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Copper-catalyzed benzylic C(sp^3)–H alkoxylation of heterocyclic compounds†

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We achieved intra- and intermolecular C(sp^3)–H alkoxylation of benzylic positions of heteroaromatic compounds using CuBr$_n$ (n = 1, 2)/5,6-dimethylphenanthroline (or 4,7-dimethoxyphenanthroline) and (^{t}BuO)$_2$ as a catalyst and an oxidant, respectively. The reaction proceeded at both terminal and internal benzylic positions of the alkyl groups. The intramolecular alkoxylation was performed on a gram scale.

Many bioactive compounds, such as natural products and drugs, *e.g.*, rivoglitazone,[1] balaglitazone,[2] PF-2545920,[3] and AMG-208,[4] have an ether moiety at the benzylic position of heterocyclic ring(s) (Fig. 1). The development of practical and effective synthetic methods of such ethers is therefore in high demand. Representative reactions for the synthesis of ethers include Williamson ether synthesis,[5] the Ullmann reaction,[6] and the Buchwald–Hartwig reaction.[7] These reactions have several drawbacks, however, such as the need for multiple reaction steps, an excess amount of copper powder or salt, and/or the formation of side products such as metal halides. To improve the efficiency of ether synthesis, direct C–H alkoxylation using alcohols as substrates is an ideal strategy. Examples of C–H alkoxylation, especially C(sp^3)–H alkoxylation, however, are rare.[8] The following C(sp^3)–H alkoxylation reactions have been reported: (a) palladium-catalyzed benzylic methoxylation using a quinoline-type directing group (Fig. 2a);[8a] (b) palladium-catalyzed *tert*-butoxylation using an oxazoline-type directing group (Fig. 2b);[9] (c) palladium-catalyzed alkoxylation using a bidentate directing group (Fig. 2c);[10] and (d) copper-catalyzed butoxylation at the double benzylic position (Fig. 2d).[11] These reactions have similar characteristics: (1) when palladium-salts are used as catalysts, directing groups

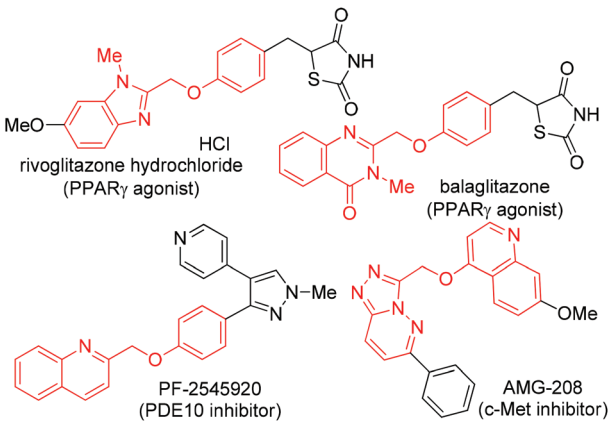

Fig. 1 Drug candidates that contain an ether moiety with a heterocyclic ring at the α-position.

are indispensable for promoting the reaction, and alkoxylation proceeds only at the terminal position (Fig. 2a–2c);[12] (2) alcohols (alkoxylation reagents) are used as a solvent (Fig. 2a, 2c, and 2d); and, (3) only one substrate example was reported (Fig. 2a, 2b, and 2d). In this paper, we report copper-catalyzed intramolecular and intermolecular C–H alkoxylation of benzylic C(sp^3)–H bonds of heteroaromatic compounds (Fig. 2e). The alkoxylation reaction proceeded regioselectively at both the terminal and internal benzylic positions of alkyl chains.

Treatment of 1-hydroxyethyl-2-methylbenzimidazole **1a** with a catalytic amount of CuCl/5,6-dimethylphenanthroline and (^{t}BuO)$_2$ in chlorobenzene at 100 °C for 4 h led to an intramolecular C(sp^3)–H alkoxylation reaction, and the desired alkoxylated product **2a** was obtained in 47% yield (Table 1, entry 1). Changing the catalyst to CuBr and extending the reaction time to 6 h improved the yield of **2a** (Table 1, entries 2 and 3).[13–15] Although other copper salts showed catalytic activities, the yield of **2a** was lower than that with CuBr (Table 1, entries 4–7). In this reaction, the addition of a ligand was indispensable (Table 1, entry 8). Other phenanthroline- and bipyridine-

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†Electronic supplementary information (ESI) available: Experimental procedures, spectral data of substrates (alcohols) and alkoxylated products, and ^{1}H and ^{13}C NMR charts. See DOI: 10.1039/c4ob00215f

