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Pharmaceutical-Oriented Methoxylation of Aryl C(sp²)–H Bonds using Copper Catalysts

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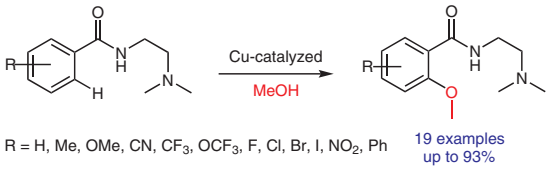

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Abstract A pharmaceutical-oriented, copper(II)-catalyzed methoxylation of aryl C(sp²)–H bonds has been developed. This simple and environmentally benign reaction system occurs efficiently using oxygen as oxidant with broad substrate scope and high functional group tolerance.

Key words pharmaceutical development, C–H methoxylation, copper catalysis, oxygen, DMEDA

Aromatic ethers are chemically and metabolically stable functional groups that are omnipresent in natural products and biologically active compounds.[1] The majority of methods for the synthesis of aromatic ethers involve transition-metal-catalyzed C–O bond coupling reactions, such as Ullmann, Buchwald–Hartwig and Chan–Evans–Lam reactions.[2] In recent decades, transition-metal-catalyzed functionalization of C–H bonds has attracted tremendous interest for the synthesis of complex natural and unnatural compounds since carbon–carbon and carbon–heteroatom bonds can be constructed directly from stable organic molecules.[3] It provides a new pathway for C–O bond coupling to generate aromatic ethers.

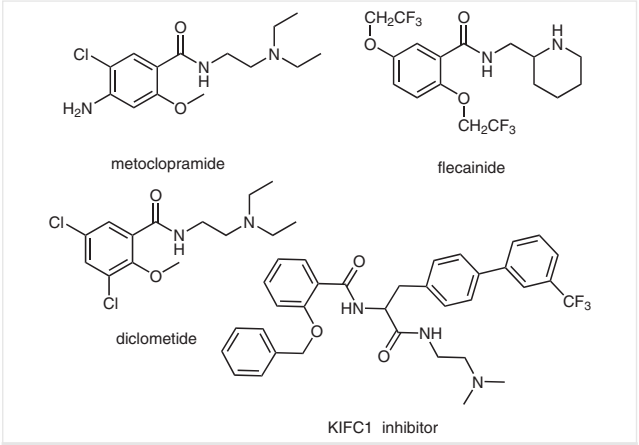
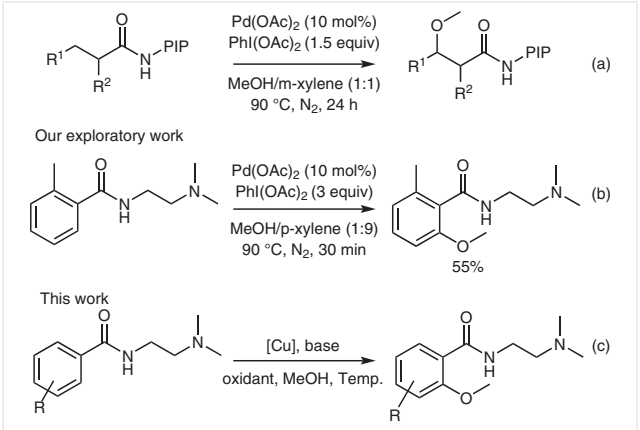


Figure 1 A selection of pharmaceuticals containing bidentate groups

Due to the intrinsic inertness of the C–H bond, the introduction of directing groups is a common means for C–H activation.[4] However, it usually requires additional operations to remove the directing groups in addition to the introduction of exogenous groups.[5] Clearly, this imposes some limitations in terms of atom- and step-economy. However, if the directing group itself is a part of the pharmaceutical molecule, the transition-metal-catalyzed C–H bond to C–O bond will be more valuable.



Scheme 1 Direct Alkoxylation of C–H Bonds

This approach will provide a new method for efficient synthesis of compounds for drug activity screening. Some pharmaceuticals such as metoclopramide and diclometide aroused our interest because of their intrinsic N,N-bidentate groups (Figure 1).[6] Therefore, the primary purpose is to make it clear whether these groups or similar structures

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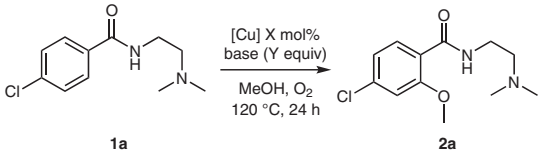
Table 1 Optimization of Reaction Conditions[a]



