J|A|C|S
COMMUNICATIONS

Copper-Catalyzed Synthesis of Azaspirocyclohexadienones from α-Azido-*N*-arylamides under an Oxygen Atmosphere

Shunsuke Chiba,* Line Zhang, and Jian-Yuan Lee

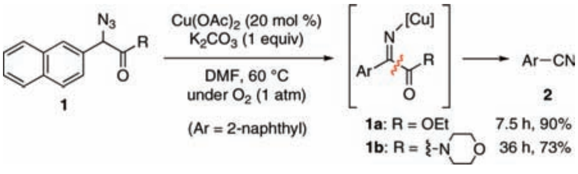
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Received April 1, 2010; E-mail: shunsuke@ntu.edu.sg

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 non-biomimetic 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. Herein, we wish to report a copper-catalyzed synthesis of azaspirocyclohexadienones from α-azido-*N*-arylamides under an oxygen atmosphere. The present transformation is carried out by a sequence of denitrogenative formation of iminyl copper species from α-azido-*N*-arylamides and their imino-cupration with an intramolecular benzene ring on the amido nitrogen followed by consecutive formation of C═O bonds. A preliminary investigation revealed that molecular oxygen is a prerequisite for achieving the present catalytic cyclization and that one of the oxygen atoms of O_2 was found to be incorporated into the cyclohexadienones.

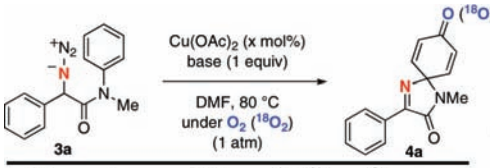
We have recently reported a copper-catalyzed reaction of α-azido carbonyl compounds such as **1a** under an oxygen atmosphere to provide nitriles **2** via C−C bond cleavage of a transient iminyl copper intermediate (Scheme 1).[6] To further broaden our search in terms of the substrate scope, α-azido amides were examined. The morpholine amide **1b** provided the corresponding nitrile **2** in good yield, although a longer reaction time (36 h) was required compared to that for ester **1a**.

Scheme 1. $Cu(OAc)_2$-Catalyzed Formation of Nitriles

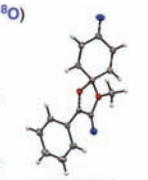


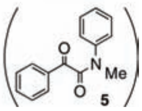
N-Phenyl amide **3a** was next subjected to 20 mol % of $Cu(OAc)_2$ in the presence of various bases at 80 °C under an oxygen atmosphere (Table 1). In this case, the reactions were complete within several hours and, unexpectedly, azaspirocyclohexadienone **4a**[7] was isolated in good yields, the highest of which was provided by K_3PO_4 (run 3). Utilization of $^{18}O_2$ showed that one of the oxygen atoms from O_2 was incorporated into a resulting carbonyl group of the azaspirodienones. A reaction with 1 equiv of $Cu(OAc)_2$ under an Ar atmosphere exclusively provided α-keto amide **5** which was formed via hydrolysis of the corresponding iminyl copper species or *N*-H imine (run 4). This indicates that molecular oxygen is essential for the C−N bond formation.

Table 1. Formation of Azaspirocyclohexadienone



run	x	base	time / h	4a
1	20	K_2CO_3	3	69%
2	20	NaOMe	2	63%
3[a]	**20**	**K_3PO_4**	**4**	**77%**
4[b]	100	K_3PO_4	4	0% (**5**: 68%)


X-ray of 4a



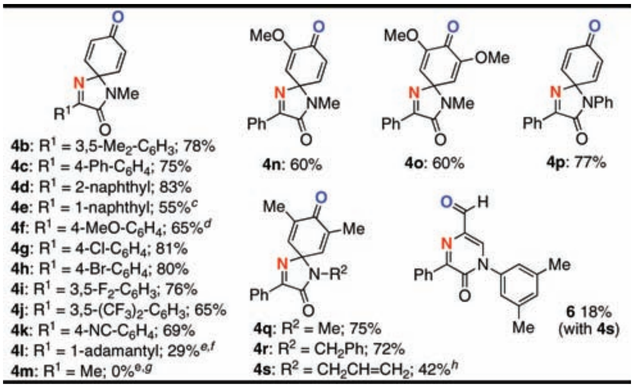
[a] 70% yield of **4a** was obtained when $^{18}O_2$ was used as an atmosphere. [b] The reaction was run under an Ar atmosphere in degassed DMF.

