthesis of anti-emetic drug metoclopramide is accomplished.

Transition-metal catalyzed direct functionalization of C–H bond has emerged as a valuable tool in the contemporary organic synthesis.[1] In this regard, synthetic methodology for the construction of C–O bond is of fundamental interest because molecules containing this functionality are ubiquitous in diverse natural products and functional materials.[2] While considerable progresses have been accomplished in direct hydroxylation, acetoxylation, and phenoxylation processes, selective installation of alkoxy substituents *en route* to alkyl aryl ethers is increasingly challenging.[3] This is likely because alkanols are easily dehydrated,[4] sensitive towards oxidation[5] and furthermore, metal-alkoxide intermediates are prone to β-hydride elimination.[6] In this scenario, success has largely been restricted to the use of second-row transition metals and several protocols have been established with the use of monodentate directing groups, particularly under palladium catalysis (Scheme 1a).[7] Recently, Gooßen's group also disclosed a bimetallic copper/silver catalyst for dehydrogenative cross-coupling of 2-aryl pyridines with alcohols at elevated temperature (140 °C).[8]

Since the pioneering work of Daugulis and co-workers, removable bidentate auxiliaries have come in the limelight owing to their unique potential for the activation of inert C–H bonds using abundant and inexpensive first-row transition metals.[9] Consequently, a series of new reactions including alkoxylation have been developed (Scheme 1b). In 2013, Daugulis and co-workers reported copper catalyzed 8-aminoquinoline (8-AQ) directed alkoxylation of benzamides.[10a] Stahl's group also performed mechanistic studies on copper-mediated C–H methoxylation of *N*-(8-quinolinyl)-benzamide in methanol.[10b] Recently, Shi et al. and Song et al. independently contributed in this field using (pyridine-2-yl)isopropyl amine (2-PIP) and *N*,*O*-bidentate directing group (PyO) respectively.[11]

All of these alkoxylation processes are good; however, the use of large excess of alkanols is essential and most often they have been considered as the reaction solvents. This pitfall will be more prominent in the case of precious alkanols. Moreover, the requirements of higher reaction temperature, longer reaction time, and expensive oxidants/additives, such as silver salts, are also putative issues. Furthermore, the source of alkoxy substituents has generally been paved with alcohol substrates and search for alternative sources is underdeveloped.[12] Thus, selective installation of alkoxy substituents for the direct synthesis of alkyl aryl ethers using stoichiometric amount of alkoxy sources under mild reaction conditions is highly desirable.



Scheme 1. Transition-metal-catalyzed alkoxylation of C(sp^2)–H bonds

Herein, we report an unprecedented method for the rapid synthesis of alkyl aryl ethers through the copper-mediated alkoxylation of (hetero)arenes with a range of alkoxysilanes and alcohols in combination with hexamethyldisilane using (2-aminophenyl)pyrazole (2-APP) as a removable auxiliary

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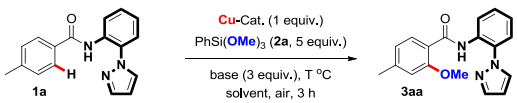
† Electronic Supplementary Information (ESI) available: Detailed experimental procedures, crystallographic details of **3da**, **3la** & **3bi** and NMR spectra of the products. See DOI: 10.1039/x0xx00000xAddress here

(Scheme 1c). This reaction can be performed in *open-flask* with *reagent-amount* of alkoxide sources at moderate temperature while obviating the need for expensive silver salts. In addition, to demonstrate the utility of this strategy, the formal synthesis of anti-emetic drug metoclopramide is accomplished.