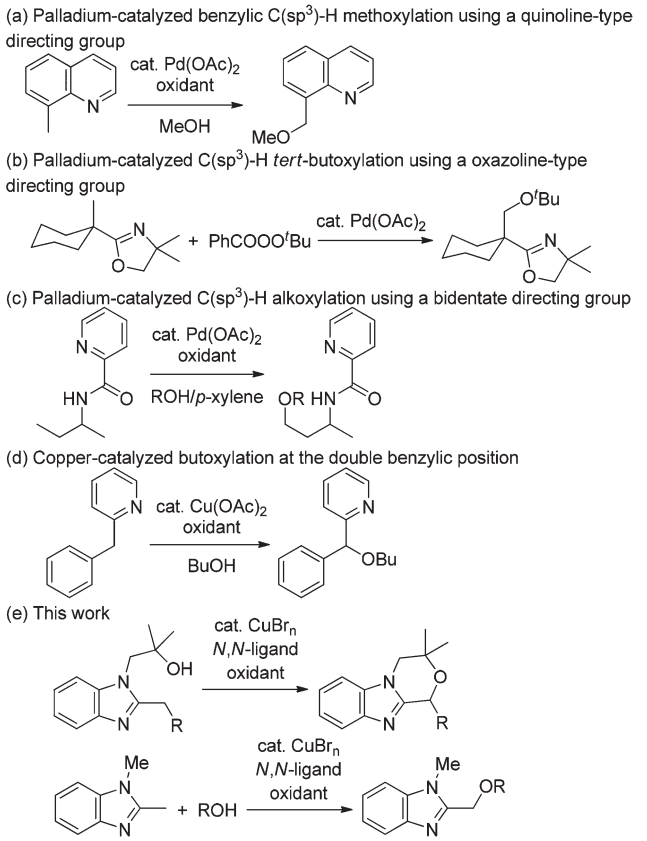


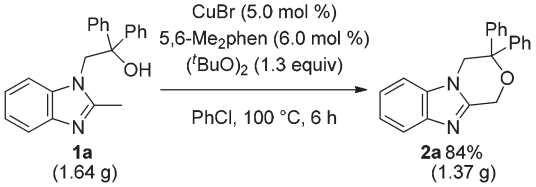
Fig. 2 Previous and present C(sp^3)–H alkoxylation reactions. (a) Palladium-catalyzed benzylic C(sp^3)–H methoxylation using a quinoline-type directing group. (b) Palladium-catalyzed C(sp^3)–H *tert*-butoxylation using a oxazoline-type directing group. (c) Palladium-catalyzed C(sp^3)–H alkoxylation using a bidentate directing group. (d) Copper-catalyzed butoxylation at the double benzylic position. (e) This work.

type ligands did not improve the yield of **2a** (Table 1, entries 9–16).

We next investigated the substrate scope and limitations (Table 2). Diaryl-substituted alcohols **1b–1e** produced the corresponding alkoxylated products **2b–2e** in 55%–81% yields (entries 1–4). The yield of the product **2f** decreased when dimethyl-substituted alcohol **1f** was used (entry 5).[16] A spiro compound **2g** was obtained from **1g** (entry 6). The alkoxylation reaction proceeded with moderate to good yields when using 2-methylbenzimidazoles with a substituent at the aromatic ring, **1h–1j** (entries 7–9). In entry 9, the alkoxylation reaction proceeded selectively at the 2-methyl group and did not occur at the 7-methyl group. Alkoxylation reactions are generally more difficult at the internal positions of alkyl chains than at the terminal positions. Interestingly, the C(sp^3)–H alkoxylation reaction also proceeded in high yield at the internal position of the alkyl chains (entries 10–13).[17] The conditions were also applicable to seven-membered ring formation (entry 14), aryloxylation reaction (entry 15), and heterocyclic substrates **1q–1s** other than benzimidazole (entries 16–18).