The most common method to construct spirodienone structures involves oxidative treatment of phenol derivatives.[8,9] Inspired by this unprecedented and mechanistically distinct formation of azaspirodienones as well as potential pharmaceutical properties of their derivatives,[10] we further explored the substrate scope (Table 2). By varying substituent R^1, aryl rings bearing both electron-donating and -withdrawing groups could be introduced (for **4b**−**4k**). This process could keep C−halogen bonds intact (for **4g**−**4i**). For **4e** and **4f**, which bear 1-naphthyl and 4-methoxyphenyl moieties, respectively, the corresponding nitriles and *N*-methylaniline were isolated as side products generated via C−C bond cleavage of the transient iminyl copper.[6] Alkyl groups as R^1 were not viable for this transformation (for **4l**, **4m**). Azaspirodienones bearing electron-donating substituents on the cyclohexadienone ring produced good yields (for **4n**, **4o**, **4q**−**s**). It is noteworthy that, in addition to methyl, phenyl (for **4p**) and benzyl (for **4r**) groups could be introduced as substituent R^2 on the amido nitrogen. *N*-Allyl-*N*-phenylamide **3s** delivered azaspirodienone **4s** in 42% yield along with 18% yield of pyrazinone **6**, which could be formed via imino-cupration of iminyl copper with the terminal alkene followed by oxidation (see Supporting Information for more detail).

During the course of this study, certain substrates provided significant mechanistic information. A reaction of azide **3t** bearing a sterically hindered 2,6-dimethylphenyl moiety afforded 25% yield of azaspirodienone **4t** along with *N*-phenyl imine **7** in 36% yield (eq 1), which could be formed by transfer of the phenyl group from amido-nitrogen to imino-nitrogen via an intramolecular *ipso*-substitution reaction of the iminyl copper.[11] A chlorine atom on the amido benzene ring retarded the formation of azaspirodienones (eq 2 for **4u**, **4v**). In these cases,

10.1021/ja1027327

Table 2. Reaction Scope[a,b]



4b: R^1 = 3,5-Me_2-C_6H_3; 78%
4c: R^1 = 4-Ph-C_6H_4; 75%
4d: R^1 = 2-naphthyl; 83%
4e: R^1 = 1-naphthyl; 55%[c]
4f: R^1 = 4-MeO-C_6H_4; 65%[d]
4g: R^1 = 4-Cl-C_6H_4; 81%
4h: R^1 = 4-Br-C_6H_4; 80%
4i: R^1 = 3,5-F_2-C_6H_3; 76%
4j: R^1 = 3,5-$(CF_3)_2$-C_6H_3; 65%
4k: R^1 = 4-NC-C_6H_4; 69%
4l: R^1 = 1-adamantyl; 29%[e,f]
4m: R^1 = Me; 0%[e,g]

4n: 60%

4o: 60%

4p: 77%

4q: R^2 = Me; 75%
4r: R^2 = CH_2Ph; 72%
4s: R^2 = $CH_2CH{=}CH_2$; 42%[h]

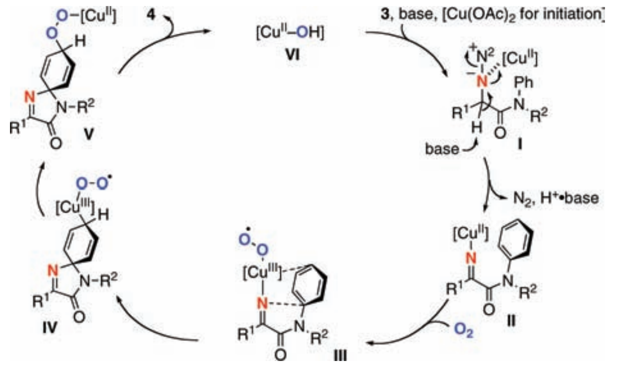
6 18%
(with **4s**)

[a] Reactions were carried out in the scale of 0.5 mmol of azides **3** using 20 mol % of $Cu(OAc)_2$ and 1 equiv of K_3PO_4 in DMF (0.1 M) at 80 °C under an O_2 atmosphere. [b] Isolated yields were recoreded above. [c] 1-Naphthonitrile and *N*-methyl-aniline were obtained in 21 and 19% yields, respectively. [d] 4-Methoxybenzonitrile and *N*-methylaniline were obtained in 27 and 12% yields, respectively. [e] NaOMe (1 equiv) was used as a base. [f] See Supporting Information for more detail. [g] *N*-Methylaniline was obtained in 45% yield. [h] Pyrazinone **6** was also obtained in 18% yield.

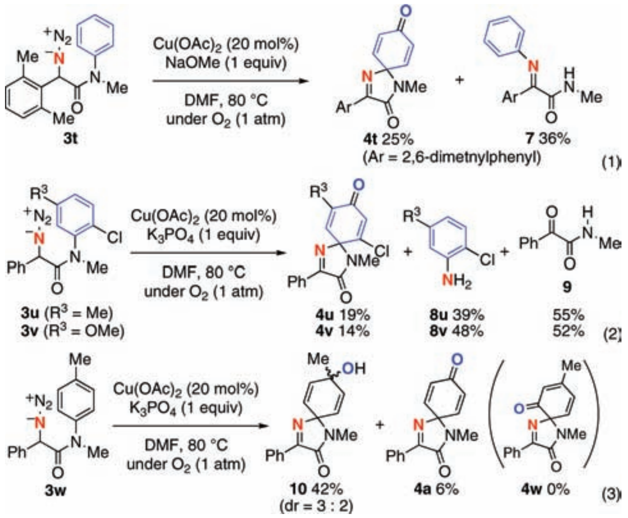
the corresponding anilines **8** and *N*-H amides **9** were isolated as side products generated probably via aryl transmission followed by hydrolysis of the resulting *N*-aryl imines. Interestingly, treatment of *p*-tolylamide derivative **3w** under the present catalytic conditions afforded azaspirocyclohexadienol **10** and demethylated azaspirodienone **4a** in 42 and 6% yields respectively, without formation of expected spirocyclohexa-2,4-dienone **4w** (eq 3) (see Supporting Information for more detail).

