Oxidative Rearrangement

DOI: 10.1002/anie.201003646

# Copper-Catalyzed Rearrangement of Tertiary Amines through Oxidation of Aliphatic C–H Bonds in Air or Oxygen: Direct Synthesis of α-Amino Acetals**

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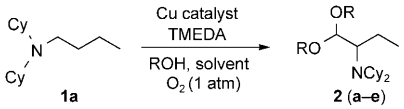
Many natural products or biomolecules contain α-amino acid or β-amino alcohol units in their structures.[1] Although these units may be obtained from naturally occurring α-amino acids, general methods for the synthesis of other non-natural α-amino acids are highly sought after. Among many reported approaches, the direct synthesis of α-amino acids in air by means of biomimetic methods has been regarded as one of the most challenging tasks.[2] The biological method involving the activation of dioxygen by copper enzymes has attracted considerable attention owing to the existence of important copper monooxygenases.[3] This system has been mimicked in many studies for the investigation of copper–dioxygen interactions[4] and further applications of dioxygen–copper systems in organic synthesis, especially in the development of oxidation reactions of aliphatic C–H bonds.[5] For C–H bond activation, dioxygen–copper systems[6] provide an alternative to the commonly employed methods based on the use of expensive metal catalysts and stoichiometric metal oxidants.[7] Herein we report a novel rearrangement of tertiary amines through oxidation of aliphatic C–H bonds with dioxygen–copper catalytic systems for the direct synthesis of α-amino acetals. Furthermore, a mechanism to account for the product observed is proposed on the basis of trapping, control, and isotope-labeling experiments.

When we treated *N*,*N*-dicyclohexyl-*n*-butylamine (**1a**) with copper(II) bromide and oxygen in methanol/acetonitrile (1:4, v/v) at 40 °C, we were surprised to obtain the α-amino acetal **2a** in low yield (11 %; Table 1, entry 2). The structure of **2a** was confirmed by single-crystal X-ray analysis (see the Supporting Information). Interestingly, most of substrate **1a** was converted into *N*,*N*-dicyclohexylformamide[8] (62 %). During optimization of the reaction conditions (see the Supporting Information), we found that the reaction did not proceed without the copper catalyst (Table 1, entry 1). Since nitrogen donor ligands play an important role in dioxygen activation,[3a] we tested a series of these ligands in the reaction. We obtained the best result with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). When this ligand was used with copper(II) bromide in a 2:1 ratio, the formation of *N*,*N*-dicyclohexylformamide was suppressed, and the desired α-amino acetal **2a** was isolated in 66 % yield (Table 1, entry 3). The reaction proceeded even in air without a significant decrease in yield (Table 1, entry 4). Primary alcohols, such as ethanol, were suitable for this reaction, although the yields were low, whereas secondary alcohols, such as 2-propanol, did not yield the desired product (Table 1, entries 5–8). Therefore, the optimal reaction conditions found for the rearrangement of tertiary amines involved treatment with methanol in acetonitrile (1:4, v/v) under an oxygen atmosphere (1 atm) at 40 °C in the presence of copper(II) bromide (25 mol %) and TMEDA (50 mol %) as the catalytic system.

***Table 1:*** Optimization of the reaction conditions.[a]




| Entry | Catalyst | R | *t* [h] | Product | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | – | Me | 48 | **2a** | 0 |
| 2[c] | $CuBr_2$ | Me | 48 | **2a** | 11 |
| **3** | **$CuBr_2$** | **Me** | **5** | **2a** | **66** |
| **4**[d] | **$CuBr_2$** | **Me** | **6** | **2a** | **58** |
| 5 | $CuBr_2$ | Et | 24 | **2b** | 25 |
| 6 | $CuBr_2$ | *n*Pr | 48 | **2c** | 19 |
| 7 | $CuBr_2$ | *i*Pr | 48 | **2d** | 0 |
| 8 | $CuBr_2$ | *n*-pentyl | 48 | **2e** | 12 |

[a] Reaction conditions: **1a** (0.5 mmol), copper catalyst (0.25 equiv), TMEDA (0.5 equiv), MeOH (0.5 mL, 25 equiv), MeCN (2.0 mL), $O_2$ (1 atm), 40 °C. [b] Yield of the isolated product. [c] The reaction was carried out without TMEDA; the by-product *N*,*N*-dicyclohexylformamide was obtained in 62 % yield. [d] The reaction was carried out in air.