The proposed mechanism for the alkoxylation reaction is shown in Scheme 1: (1) formation of CuBrX (X = Br or O^{t}Bu) and a *tert*-butoxy radical from CuBr$_n$ (n = 1 or 2) and (^{t}BuO)$_2$; (2) formation of an alkoxycopper intermediate[8i] with a benzyl radical *via* the elimination of HX (X = Br or O^{t}Bu) and ^{t}BuOH;[18] (3) formation of the product **2** by C–O bond formation between the benzyl radical and the oxygen atom of the alkoxycopper moiety.[18–22]

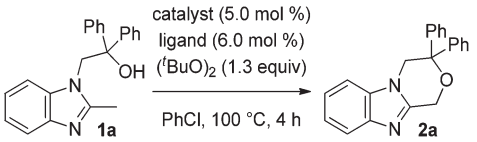
This reaction also proceeded in high yield on the gram scale. Using 1.64 g of **1a** as a substrate, the reaction produced 1.37 g of **2a** in 84% yield (eqn (1)). The yield of **2a** was slightly higher than that shown in Table 1, entry 3 (**1a**: 41.1 mg).



(1)

Intermolecular C(sp^3)–H alkoxylation also proceeded under the present conditions. Treatment of 1,2-dimethyl-1*H*-benzo[*d*]-imidazole (**3**) with butanol (**4a**) or 2-phenylethanol (**4b**) gave the corresponding alkoxylated products **5a** and **5b** in 33% and 37% yields, respectively (eqn (2)). In addition, the intermolecular alkoxylation reaction occurred at the benzylic C(sp^3)–H bond of quinazolinone **6** (eqn (3)). Although yields are moderate, these are the first entries to catalytic benzylic C(sp^3)–H alkoxylation using a reagent amount (*i.e.*, not a solvent amount) of alcohols.

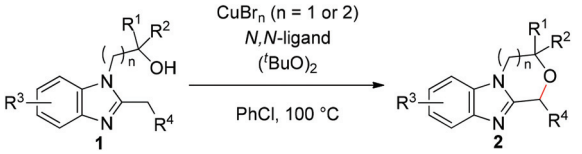
Table 1 Investigation of several copper catalysts and ligands



Entry	Catalyst	Ligand[a]	Yield[b] (%)
1	CuCl	5,6-Me$_2$phen	47
2	CuBr	5,6-Me$_2$phen	70
3[c]	CuBr	5,6-Me$_2$phen	77 (75)[d]
4	CuI	5,6-Me$_2$phen	62
5	$[(CH_3CN)_4Cu]^+(PF_6)^-$	5,6-Me$_2$phen	2
6	$CuCl_2$	5,6-Me$_2$phen	40
7	$CuBr_2$	5,6-Me$_2$phen	60
8	CuBr	None	0
9	CuBr	Phen	50
10	CuBr	4,7-Me$_2$phen	0
11	CuBr	3,4,7,8-Me$_4$phen	18
12	CuBr	5,6-(MeO)$_2$phen	38
13	CuBr	4,7-(MeO)$_2$phen	67
14	CuBr	4,7-Ph$_2$-phen	50
15	CuBr	2,2′-Bipyridine	4
16	CuBr	4,4′-di-*tert*-butyl-2,2′-bipyridine	7

[a] Phen = 1,10-phenanthroline. [b] Yield determined by ^{1}H NMR of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. [c] 6 h. [d] Isolated yield.

Table 2 Investigation of several substrates[a]



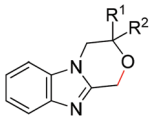
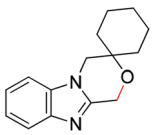
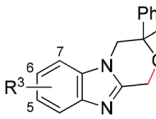
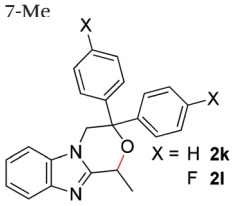
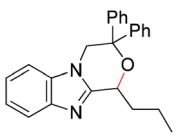
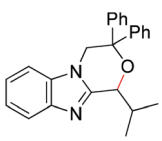
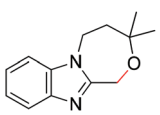
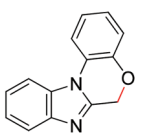
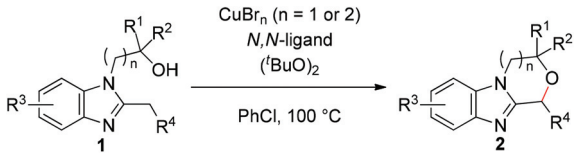
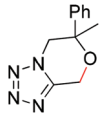
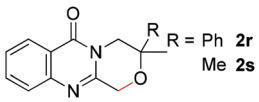
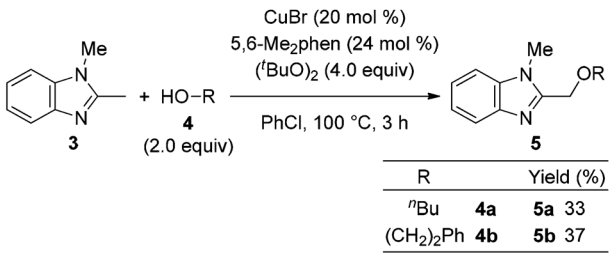
Entry	Catalyst (mol%)	Ligand[b] (mol%)	2		Yield[c] (%)
					