It is worth noting that the 2-AAP directing group is commercially available and can also be readily synthesized in large scale from inexpensive starting materials.[13] During the preparation of our manuscript Li's group reported an efficient amidation protocol using 2-APP as a directing group and motivated us to disclose our findings on etherification of arenes.[14]

We commenced our investigation with model substrate **1a** derived from 2-APP directing group (Table 1). Initially, phenyltrimethoxysilane (**2a**) was selected as the source of alkoxy functionality. Of note, unsymmetrical organosilane **2a** is well-known as aryl donor and it has been never considered in alkoxylation reaction, conjecturing a distinct reaction paradigm. After extensive screening of reaction conditions by varying catalysts (entries 1-4), bases (entries 5-6), temperature (entries 7-8), and solvents (entries 9-10), we were delighted to find that the amide **1a** smoothly reacted with *reagent-amount* of **2a** in the presence of one equivalent of $Cu(OAc)_2$ delivering the methoxylated product **3aa** in 87% isolated yield (Table 1, for complete optimization conditions, see the ESI, page S6). When loading of the organosilane **2a** was reduced to four and three equivalents, the reaction yields also decreased gradually (entries 13-14).

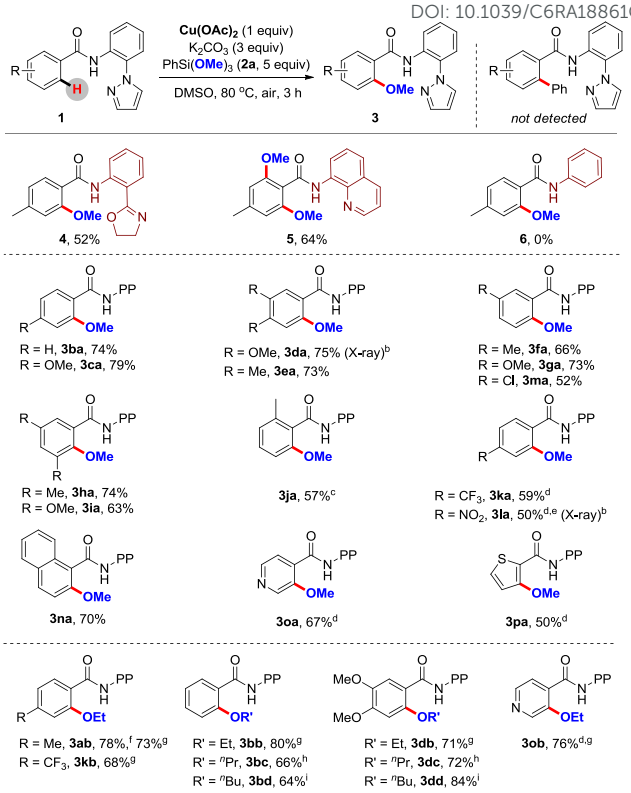
Table 1. Optimization of the reaction conditions[a]



Entry	Cu-Cat.	Base	Solvent	Temp (°C)	Yield (%)[b]
1	$CuCl_2$	K_2CO_3	DMSO	80	54
2	$Cu(OTf)_2$	K_2CO_3	DMSO	80	Trace
3	**$Cu(OAc)_2$**	**K_2CO_3**	DMSO	**80**	**87**
4[c]	$Cu(OAc)_2$	K_2CO_3	DMSO	80	26
5	$Cu(OAc)_2$	$KHCO_3$	DMSO	80	78
6	$Cu(OAc)_2$	Na_2CO_3	DMSO	80	48
7	$Cu(OAc)_2$	K_2CO_3	DMSO	100	50
8	$Cu(OAc)_2$	K_2CO_3	DMSO	90	82
9	$Cu(OAc)_2$	K_2CO_3	DMF	80	46
10	$Cu(OAc)_2$	K_2CO_3	CH_3CN	80	0
11[d]	$Cu(OAc)_2$	K_2CO_3	DMSO	80	trace
12[e]	$Cu(OAc)_2$	K_2CO_3	DMSO	80	trace
13[f]	$Cu(OAc)_2$	K_2CO_3	DMSO	80	78
14[g]	$Cu(OAc)_2$	K_2CO_3	DMSO	80	62

[a]Conditions: **1a** (0.1 mmol), $Cu(OAc)_2$ (0.1 mmol), $PhSi(OMe)_3$ (**2a**), Base (3 equiv.), air, DMSO (1 mL), 80 °C, 3h. [b]Yields are isolated quantities. [c]Reaction under N_2 atmosphere. [d]Reaction was performed with $Cu(OAc)_2$ (30 mol%) and oxidant Ag_2CO_3 (2 equiv.) under N_2 atmosphere. [e]Reaction was performed with $Cu(OAc)_2$ (30 mol%) and oxidant $K_2S_2O_8$ (2 equiv.) under N_2 atmosphere. [f]4 equivalents of **2a** was used. [g]3 equivalents of **2a** was used.