1a **2a**

Entry	[Cu] (X mol%)	Base (equiv)	Additive (Y mol%)	Yield (%)[b]
1	$Cu_2(OH)_2CO_3$ (5)	Cs_2CO_3 (2.0)		21
2	$Cu_2(OH)_2CO_3$ (5)	$KHCO_3$ (2.0)		4
3	$Cu_2(OH)_2CO_3$ (5)	K_2CO_3 (2.0)		4
4	$Cu_2(OH)_2CO_3$ (5)	CsOAc (2.0)		16
5	$Cu_2(OH)_2CO_3$ (5)	Na_2CO_3 (2.0)		27
6	$Cu_2(OH)_2CO_3$ (5)	KOCN (2.0)		90
7	$CuCl_2$ (5)	KOCN (2.0)		87
8	CuO (5)	KOCN (2.0)		ND
9	$Cu(OAc)_2$ (5)	KOCN (2.0)		86
10	$CuSO_4$ (5)	KOCN (2.0)		36
11	$C_{18}H_{12}CuN_2O_2$ (5)	KOCN (2.0)		15
12[d]	$Cu_2(OH)_2CO_3$ (5)	KOCN (2.0)		71
13[e]	$Cu_2(OH)_2CO_3$ (5)	KOCN (2.0)		3
14	$Cu_2(OH)_2CO_3$ (5)	KOCN (1.5)		85
15	$Cu_2(OH)_2CO_3$ (5)	KOCN (2.5)		87
16	$Cu_2(OH)_2CO_3$ (20)	KOCN (2.0)		92
17	$Cu_2(OH)_2CO_3$ (20)	KOCN (2.0)	$C_6H_{12}N_4$ (20)[f]	95 (90)[c]

[a] Reaction condition: **1a** (0.2 mmol), [Cu] X mol%, base (Y equiv), O_2 (1 atm), MeOH (2 mL).
[b] Yield based on ^1H NMR analysis using CH_2Br_2 as internal standard.
[c] Isolated yield.
[d] The reaction was carried out under air atmosphere.
[e] The reaction was carried out under N_2 atmosphere.
[f] Methenamine.

can be used as efficient directing groups for C–H alkoxylation. To date, a number of research groups have made considerable progress in palladium-catalyzed alkoxylation of arenes.[7] In 2013, Shi and co-workers[7a] reported the alkoxylation of unactivated C(sp^3)–H bonds with $Pd(OAc)_2$ and $PhI(OAc)_2$ using a 2-(pyridine-2-yl)propan-2-amine (PIP) directing group (Scheme 1a). In 2014, Zhang and Sun[7b] reported a C(sp^2)–H bond alkoxylation with $Pd(OAc)_2$ and $PhI(OAc)_2$. Recently, a novel example of C(sp^2)–H bond alkoxylation has been reported by Liu et al.[7c] with $Pd(OAc)_2$ and $PhI(OAc)_2$ using amino acids as directing groups. It is noteworthy that the combination of $Pd(OAc)_2$ and $PhI(OAc)_2$ is very efficient for promoting C–H alkoxylation.

Based on the above observations, the use of *ortho*-methylbenzoic acid as a model substrate, *N*,*N*′-diethylethylenediamine (DEEDA) as directing group, $Pd(OAc)_2$ as catalyst, $PhI(OAc)_2$ as oxidant and methanol as the alkoxylation reagent were used in some exploratory work. The desired product could be obtained with this directing group, albeit in low yield. Interestingly, further work established that when *N*,*N*′-dimethylethylenediamine (DMEDA) was used as directing group, 10 mol% $Pd(OAc)_2$ as catalyst, 3 equivalent $PhI(OAc)_2$ as oxidant at 90 °C under N_2 atmosphere, the desired product was obtained in 55% yield in 30 min (Scheme 1b).

DMEDA proved to be an effective directing group in view of the above. Given that palladium is rare and expensive, we turned our attention to the use of alternative catalysts.[8] In comparison to the Pd catalyst, Cu catalysis exhibits advantages because it is inexpensive and environmentally benign.[9] To our knowledge, only a few examples of copper-catalyzed C–H alkoxylation with oxygen as a clean and cheap oxidant have been reported.[10] Based on these reports, we suspect that the structure of DMEDA will also lead to equally efficient reactions using copper as catalyst.

