ORGANIC LETTERS

2011
Vol. 13, No. 7
1622–1625

Copper-Catalyzed Benzylic C−H Oxygenation under an Oxygen Atmosphere via *N*-H Imines as an Intramolecular Directing Group

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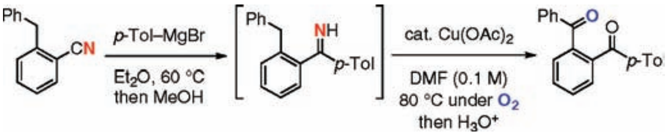
Received January 5, 2011

ABSTRACT



Copper-catalyzed benzylic C−H oxygenation under an oxygen atmosphere was developed starting from carbonitriles and Grignard reagents via *N*-H imine intermediates. The present process is characterized by the following two-step sequence in a one-pot manner: (1) addition of Grignard reagents to carbonitriles to form *N*-H imines and (2) benzylic C−H oxygenation (C=O bond formation) triggered by 1,5-hydrogen atom transfer with transient iminyl copper species.

The incorporation of an oxygen atom into the organic frameworks from atmospheric molecular oxygen (O_2) offers one of the most ideal processes in organic synthesis. Activation of O_2 by copper enzymes has been observed in some biological oxygenase systems such as monooxygenase tyrosinase and dopamine β-monooxygenase that effect hydroxylation of C−H bonds.[1] Biomimetic studies of such enzymatic reactions using rather simple models have been intensively studied.[2,3] Although there have been various reported nonbiomimetic approaches for copper-mediated oxygenation of organic molecules[4] as well as with other metals,[5] it is still challenging to develop catalytic oxygenase processes that possess distinct reaction mechanisms and are highly efficient.

Our group has explored the intriguing chemical reactivity of the iminyl copper species for aerobic oxidation reactions.[6] Recently we have disclosed a copper-catalyzed synthesis of azaspirocyclohexadienones from α-azido-*N*-arylamides under an O_2 atmosphere via a sequence of denitrogenative formation of the iminyl copper species from α-azido-*N*-arylamides and their imino-cupration with an intramolecular benzene ring on the amido nitrogen

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(1) For reviews, see: (a) Solomon, E. I.; Chen, P.; Metz, M.; Lee, S.-K.; Palmer, A. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 4570. (b) Solomon, E. I.; Sundaram, U. M.; Machonkin, T. E. *Chem. Rev.* **1996**, *96*, 2563.

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(5) For selected reports, see: (a) Zhu, M.-K.; Zhao, J.-F.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 6284. (b) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654. (c) Wang, A.; Jiang, H. *J. Am. Chem. Soc.* **2008**, *130*, 5030. (d) Liu, Y.; Song, F.; Guo, S. . *J. Am. Chem. Soc.* **2006**, *128*, 11332. (e) Baucherel, X.; Uziel, J.; Jugé, S. *J. Org. Chem.* **2001**, *66*, 4504. (f) Jintoku, T.; Nishimura, K.; Takai, K.; Fujiwara, Y. *Chem. Lett.* **1990**, 1687.

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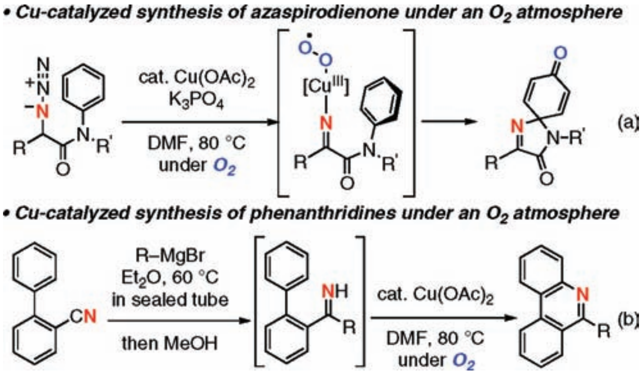
10.1021/ol200425c