Table 2. Alkoxylation of Arene C-H bond using alkoxysilanes.[a]



[a]Reaction conditions: **1** (0.1 mmol), $Cu(OAc)_2$ (0.1 mmol), **2** (5 equiv), K_2CO_3 (3 equiv), DMSO (1 mL), 80 °C, air, 3 h. Yields are isolated quantities. [b]For CCDC number, see ref 15. [c]Reaction was conducted at 90 °C. [d]TBAI (0.1 mmol) was used as additive. [e]Reaction was carried out at r.t. [f]$PhSi(OEt)_3$ **2b** (5 equiv) was used. [g]$Si(OEt)_4$ **2c** (5 equiv) was used. [h]$Si(OnPr)_4$ **2d** (5 equiv) was used. [i]$Si(OnBu)_4$ **2e** (5 equiv) was used.

Effect of other directing groups has also been examined. Consequently, the substrates containing well-known Yu's aminophenyloxazoline and Daugulis's 8-aminoquinoline directing groups were subjected to the optimized reaction conditions. However, the desired methoxylated products **4** and **5** were obtained in moderate yields (Table 2). The amide derived from simple aniline failed to produce the corresponding methoxylated product **6**. These findings disclose the aptitude of 2-APP directing group for the C–H activation strategy.

With this optimized conditions in hand, we have moved to verify the methoxylation reaction for various substituted amides (Table 2). The reaction is quite general. The carboxamides with various donating substituent at *p*-, *m*-, and *o*- position (**3ba**–**3ja**) generally gave high yields (57–74%). The electron deficient amides having *p*-CF_3, *p*-NO_2, and *m*-Cl moieties also delivered the corresponding methoxylated products (**3ka**–**3ma**) in good yields. However, the presence of TBAI additive was necessary to mitigate homo-coupling by products. The 1-naphthylamide **1n** regioselectively produced the desired compound **3na** in 70% yield. The carboxamides derived from heterocyclic compounds, such as pyridyl and thienyl derivatives, are also suitable substrates for this

reaction, delivering methoxylated products **3oa** and **3pa** in 67% and 50% yields respectively.

The generality of the C–H methoxylation reaction with unsymmetrical organosilane **2a** prompted us to examine the feasibility of this protocol to install the higher alkoxide functionalities. Thus, various commercially available unsymmetrical (**2b**) and symmetrical (**2c–e**) alkoxides were employed (Table 2, below). Gratifyingly, under the optimized conditions, reactions of all these alkoxysilanes uniformly delivered the corresponding alkyl aryl ethers in high yields (64-84%). Importantly, this methodology allows to access multi-substituted arenes having different alkyl ether units (**3db–3dd**), for which direct synthetic protocol is still limited.