To verify our hypothesis, we initiated our investigation with 4-chloro-*N*-(2-(dimethylamino)ethyl)benzamide (**1a**) as a model substrate (Table 1). Gratifyingly, the desired product was obtained in 21% yield in the presence of Cs_2CO_3 (2.0 equiv) as a base with 5 mol% $Cu_2(OH)_2CO_3$ under O_2 at 120 °C (entry 1). Screening of different bases revealed that the reaction with KOCN gave the best yield (entries 2–6). We next screened a series of copper salts, including $CuCl_2$, CuO, $Cu(OAc)_2$, $CuSO_4$, and $C_{18}H_{12}CuN_2O_2$, but no better result was observed (entries 7–11). When CuO was used as catalyst, the desired product was not detected (entry 8). The results above revealed that suitable anions could promote the reaction and Cu(II) was the species in solution ready to coordinate the substrate **1a**. The yield was 71% when the reaction was carried out under air atmosphere (entry 12). The reaction was low yielding under N_2 atmosphere (3%; entry 13). Clearly, it was necessary to use O_2 as atmosphere. To further improve the yield, the amount of KOCN was screened, but no significant change was observed (entries 14 and 15; see the Supporting Information). By increasing the amount of $Cu_2(OH)_2CO_3$ to 20 mol%, the yield was improved to 92% (entry 16). To our delight, when methenamine (20 mol%) was added to the reaction system, a better result was observed (90% isolated yield, entry 17).

With the optimal reaction conditions in hand, the reaction scope with respect to aromatic substrates was established (Scheme 2). Various kinds of benzamide derivatives either both electron-donating or electron-withdrawing groups on the phenyl rings (**2b–s**), were also tolerated under the optimized conditions, and the reaction proceeded with moderate to good yields. The reaction protocol was sensitive to steric hindrance, with almost no methoxylated product being produced from *ortho*-substituted substrates. *para*-Substituted substrates bearing Br (**2b**) or CF_3(**2c**) groups were well tolerated, and those with I (**2e**), NO_2 (**2f**), F (**2g**), CN (**2h**), CH_3 (**2i**), and OMe (**2j**) gave the methoxylation product in moderate to good yields. Methoxylation of *meta*-substituted substrates proceeded exclusively at the

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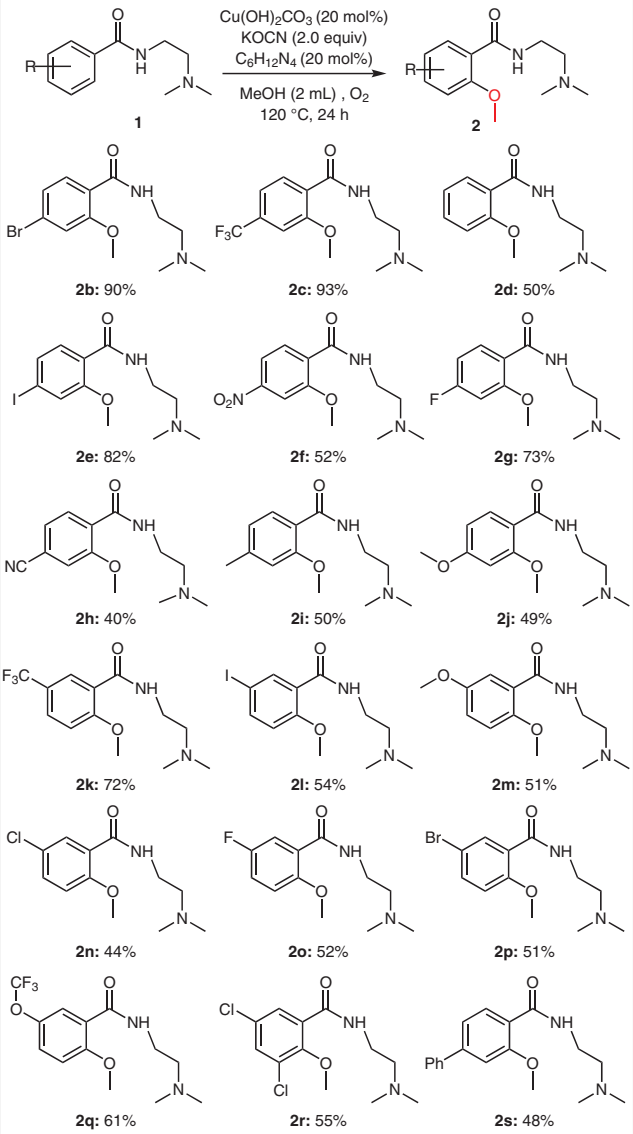
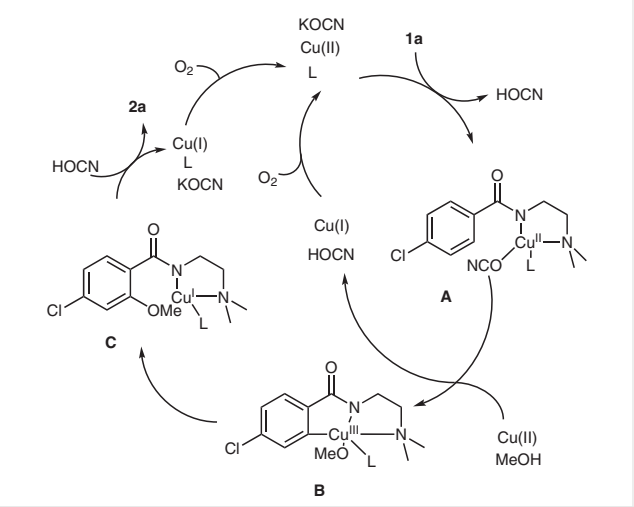
less hindered C–H bonds, irrespective of the electronic nature of the substituents (**2k–q**). Substrates with more complex structure were also tolerated under the optimized conditions; 3,5-dichloro-*N*-(2-(dimethylamino)ethyl)benzamide gave the methoxylated product **2r** in 55% yield, *N*-(2-(dimethylamino)ethyl)-[1,1′-biphenyl]-4-carboxamide (**2s**) was also tolerated under the reaction conditions.