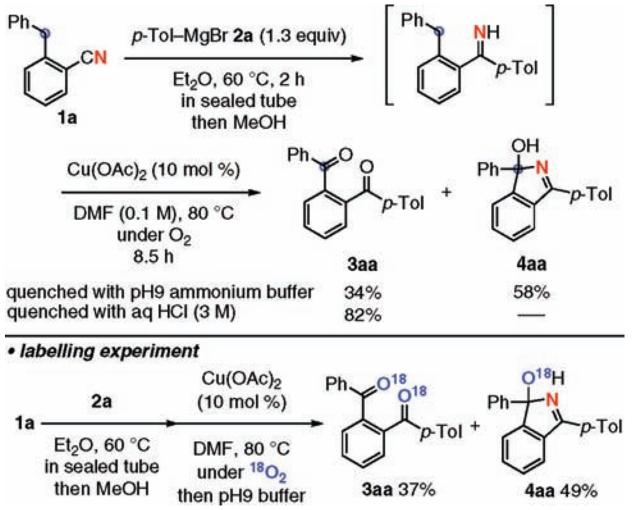
followed by consecutive formation of C–O bonds (Scheme 1a).[6a] We have also demonstrated a copper-catalyzed one-pot synthesis of phenanthridine derivatives starting from biaryl-2-carbonitriles and Grignard reagents via intramolecular C–N bond formation of transient iminyl copper species on the aromatic C–H bond under an O_2 atmosphere (Scheme 1b).[6b] Inspired by these reactions, we turned our attention to the reactivity of the iminyl copper species toward aliphatic C–H bonds under an O_2 atmosphere. Herein, we wish to report the copper-catalyzed benzylic C–H oxygenation under an O_2 atmosphere via the iminyl copper species as an internal directing group. The present process is characterized by the following two-step sequence in a one-pot manner: (1) addition of Grignard reagents to carbonitriles to form *N*-H imines and (2) benzylic C–H oxygenation (C=O bond formation) triggered by 1,5-hydrogen atom transfer with transient iminyl copper species.

Scheme 1. Generation of Iminyl Copper Species under an O_2 Atmosphere and Their Application



Our study commenced with the reactions of 2-benzylbenzonitrile (**1a**) and *p*-tolylmagnesium bromide (**2a**) (Scheme 2). The reaction of Grignard reagent **2a** to benzonitrile **1a** occurred smoothly in Et_2O at 60 °C (in a sealed tube). After protonation with MeOH,[7] DMF (diluted to 0.1 M) and $Cu(OAc)_2$ (10 mol %) were subsequently added, and the reaction mixture was stirred at 80 °C under an O_2 atmosphere (1 atm). After being stirred for 8.5 h, the reaction was quenched with pH 9 ammonium buffer to afford 1,2-dibenzoylbenzene **3aa** and 1*H*-isoindol-1-ol **4aa** in 34% and 58% yield, respectively. By quenching with aqueous HCl, 1,2-dibenzoylbenzene **3aa** was isolated as a sole product in 82% yield. Incorporation of the oxygen atom from O_2 was observed both in 1,2-dibenzoylbenzene **3aa** and 1*H*-isoindol-1-ol **4aa** by utilization of $^{18}O_2$ as an atmosphere. Notably, **3aa** includes two labeled oxygens in both of the carbonyl groups, suggesting that $H_2{}^{18}O$ was generated during the reaction course (see the Supporting Information).

Scheme 2. $Cu(OAc)_2$-Catalyzed Benzylic C–H Oxygenation



1,2-Diacylbenzenes have been of great interest for the precursors of various heterocycles such as isoindoles, isoindolines, and phthalazines as well as poly aromatic hydrocarbons.[8] Moreover, these molecules could be utilized as fluorescence reagents for analysis of amines and amino acids.[9] However, only few general synthetic methods of 1,2-diacylbenzenes have been reported so far.[10] Thus, versatile and efficient methodologies to synthesize 1,2-diacylbenzenes with selective control of substitution patterns are needed.

On the basis of this background, we next investigated the scope and limitation of Cu-catalyzed synthesis of 1,2-diacylbenzenes starting from readily available 2-benzylbenzonitrile derivatives **1**[11] and Grignard reagents **2** (Scheme 3). First, the scope of Grignard reagents was examined by using 2-benzylbenzonitrile (**1a**) (for **3aa–ae**). Both electron-rich (**3ab**, **3ac**) and -deficient (**3ad**, **3ae**) benzene rings as well as a 2-thienyl moiety (**3ah**) could be installed with good yields, whereas the reactions with alkyl Grignard reagents did not provide any desired products. Next, various 2-benzylbenzonitriles **1** were utilized with *p*-tolylmagnesium bromide (**2a**) to prepare substituted 1,2-diacylbenzene derivatives. By varying substituent R^1 on the benzene ring **I**, both electron-donating and -withdrawing groups could be installed (for **3ba–ga**). 1,2-Diacylbenzene bearing sterically hindered 2-methylphenyl and 1-naphthyl moieties as the aromatic ring **I** were prepared in good yields (for **3ha** and **3ia**). Several substituents such as F, Cl, and alkoxy groups were also successfully

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(7) Pickard, P. L.; Tolbert, T. L. *J. Org. Chem.* **1961**, *26*, 4886.