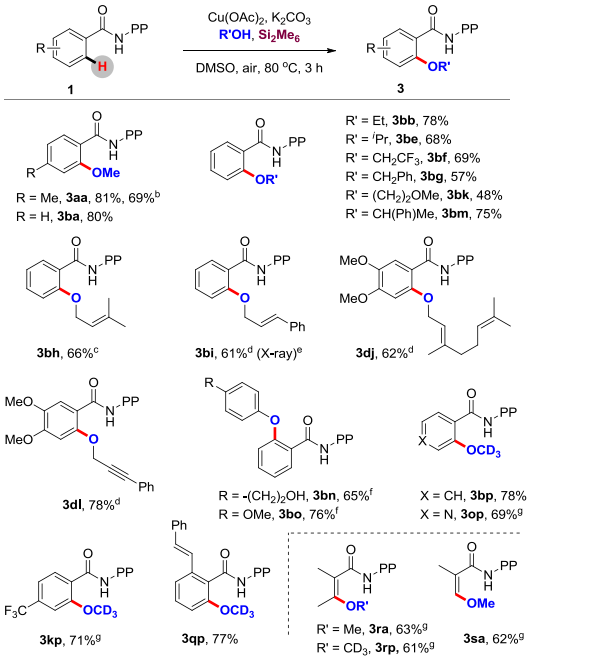
The reaction conditions of the present protocol are quite mild; the 2-APP-directed C-H alkoxylation reaction was achieved at 80°C. Hence, we envisaged that the dehydrogenative coupling of C_{sp2}–H bond and alcohols is also feasible in the presence of a suitable silicon additive and only use of a *reagent-amount* of alcohol, in contrast to the use of alcohol as solvent, would be adequate to offer the desired output. These will broadly extent the scope of this methodology. Accordingly, the reaction was performed with 1 equiv. of Si_2Me_6 additive with methanol substrate (Table 3). To our delight, the etherification took place with equal efficiency delivering **3aa** in 81% yield. When the reaction was performed in the absence of Si_2Me_6 additive, erosion in yield was observed (69%). This reaction conditions is also suitable for various primary and secondary alcohols to produce aryl alkyl ethers in high yields (Table 3). As a highlight, functionalized and sensitive alcohols such as prenyl alcohol (**3bh**), cinnamyl alcohol (**3bi**), geraniol (**3dj**), methyl cellosolve (**3bk**), and propargyl alcohol (**3dl**) gave desired products in good yields. Substituted phenols (**3bn–3bo**) are also suitable reagent for this reaction. Particularly, 4-(2-hydroxyethyl)phenol, bearing both phenolic and alcoholic functionality, undergoes preferentially phenoxylation reaction to give **3bn** in 65% yield.

Though deuterated molecules are very important in drug discovery,[16] trideuteromethoxylation through direct C-H alkoxylation reaction remained elusive. This is likely because the reported methodologies generally demand solvent level of expensive deuterated alcohols. In this scenario, our approach is highly rewarding. Using reagent amount of methanol-d_4 under our standard conditions, trideuteromethoxylated product **3bp** was obtained in 78% yield. The deuteromethoxylation reaction was also successfully extended to the trifluoromethyl and styryl-substituted amides and heterocyclic amide to generate **3kp**, **3qp** and **3op** in 71, 77, and 69% yields respectively.

Of note, the 2-APP directed alkoxylation protocol is also efficient with alkene substrates, showcasing β-alkoxy substituted tiglic (**3ra** and **3rp**) and methacrylic (**3sa**) amides with good yields.

Pleasingly, the directing group can be easily be removed by Lewis acid mediated methanolysis of the amide bond, resulting alkyl aryl ether **7** in 90% yield with the recovery of 2-APP directing group in 77% yield (Scheme 2a).

Table 3. Cross-dehydragenative coupling of arenes and alcohols.[a]



[a]Conditions: **1** (0.1 mmol), $Cu(OAc)_2$ (0.1 mmol), R'OH (15 equiv), Si_2Me_6 (1 equiv), K_2CO_3 (3 equiv), DMSO (1 mL), 80 °C, air, 3 h. Yields are isolated quantities. [b]Reaction was carried out without Si_2Me_6. [c]Reaction was performed at 70 °C for 6 h. [d]Alcohol (5 equiv) was used. [e]For CCDC number, see ref 15. [f]Alcohol (2 equiv) was used. [g]TBAI (0.1 mmol) additive was used

To display the synthetic utility of the present protocol, we have implemented it as a key step in the formal synthesis of anti-emetic drug metoclopramide (Scheme 2b).[17] The synthesis starts from the Cbz-protected 4-amino benzoic acid. After installation of APP-directing group, the amide **1t** was exposed to our standard methoxylation conditions delivering the key intermediate **3ta** in gram scale. Treatment of **3ta** with *N*-chlorosuccinimide selectively delivered chlorination at the C5-position. Sequential removal of 2-APP directing group and Cbz-deprotection yielded the compound **8** (74% yield in three steps), a key precursor to synthesize metoclopramide and its family of 5-HT_4 receptor agonists.[17b]

