Cu(II)-mediated oxidative intermolecular *ortho* C–H functionalisation using tetrahydropyrimidine as the directing group†

Tsukasa Mizuhara, Shinsuke Inuki, Shinya Oishi, Nobutaka Fujii* and Hiroaki Ohno*

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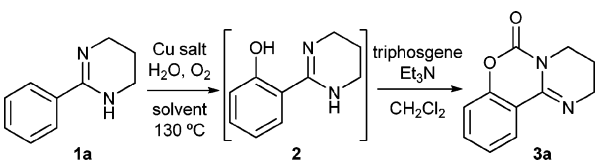
Tetrahydropyrimidine works efficiently as a directing group in Cu(II)-mediated oxidative aromatic C–H functionalisation for the selective introduction of oxygen or nitrogen to the *ortho*-position.

Transition metal-catalysed C–H functionalisation has received considerable attention in recent years. Notable progress has been made especially with Pd, Ru, Rh, and Pt catalysts, which allow atom-economical transformations using simple substrates. Directing group assisted intra/intermolecular C–H functionalisation[1] is considered to be one of the most promising approaches as a new carbon–carbon[1] or carbon–heteroatom bond[2,3] is selectively formed at a non-functionalised position proximal to the directing group. Recent research in this area has revealed that nitrogen-containing functional groups such as pyridines,[4] imines,[5] oximes (and ethers),[6] oxazolines[7] and amidines[8] as well as oxygen-containing functional groups such as amides,[9] esters,[10] ketones,[11] carboxylic acids[12] and phenols[13] effectively act as directing groups for regioselective C–H functionalisation. These functional groups and their equivalents are involved in biologically active natural and synthetic compounds while directing group-assisted C–H functionalisation serves as a powerful tool for the synthesis and modification of these molecules.

As part our ongoing program directed toward the development of C–H functionalisation reactions for the efficient construction of heterocyclic frameworks,[14] we designed an experiment for the oxidative introduction of a heteroatom by aromatic C–H functionalisation with the assistance of an *ortho*-tetrahydropyrimidinyl group. This group can be considered as a promising drug-like structure as well as a synthetic equivalent of a carboxylic group. Reinaud and co-workers previously reported a copper-catalysed *ortho*-hydroxylation reaction of benzoic acid using carboxyl as a directing group.[15] Yu *et al.*[16a] and Chatani *et al.*[16b] independently reported copper-mediated oxidative intermolecular C–H functionalisation using a pyridine moiety as the directing group. The latter reactions provide efficient access to functionalised pyridines with a biaryl structure by simply treating the biaryl substrates with a copper salt for several hours. More recently, copper-catalysed syntheses of benzimidazoles[17a] and benzoxazoles[17b] by oxidative intramolecular C–H functionalisation using amidine or amide as the directing/nucleophilic group were reported. Herein, we describe copper-mediated oxidative intermolecular C–H functionalisation using tetrahydropyrimidine as the directing group. In most cases, the reaction is complete within 1 h to provide 2-(tetrahydropyrimidinyl)phenol and aniline derivatives by the *ortho*-selective introduction of an oxygen or nitrogen atom.[18]

We initially investigated the reaction conditions for this C–H hydroxylation (Table 1). In the presence of H_2O (1.0 equiv.), treatment of 2-phenyl-1,4,5,6-tetrahydropyrimidine (**1a**) with CuO, $Cu(OH)_2$, $Cu(OTf)_2$ or $Cu(tfa)_2$ (1.0 equiv.) in DMF at 130 °C under an oxygen atmosphere led to the recovery of unchanged starting material and the desired C–H oxidation did not occur (entries 1–4). Using $Cu(OAc)_2$,[16a] however, led to the formation of the desired *ortho*-hydroxylated compound **2** (*ca.* 69% yield) although the isolation of **2** in its pure form was extremely difficult because of its basicity. We then attempted to isolate **3a** as the protected form: after the disappearance of **1a** (monitored by TLC), the reaction mixture was evaporated *in vacuo* and treated with triphosgene

Table 1 Optimisation of reaction conditions for C–H hydroxylation[a]