(8) For a review, see: Kotali, A.; Harris, P. A. *Org. Prep. Proced. Int.* **2003**, *35*, 583.

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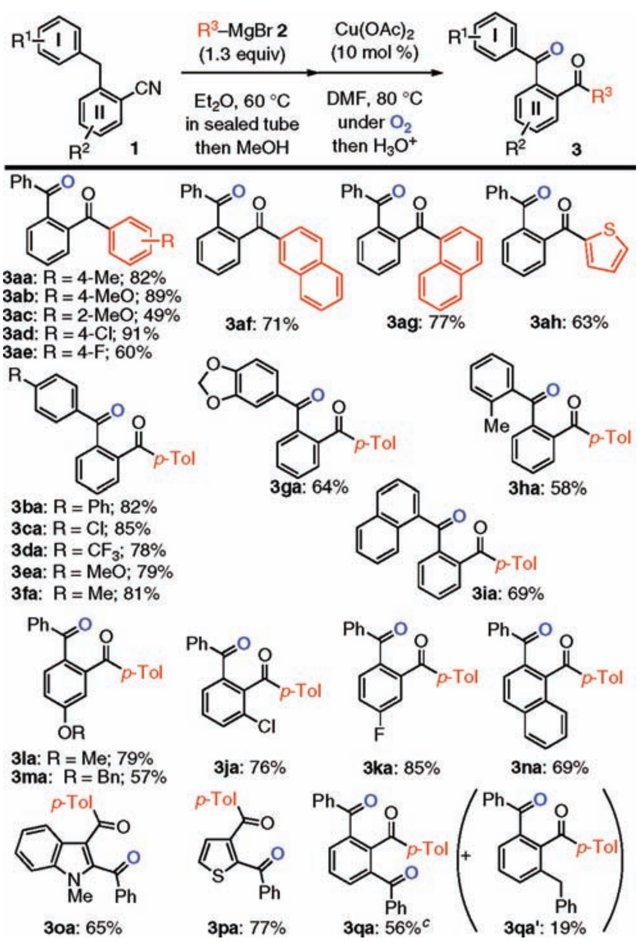
(11) 2-Benzylbenzonitriles **1** were prepared from the corresponding 2-bromomethylbenzonitriles via Friedel–Crafts or Suzuki coupling reactions, see the Supporting Information.

introduced at the benzene ring **II** (for **3ja**−**ma**). This method allowed for preparation of 1,2-diacylnaphthalene, 2,3-diacylindole, and 2,3-diacylthiophene (for **3na**−**pa**). 1,2,3-Triacylbenzene **3qa** could be synthesized in 58% yield from 2,6-dibenzoylbenzonitrile (**1q**) along with monocarbonylated product **3qa′** in 19% yield.

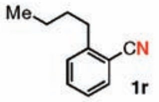
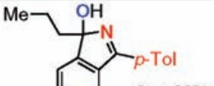
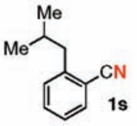
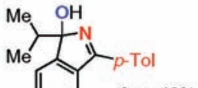
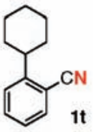
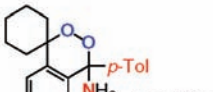
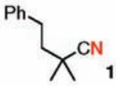
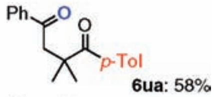
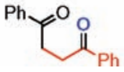
Scheme 3. Substrate Scope I[a−c]



[a] Reactions were carried out with 0.5 mmol of carbonitriles **1** with 1.3 equiv of Grignard reagents **2** in Et_2O (0.5 mL) at 60 °C (sealed tube) for 2 h followed by addition of MeOH (60 μL), DMF (4 mL), and $Cu(OAc)_2$ (10 mol %), and the mixture was stirred at 80 °C under an O_2 atmosphere before being quenched with 3 N aqueous HCl. [b] Isolated yields are recorded. [c] Monocarbonylated product **3qa′** was obtained in 19% yield.