In order to probe the alkoxylation mechanism, a series of control experiments have been conducted. The methoxylation reactions using **2a** and methanol were completely arrested in the presence of radical scavengers such as TEMPO and BHT, suggesting the involvement of a radical species in the reaction pathway (Scheme 3a). When the methoxylation reaction was performed with an equal mixture of **2a** with **1b** and **d_5-1b** respectively under standard reaction conditions for 1h, a moderate kinetic isotope effect of k_H/k_D = 2.5 was observed (Scheme 3b). In case of methanol, the kinetic isotope effect was much prominent (k_H/k_D = 5.1). Further, when the reaction was performed with methanol-d_4, no deuterium incorporation was detected in the recovery starting material (Scheme 3c). These cumulative results suggest that the 2-APP-directing group assisted C–H bond cleavage is irreversible and possibly involved in the rate determining step.

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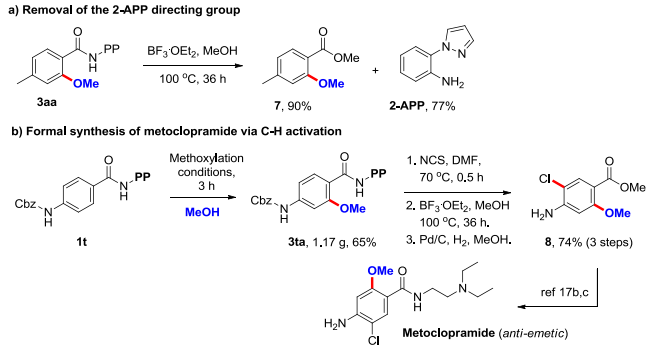
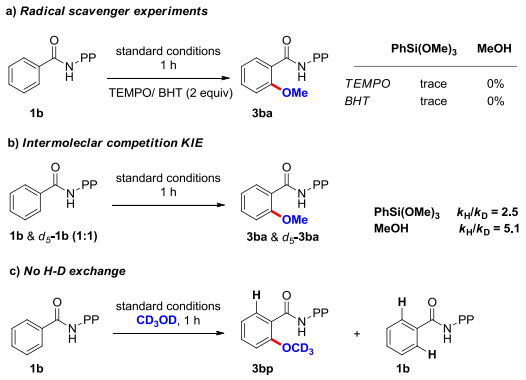
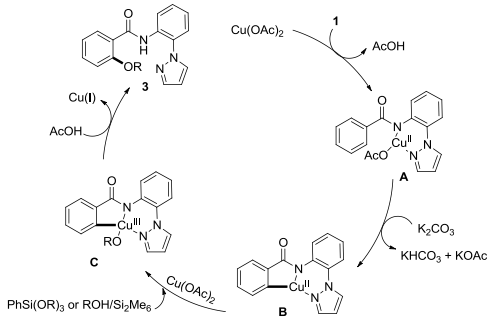


Scheme 2. (a) Removal of the 2-APP directing group and (b) formal synthesis of anti-emetic drug metoclopramide via C–H activation.



Scheme 3. Control experiments.

Although mechanistic details must await further investigation, based on preceding discussion a plausible reaction mechanism was depicted in Scheme 4. After complexation of **1** with copper catalyst, Cu(II)cyclometalated species **B** is formed via base-assisted C–H bond cleavage. Single electron oxidation promoted by copper acetate followed by ligand exchange gives Cu(III)metallacycle **C** and subsequent reductive elimination leads to the alkoxylated product **3**.



Scheme 4. Plausible etherification mechanism

In conclusion, we have utilized 1-(2-aminophenyl)pyrazole (2-APP) as a removable directing group for C–H bond activation strategy and developed an unprecedented copper mediated C_{sp2}–H alkoxylation reaction using *reagent-amount* of alkoxide source delivering aryl alkyl ethers in high yield (up to 87%). This protocol is operationally simple, scalable, can be performed in open-flask conditions, displays a broad substrates scope with respect to both arenes and alkoxide sources, and also suitable to prepare deuterated molecules. As an application of this methodology, we have presented a formal synthesis of anti-emetic drug metoclopramide. Mechanistic studies demonstrated an involvement of radical pathway. The further effectiveness of the 2-APP directing group for various C–H bond functionalizations and detailed mechanistic studies are underway.

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Table of Content

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