			R^1	R^2	
1	CuBr (5.0)	**A** (6.0)	4-MeOC$_6$H$_4$	Ph	**2b** 71%
2	CuBr (5.0)	**A** (6.0)	4-MeC$_6$H$_4$	4-MeC$_6$H$_4$	**2c** 55%
3	CuBr (5.0)	**A** (6.0)	4-FC$_6$H$_4$	4-FC$_6$H$_4$	**2d** 81%
4	CuBr (5.0)	**A** (6.0)	4-ClC$_6$H$_4$	4-ClC$_6$H$_4$	**2e** 81%
5	CuBr (5.0)	**B** (6.0)	Me	Me	**2f** 55%
6	CuBr (5.0)	**B** (6.0)			**2g** 52%
7	CuBr (5.0)	**A** (6.0)	R^3 = 5-CF$_3$		**2h** 45%
8	CuBr (10)	**A** (12)	6-MeO		**2i** 70%
9	CuBr (5.0)	**A** (6.0)	7-Me		**2j** 80%
10	CuBr (10)	**B** (12)			**2k** 70%
11	CuBr (10)	**B** (12)			**2l** 67%
12	CuBr (10)	**B** (12)			**2m** 71%
13	CuBr (10)	**B** (12)			**2n** 41%
14	CuBr (5.0)	**A** (6.0)			**2o** 21%
15	CuBr (20)	**A** (24)			**2p** 59%

Table 2 *(Contd.)*



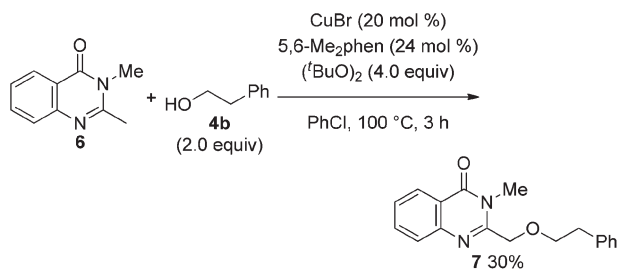
Entry	Catalyst (mol%)	Ligand[b] (mol%)	2	Yield[c] (%)
16	CuBr$_2$ (10)	**B** (12)		**2q** 44%
17	CuBr$_2$ (5.0)	**B** (6.0)	 R = Ph **2r**, Me **2s**	**2r** 49%
18	CuBr$_2$ (5.0)	**B** (6.0)		**2s** 50%

[a] For detailed experimental procedures, see ESI. [b] **A**: 5,6-dimethyl-1,10-phenanthroline; **B**: 4,7-dimethoxy-1,10-phenanthroline. [c] Isolated yield.



R		Yield (%)
^{n}Bu	**4a**	**5a** 33
(CH$_2$)$_2$Ph	**4b**	**5b** 37

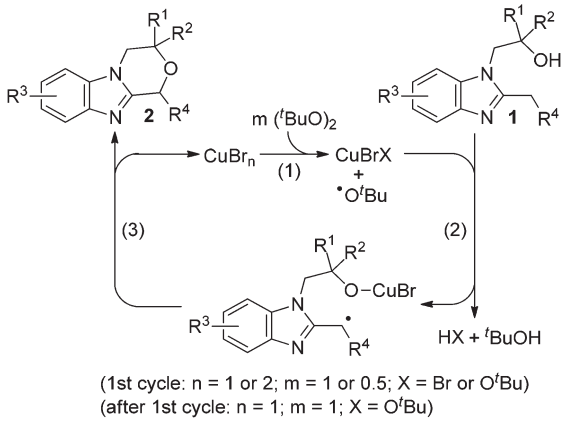
(2)



(3)

Conclusions

In summary, we successfully developed a benzylic C(sp^3)–H alkoxylation reaction of heterocyclic compounds using alcohols as alkoxylating reagents under copper catalysis. In this reaction, alkoxylation proceeded selectively at the benzylic position of heteroaromatics and not at the benzylic position of a benzene ring. The present reaction is a rare example of copper-catalyzed C(sp^3)–H alkoxylation, and proceeded at both the terminal and internal positions of the alkyl chains without



Scheme 1 Proposed mechanism for the catalytic benzylic C(sp^3)–H alkoxylation.

the use of a directing group or an excess amount of the alkoxylating reagents (alcohols). The alkoxylated product was obtained on the gram scale, and an intermolecular reaction also occurred. This reaction provides a useful strategy for synthetic organic chemistry.