Based on these results, a proposed mechanistic possibility was outlined in Scheme 2. It commences with denitrogenative formation of iminyl copper **II** followed by its oxidation with O_2 to form peroxycopper(III) **III**. The reaction of *p*-tolylamide **3w** (eq 3) suggests that the intramolecular imino-cupration of **III** might form C−N and C−Cu bonds concurrently at the *ipso* and its *para* position of the benzene ring respectively, affording **IV**.[12] Subsequent isomerization of **IV** to peroxydiene **V** followed by elimination of [Cu(II)−OH] species **VI**[3b] would deliver azaspirodienones **4**. In the cases of eqs 1 and 2, transfer of the aryl group might proceed via C−N bond cleavage of **IV**.

Scheme 2. A Proposed Catalytic Cycle



Further investigation of the scope, detailed mechanisms, and synthetic application of the present catalytic organocopper oxygenase system to intermolecular reactions is currently underway.



Acknowledgment. This work was supported by funding from Nanyang Technological University and Singapore Ministry of Education. We thank Dr. Yongxin Li (Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University) for assistance in X-ray crystallographic analysis.

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

References

(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.
(2) For recent reviews, see: (a) Rolff, M.; Tuczek, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2344. (b) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047. (c) Gamez, P.; Aubel, P. G.; Driessen, W. L.; Reedijk, J. *Chem. Soc. Rev.* **2001**, *30*, 376. (d) Fontecave, M.; Pierre, J.-L. *Coord. Chem. Rev.* **1998**, *170*, 125.
(3) (a) Würtele, C.; Sander, O.; Lutz, V.; Waitz, T.; Tuczek, F.; Schindler, S. *J. Am. Chem. Soc.* **2009**, *131*, 7544. (b) Lucas, H. R.; Li, L.; Narducci Sarjeant, A. A.; Vance, M. A.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2009**, *131*, 3230. (c) Aboelella, N. W.; Gherman, B. F.; Hill, L. M. R.; York, J. T.; Holm, H.; Young, Jr, V. G.; Cramer, C. J.; Tolman, W. B. *J. Am. Chem. Soc.* **2006**, *128*, 3445. (d) Shearer, J.; Zhang, C. X.; Zakharov, L. N.; Rheingold, A. L.; Karlin, K. D. *J. Am. Chem. Soc.* **2005**, *127*, 5469. (e) Itoh, S.; Nakao, H.; Berreau, L. M.; Kondo, T.; Komatsu, M.; Fukuzumi, S. *J. Am. Chem. Soc.* **1998**, *120*, 2890.
(4) For selected reports, see: (a) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (b) Moghaddam, F. M.; Mirjafary, Z.; Javan, M. J. *Synlett* **2008**, 892. (c) Tokunaga, M.; Shirogane, Y.; Aoyama, H.; Obora, Y.; Tsuji, Y. *J. Organomet. Chem.* **2005**, *690*, 5378. (d) Komiya, N.; Naota, T.; Murahashi, S.-I. *Tetrahedron Lett.* **1996**, *37*, 1633.
(5) For selected reports, see: (a) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654. (b) Wang, A.; Jiang, H. *J. Am. Chem. Soc.* **2008**, *130*, 5030. (c) Liu, Y.; Song, F.; Guo, S. *J. Am. Chem. Soc.* **2006**, *128*, 11332. (d) Baucherel, X.; Uziel, J.; Jugé, S. *J. Org. Chem.* **2001**, *66*, 4504. (e) Jintoku, T.; Nishimura, K.; Takai, K.; Fujiwara, Y. *Chem. Lett.* **1990**, 1687.
(6) Chiba, S.; Zhang, L.; Ang, G. Y.; Hui, B. W.-Q. *Org. Lett.* **2010**, *12*, 2052.
(7) The structures of **4a**, **4d**, **4q**, **7**, and **10** were confirmed by X-ray crystallographic analyses; see Supporting Information.
(8) For reviews, see: (a) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (b) Quideau, S.; Pouysegu, L.; Deffieux, D. *Synlett* **2008**, 467. (c) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, 3759.
(9) Kusama, H.; Yamashita, Y.; Uchiyama, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 965.
(10) For GlyT1 transporter inhibitors bearing diazaspiro stuructures, see: (a) Marshall, H. R. WO Patent 2008,092,879, 2008. (b) Dean, A. W.; Porter, R. A. WO Patent 2007,014,762, 2007.
(11) (a) Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147. (b) Paradisi, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 423.
(12) For a report on oxy-cupration of arene rings mediated by Cu(III)-aryl species, see: Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.

JA1027327