Entry	Cu salt (equiv.)	Solvent	Time/min	Yield (%)[b]
1	CuO (1.0)	DMF	20	N.r.[e]
2	$Cu(OH)_2$ (1.0)	DMF	20	N.r.[e]
3	$Cu(OTf)_2$ (1.0)	DMF	20	N.r.[e]
4	$Cu(tfa)_2$ (1.0)	DMF	20	N.r.[e]
5	$Cu(OAc)_2$ (1.0)	DMF	20	61
6	$Cu(OAc)_2$ (1.0)	Acetonitrile	60	11
7	$Cu(OAc)_2$ (1.0)	Dioxane	60	11
8	$Cu(OAc)_2$ (0.2)	DMF	60	30
9	$Cu(OAc)_2$ (2.0)	DMF	15	27
10[c]	$Cu(OAc)_2$ (1.0)	DMF	20	70
11[cd]	$Cu(OAc)_2$ (1.0)	DMF	20	56

[a] After completion of C–H hydroxylation (monitored by TLC), the reaction mixture was evaporated and treated with triphosgene (1.05 equiv.) and Et_3N (4.0 equiv.) in CH_2Cl_2 at 0 °C to rt for 1 h. [b] Isolated yields. [c] After completion of C–H hydroxylation (monitored by TLC), the reaction mixture was treated with TMEDA (4.0 equiv.) at 130 °C for 1 min. In this case, TMEDA (additional 4.0 equiv.) was used for the next step instead of Et_3N. [d] Reaction was carried out under air. [e] No reaction. Abbreviation: TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto, 606-8501, Japan.
E-mail: hohno@pharm.kyoto-u.ac.jp; Fax: +81 75 753 4570; Tel: +81 75 753 4571

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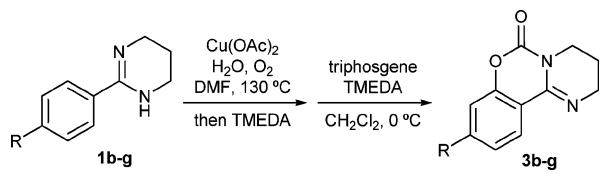
(1.05 equiv.) and triethylamine (4.0 equiv.) in CH_2Cl_2 to afford pure **3a** in a yield of 61% (entry 5). When acetonitrile or dioxane was used as the solvent instead of DMF, yields of **3a** decreased considerably (11%, entries 6 and 7). Lowering the loading of $Cu(OAc)_2$ to 0.2 equiv. also resulted in a decreased yield for **3a** (30%, entry 8), which indicates low catalyst efficiency. When using 2.0 equiv. of $Cu(OAc)_2$, the yield also decreased and this was contrary to our expectation (27%, entry 9). Considering that the *ortho*-hydroxylated product **2** may form a complex with the copper salt, we further optimised the reaction conditions including the carbonylation procedure. Initially, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) was added as a bidentate ligand to the oxidative C–H functionalisation reaction mixture and this resulted in the complete inhibition of the desired transformation. Similarly, use of TMEDA instead of triethylamine as the base for carbonylation did not improve the yield of **3a**. On the other hand, treatment with TMEDA (4.0 equiv.) at 130 °C for 1 min after the C–H hydroxylation followed by the carbonylation using additional TMEDA (4.0 equiv.) increased the yield to 70% (entry 10). The reaction under air resulted in a decreased yield (56%, entry 11), which indicates that molecular oxygen participates in the re-oxidation of the copper catalyst.

Using the optimised conditions (Table 1, entry 10), we examined the reaction of several substituted substrates (Table 2). Substitution with electron-donating groups such as methoxy (**1b**, entry 1) or methyl groups (**1c**, entry 2) was tolerated to afford the desired products **3b** and **3c** in 64% and 61% yields, respectively. The chemoselectivity of this reaction was evaluated by a reaction where aryl bromide **1d** was used and the desired product **3d** was obtained in a 45% yield (entry 3). Methoxycarbonyl (entry 4) and trifluoromethyl groups (entry 5) had a relatively small effect on the reactivity of these substrates and the use of the highly electron-deficient arene **1g** bearing a nitro group decreased the yield considerably (19%, entry 6). These results indicate that this reaction is sensitive to the presence of electron-withdrawing groups on the aromatic ring. In all cases, reactions without TMEDA gave less favourable results.