Acknowledgements

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13 The intramolecular alkoxylation did not proceed using the following transition metal salts and complexes as a catalyst: $MnCl_2$, $MnBr(CO)_5$, $FeCl_2$, $CoCl_2$, $RhCl(PPh_3)_3$, $NiCl_2$, $NiBr_2$, NiI_2, $Ni(OAc)_2$, $Ni(OTf)_2$, $[IrCl(cod)]_2$, $PdCl_2$, $PdBr_2$, $Pd(OAc)_2$, $Pd(Opiv)_2$, $Pd(acac)_2$.

14 Investigation of several solvents: hexane, 0%; $PhCF_3$, 9%; *o*-xylene, 18%; *m*-xylene, 6%; CH_2ClCH_2Cl, 4%; NMP, 0%.

15 Investigation of several oxidants: Ag_2CO_3, 11%; no reaction: ^{t}BuOOBz, *tert*-butyl hydroperoxide (TBHP), oxone, PhI-$(OAc)_2$, $K_2S_2O_8$, O_2 (1.0 atm).

16 1-(2-Methyl-1*H*-benzo[*d*]imidazol-1-yl)-2-propanol (**1t**, R^1 = Me, R^2 = H) and 2-(2-methyl-1*H*-benzo[*d*]imidazol-1-yl)-ethanol (**1u**, $R^1 = R^2$ = H) also gave the corresponding intramolecular alkoxylated products **2t** and **2u** in 40% and 24% yields, respectively.

17 An asymmetric reaction proceeded using a chiral ligand instead of 5,6-dimethylphenanthroline though the yield and enantiomeric excess were low. Treatment of benzimidazole **1l** bearing an ethyl group at 2-position with a catalytic amount of $CuBr_2$/(−)-sparteine and $(^tBuO)_2$ gave **2l*** in 14% yield and 11% ee. For several examples of asymmetric

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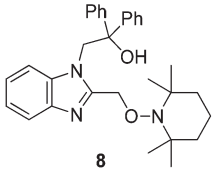
19 To elucidate the rate-determining step of the C(sp^3)–H alkoxylation, we investigated a deuterium labeling experiment using 2-methyl group-deuterated **1a**. However, the kinetic isotope effect (KIE) value could not be determined because of a scrambling between the deuterium atom of the 2-methyl group and the hydrogen atom of the hydroxy group.

20 The alkoxylation reaction was inhibited by adding a radical scavenger. Treatment of 1-hydroxyethyl-2-methylbenzimidazole **1a** with a catalytic amount of CuBr (5.0 mol%)/5,6-dimethylphenanthroline (6.0 mol%) and (^{t}BuO)$_2$ (1.3 equiv.) in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 5.0 mol%) in chlorobenzene at 100 °C for 4 h gave the alkoxylated product **2a** in 27% yield. By increasing the amount of TEMPO to 100 mol%, both **2a** and coupling product **8** were formed in 21% and 45% yields, respectively. These results suggest that the reaction proceeded via intermediary of a benzyl radical derived from **1a**.



8

21 Another possible pathway is that the reaction proceeds via alkoxy benzylcopper(III) species. For the details, see the ESI, Scheme S1.†

22 Another possible pathway is that the alkoxylation reaction proceeds via formation of α-bromomethylheterocyclic intermediates from the starting heterocyclic compounds and copper bromide catalyst. To validate the possibility, we investigated reactions between 1,2-dimethyl-1*H*-benzo[*d*]-imidazole (**3**) and CuBr (1.0 equiv.)/5,6-dimethylphenanthroline (1.2 equiv.) (or $CuBr_2$ (1.0 equiv.)/5,6-dimethylphenanthroline (1.2 equiv.)) with or without (^{t}BuO)$_2$ (4.0 equiv.) in chlorobenzene at 100 °C for 4 h. However, 2-(bromomethyl)-1-methyl-1*H*-benzo[*d*]imidazole was not formed at all in the reactions. In addition, such α-bromomethylheterocyclic intermediates were not detected in all entries. Therefore, the pathway through α-bromination is less likely.