Further investigation on the reactivity of various carbonitriles other than 2-benzylbenzonitriles was conducted and the results are summarized in Table 1. The reactions of 2-butyl- and 2-isobutylbenzonitriles (**1r** and **1s**) with *p*-tolylmagnesium bromide (**2a**) provided 1*H*-isoindoles **4** as a sole product after being quenched by pH 9 ammonium buffer (entries 1 and 2), whereas acid quench resulted in complex mixtures probably due to the unstability of the corresponding 1,2-diacylbenzenes. Notably, the reaction of 2-cyclohexylbenzonitrile (**1t**) bearing a tertiary benzylic C−H bond afforded benzo[*d*][1,2]dioxin-1-amine **5ta**[12] in 70% yield (entry 3) probably via formation of peroxy copper species followed by its cyclization to the C═N bond (see Scheme 3). In the case of the reaction of 2,2-dimethyl-4-phenylbutanenitrile (**1u**) with **2a**, the corresponding 1,4-diketone **6ua** was isolated in 58% yield via benzylic methylene oxygenation (entry 4). Similarly, the reaction of benzonitrile (**1v**) with phenethylmagnesium bromide (**2f**) gave 1,4-diketone **6vf** in 50% yield (entry 5).

Table 1. Substrate Scope II[a]

entry	nitriles 1	Grignard reagents 2	products/yield[b]
1[c]	 1r	*p*-TolMgBr **2a**	 **4ra**: 60%
2[c]	 1s	*p*-TolMgBr **2a**	 **4sa**: 49%
3[c]	 1t	*p*-TolMgBr **2a**	 **5ta**: 70%
4[d]	 1u	*p*-TolMgBr **2a**	 **6ua**: 58%
5[d]	Ph–CN **1v**	 **2f**	 **6vf**: 50%

[a] Reactions were carried out with 0.5 mmol of carbonitriles **1** with 1.3 equiv of Grignard reagents **2** in Et_2O (0.5 mL) at 60 °C (sealed tube) for 2 h followed by addition of MeOH (60 μL), DMF (4 mL), and $Cu(OAc)_2$ (10 mol %), and the mixture was stirred at 80 °C under an O_2 atmosphere. [b] Isolated yields. [c] The reaction was quenched with pH 9 ammonium buffer. [d] The reaction was quenched with 3 N aqueous HCl.

On the basis of these results, a proposed mechanistic possibility for the methylene C−H oxygenation is outlined in Scheme 4. Addition of Grignard reagents to carbonitriles **1** followed by protonation with MeOH provides *N*-H imines **I**. The reaction of *N*-H imines **I** with the Cu(II) catalyst leads to iminyl copper(II) species **II** that is oxidized with O_2 to form peroxycopper(III) **III**. Intramolecular 1,5-H-shift of **III**[13] proceeds to give benzylic radical **IV**, which is converted into peroxy copper species **V**.[14,15] Elimination of [Cu(II)−OH] species **VI** would deliver keto

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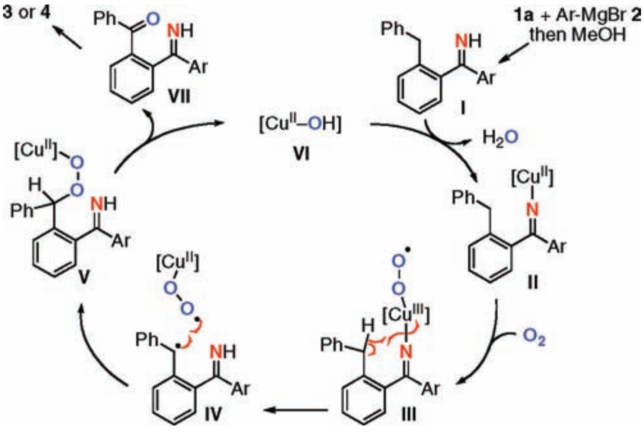
[12] The structure of **5ta** was secured by X-ray crystallographic analysis, see the Supporting Information.

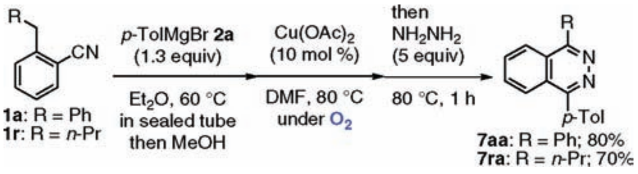
[13] (a) Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568. (b) Fujitani, M.; Tsuchiya, M.; Okano, K.; Takasu, K.; Ihara, M.; Tokuyama, H. *Synlett* **2010**, 822. (c) Robertson, M.; Peplow, M. A.; Pillai, J. *Tetrahedron Lett.* **1996**, *37*, 5825. (d) Murakami, M.; Hayashi, M.; Ito, Y. *Appl. Organomet. Chem.* **1995**, *9*, 385. (e) Williams, L.; Booth, S. E.; Undheim, K. *Tetrahedron* **1994**, *50*, 13697. (f) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896.