Table 2 Cu-catalysed C–H hydroxylation of 4-substituted 2-phenyl-1,4,5,6-tetrahydropyrimidines[a]



Entry	Substrate (R)	Product	Yield (%)[b]
1	**1b** (OMe)	**3b**	64 (53)
2	**1c** (Me)	**3c**	61 (54)
3	**1d** (Br)	**3d**	45 (37)
4	**1e** (CO_2Me)	**3e**	46 (43)
5	**1f** (CF_3)	**3f**	43 (38)
6	**1g** (NO_2)	**3g**	19 (16)

[a] These reactions were carried out using the optimised procedure (Table 1, entry 10). [b] Isolated yields. Yields in parentheses indicate those of the reactions containing Et_3N (as shown in Table 1, entry 5).

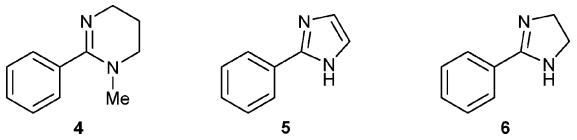
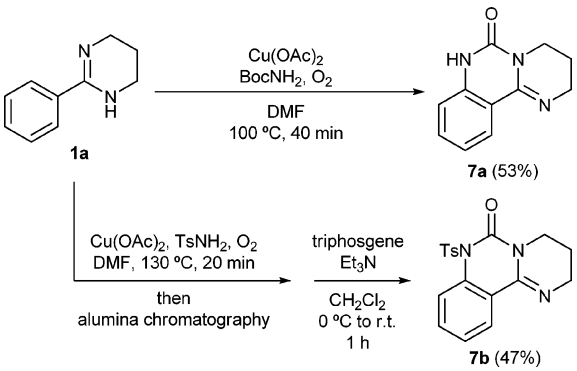


Fig. 1 Various amidine analogues.



Scheme 1 C–H amidation with $BocNH_2$ and $TsNH_2$.

Next, we investigated the ability of other amidine analogues to function as directing groups (Fig. 1). The reaction of the N-methylated analogue **4** and 2-phenylimidazole **5** did not produce the desired *ortho*-hydroxylated products under standard reaction conditions and the starting materials were recovered. Interestingly, the five-membered ring amidine in **6** was not effective as a directing group either. These results suggest that subtle differences in the intermediate formed by a copper salt and a directing group strongly affect the reactivity of the substrates.

Finally, we investigated C–H amidation (Scheme 1). We found that the reaction of amidine **1a** with $Cu(OAc)_2$ (1.0 equiv.) and *tert*-butyl carbamate (3.0 equiv.) in DMF at 100 °C for 40 min directly afforded the tricyclic aniline derivative (**7a**) in 53% yield. This reaction occurred by cyclisation involving the elimination of *tert*-butoxide. *p*-Toluenesulfonamide also reacted with **1a** under identical conditions to afford **7b** in 47% yield after alumina column chromatography[19] followed by treatment with triphosgene–Et_3N.

Although the exact mechanism of the *ortho* C–H oxidation is unclear, a single electron transfer (SET) pathway *via* a radical-cation intermediate[16a] is supported by the fact that the presence of an electron-withdrawing group on the benzene ring considerably decreased the product yields. The observed *ortho*-selectivity can be attributed to an intramolecular transfer of the coordinating group on the copper atom.

In conclusion, we have developed a copper-mediated oxidative *ortho* C–H functionalisation using tetrahydropyrimidine as a directing group. This reaction applies to 2-phenyl-1,4,5,6-tetrahydropyrimidines having an electron-donating or a weak electron-withdrawing group and affords the corresponding phenol derivatives within 1 h. Use of *tert*-butyl carbamate or tosylamide instead of H_2O promotes the introduction of a nitrogen functionality to give aniline derivatives. As far as we are aware, this is the first example of an oxidative

intermolecular C–H functionalisation using an amidine moiety as the directing group. Further studies that include an investigation of the exact reaction mechanism and the application to synthesis of biologically-active compounds are now in progress.

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