We next investigated the scope of this oxidative rearrangement with respect to the tertiary amine (Table 2). Almost all substrates containing $R^1 = R^2 = Cy$ provided the desired products in moderate yields under the standard reaction conditions (Table 2, entries 1–8). A tertiary amine with a long carbon chain was also suitable for this reaction, although the reaction time was much longer (Table 2, entry 3). The reaction tolerated a wide array of functional groups, including ester groups (Table 2, entries 4 and 8), a bromo group (Table 2, entry 5), a double bond (Table 2,

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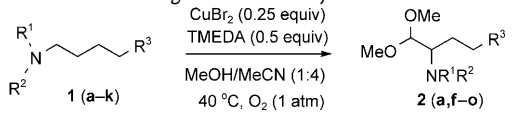
[**] We gratefully acknowledge Nanyang Technological University and the Singapore Ministry of Education Academic Research Fund Tier 2 (T206B1221, 207B1220RS) for the financial support of this research. We also thank Dr. Yong-Xin Li for X-ray crystallographic support, and Prof. K. Narasaka, Prof. S. Kim, Prof. S. Chiba, and Prof. J. (Steve) Zhou for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201003646.

***Table 2:*** Oxidative rearrangement of tertiary amines.[a]

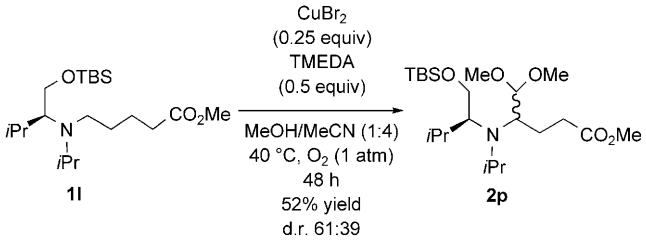



| Entry | $R^1$ | $R^2$ | $R^3$ | 2 | *t* [h] | Yield [%][b] |
|---|---|---|---|---|---|---|
| 1 | Cy | Cy | H | **2a** | 5 | 66 |
| 2 | Cy | Cy | Et | **2f** | 6 | 65 |
| 3 | Cy | Cy | *n*-octyl | **2g** | 24 | 61 |
| 4 | Cy | Cy | $CO_2Me$ | **2h** | 12 | 60 |
| 5 | Cy | Cy | $CH_2CH_2Br$ | **2i** | 6 | 54 |
| 6 | Cy | Cy | $CH{=}CH_2$ | **2j** | 24 | 61 |
| 7 | Cy | Cy | $CH_2NPhth$ | **2k** | 20 | 56 |
| 8 | Cy | Cy | $CH_2OAc$ | **2l** | 20 | 55 |
| 9 | Cy | *i*Pr | H | **2m** | 24 | 45 |
| 10 | *n*Bu | *n*Bu | H | **2n** | 72 | 12 |
| 11 | *t*Bu | *tert*-pentyl | H | **2o** | 72 | 0 |

[a] Reaction conditions: **1** (0.5 mmol), $CuBr_2$ (0.25 equiv), TMEDA (0.5 equiv), MeOH (0.5 mL), MeCN (2.0 mL). [b] Yield of the isolated product. Cy = cyclohexyl, Phth = phthalimidyl.

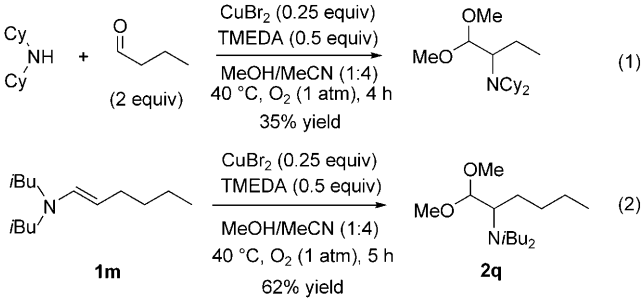
entry 6), and an imido group (Table 2, entry 7). Substrates containing $R^1$ and $R^2$ groups with more branched carbon chains (Table 2, entries 1 and 9) showed better reactivity in this reaction than those with linear carbon chains (Table 2, entry 10). Unfortunately, when *tert*-butyl-*tert*-pentyl-*n*-butylamine (**1k**), with substituents that are bulkier than the cyclohexyl group, was tested as a substrate for this rearrangement, none of the desired product was obtained (Table 2, entry 11).