[14] The reaction of diphenylmethane with benzophenone *N*-H imine under the present reaction conditions did not provide any oxygenation product. This suggested that *N*-H imines work as the intramolecular directing group in the present process, see the Supporting Information.

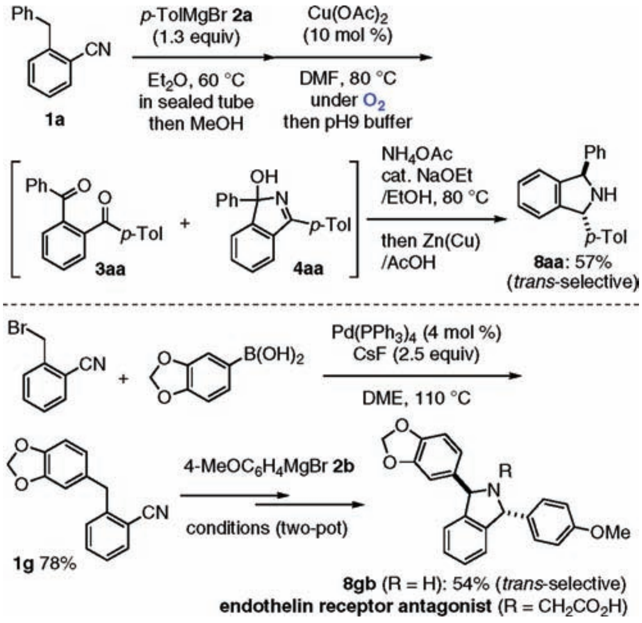
imine **VII**,[3b] which is converted into either diketones **3** or 1*H*-isoindole **4**. Benzo[*d*][1,2]dioxin-1-amine **5ta** might be formed by nucleophilic attack of putative peroxy copper species **V** to the resulting *N*-H imine moiety (Table 1, entry 3).



Scheme 4. Proposed Catalytic Cycle



Scheme 5. One-Pot Synthesis of Phthalazines



Scheme 6. Two-Pot Synthesis of Isoindolines

Finally, we demonstrated application of the present methodology for the concise synthesis of phthalazines and isoindolines. These derivatives are prevalent in potential bioactive molecules.[16,17] Upon the completion of the copper-catalyzed oxidation, subsequent addition of hydrazine afforded phthalazines **7** in good yields in the one-pot fashion from **1a** (Scheme 5). Treatment of the crude mixture of diacylbenzene **3aa** and isoindole **4aa** with NH_4OAc in the presence of a catalytic amount of NaOEt followed by zinc−copper couple in acetic acid provided isoindoline **8aa** in 57% yield (based on **1a**) in the two-pot manner (Scheme 6).[18,19] This method was successfully utilized for short-step preparation of isoindoline **8gb**, a precursor of endothelin receptor antagonists[14c] from 2-bromomethylbenzonitrile via Suzuki-coupling followed by the present two-pot isoindoline formation.

Further investigation of the reaction scope and synthetic application of the present catalytic aerobic C−H oxygenation are currently underway and will be reported in due course.

Acknowledgment. This work was supported by funding from Nanyang Technological University and Singapore Ministry of Education (Academic Research Fund Tier 2: MOE2010-T2-1-009).

Supporting Information Available. Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Other possible directing groups such as carboxylic acid, amides, and cyanide were examined for oxygenation of the *o*-benzylic position. No oxygenation was observed in these cases, see the Supporting Information.

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(17) For reports on bioactive isoindoline derivatives, see: (a) Kukkola, P. J.; Bilci, N. A.; Ikeler, T.; Savage, P.; Shetty, S. S.; DelGrande, D.; Jeng, A. Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1737. (b) Kukkola, P. J.; Bilci, N. A.; Ikeler, T. J. *Tetrahedron Lett.* **1996**, *37*, 5065. (c) Elliott, J. D.; Franz, R. G.; Lago, M. A.; Gao, A. U.S. Patent 5,736,564, 1998.

(18) For recent reports on synthesis of isoindoline derivatives, see: (a) Qian, B.; Guo, S.; Xia, C.; Huang, H. *Adv. Synth. Catal.* **2010**, *352*, 3195. (b) Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9725. (c) Fustero, S.; Moscardó, J.; Jiménez, D.; Pérez-Carrión, M. D.; Sánchez-Roselló, M.; del Pozo, C. *Chem.—Eur. J.* **2008**, *14*, 9868. (d) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465.

(19) The stereochemistry of isoindoline **8aa** was confirmed by X-ray crystallographic analysis of its tosylate, see the Supporting Information.