Scheme 2 Substrate of aromatic compounds. *Reagents and conditions*: **1** (0.2 mmol), $Cu(OH)_2CO_3$ (20 mol%), KOCN (2 equiv), methenamine (20 mol%), MeOH (2 mL), under O_2, 120 °C, 24 h.

On the basis of the above observations and on other reports, we proposed a plausible mechanism for the copper-catalyzed C–H alkoxylation of benzamide derivatives (Scheme 3).[11] Complexation of benzamide **1a** and methenamine (**L**) to the copper catalyst (intermediate **A**) followed by disproportionative C–H activation affords the Cu(III) intermediate **B**. The latter undergoes reductive elimination to give intermediate **C**, which is followed by protonation to generate the desired product **2a** and Cu(I). The copper(I) species that was generated by disproportionative C–H activation and reductive elimination could be oxidized to Cu(II) by oxygen, thus completing the catalytic redox cycle.



Scheme 3 Plausible reaction mechanism

In summary, pharmaceutical oriented methoxylation of aryl C(sp^2)–H bonds using copper catalysts has been developed.[12] This simple and environmentally benign reaction occurs efficiently using oxygen as an oxidant with broad substrate scope and high functional group tolerance. In addition, it will provide an efficient method for the synthesis of new active drug molecules according to the relevance between drug structure and efficiency. Further research to extend the applications of the DMEDA directing group in the C–H activation field is under way.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610132.

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(12) **General Procedure for Cu(II)-Catalyzed Alkoxylation:** $Cu_2(OH)_2CO_3$ (0.04 mmol), KOCN (0.40 mmol), methenamine (0.04 mmol), 4-bromo-*N*-(2-(dimethylamino)ethyl)benzamide (0.20 mmol), CH_3OH (2 mL) were introduced into a 15 mL sealed tube equipped with a magnetic stirrer in O_2. The mixture was vigorously stirred at 120 °C for 24 h. After cooling to room temperature, the solvent was evaporated under vacuum. The residue was dissolved in mixed solvent of dichloromethane (30 mL) and edetate tetrasodium (EDTA) saturated aqueous solution (30 mL). After separation, the aqueous phase was extracted twice with dichloromethane (15 mL) and the organic layers were combined and evaporated under vacuum. The crude product was purified by column chromatography using silica gel to afford 4-bromo-*N*-(2-(dimethylamino)ethyl)-2-methoxybenzamide. Isolated yield: 0.0542 g (90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (s, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 6.97 (dd, *J* = 8.4, 1.8 Hz, 1 H), 6.89 (d, *J* = 1.8 Hz, 1 H), 3.92 (s, 3 H), 3.66 (q, *J* = 5.9 Hz, 2 H), 2.87–2.80 (m, 2 H), 2.50 (s, 6 H). ^{13}C NMR (126 MHz, $CHCl_3$): δ = 164.84, 158.08, 138.54, 133.11, 121.34, 119.82, 112.04, 57.77, 56.29, 44.68, 36.56. HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{18}ClN_2O_2$: 257.1051; found: 257.1062.

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