The tertiary amine **1l** with a stereogenic center underwent this reaction to afford the desired product in a moderate yield of 52% as two diastereomers, which could be separated readily by silica-gel column chromatography (Scheme 1).



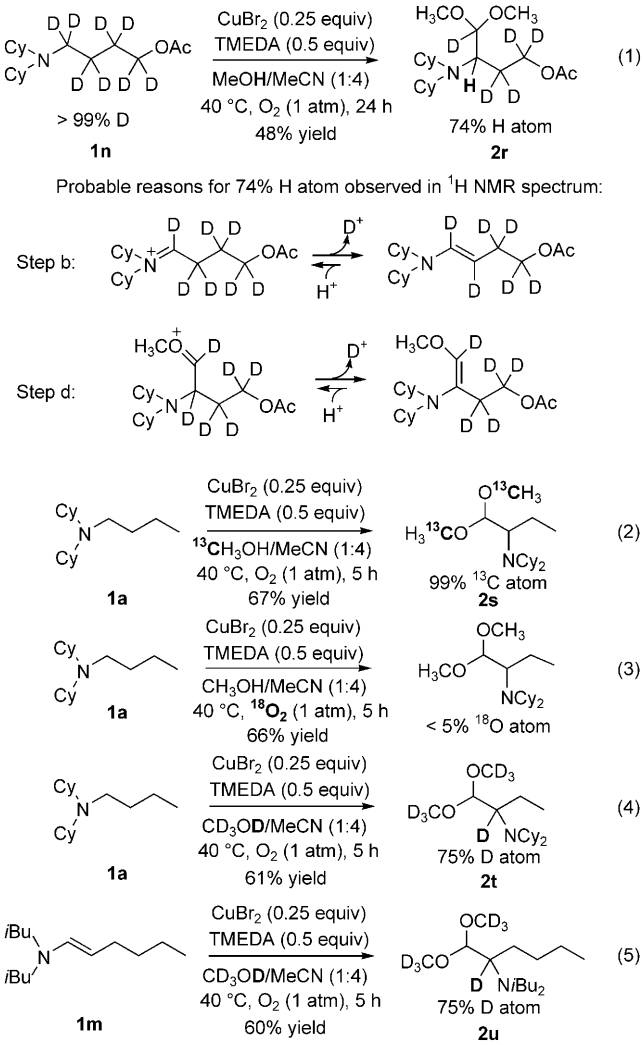

***Scheme 1.*** Oxidative rearrangement of a chiral tertiary amine. TBS = *tert*-butyldimethylsilyl.

During our investigations of this rearrangement, we made several observations of mechanistic interest. First, we isolated a white solid with the molecular structure $Cy_2NH_2Br$ (as confirmed by X-ray crystallographic analysis; see the Supporting Information) from the reaction mixture in about 8% yield by a simple filtration. The results of trapping and control experiments [Scheme 2, Eq. (1)] supported the involvement of the reversible step a (Scheme 5) in the reaction mechanism. Second, to prove the intermediacy of an enamine, we synthesized enamine **1m**[9] as a substrate for this reaction. The desired rearrangement occurred to give **2q** in 62% yield [Scheme 2, Eq. (2)].




***Scheme 2.*** Control experiments.

To explore how the rearrangement occurred, which carbon atom was involved in the reaction, and which C–H bonds of the long carbon chain were activated, we carried out isotope-labeling experiments (Scheme 3). From three such experiments [Scheme 3, Eqs. (1)–(3)] we could conclude that the α and β carbon atoms of the aliphatic chain were involved in the reaction. The use of $^{13}C$-labeled methanol in the experiment [Scheme 3, Eq. (2)] showed that methanol was

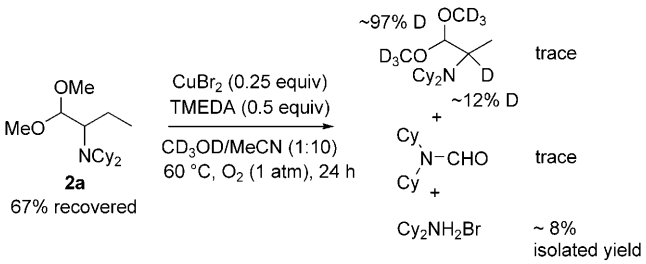



***Scheme 3.*** Isotope-labeling experiment (see Scheme 5 for where steps b and d occur in the proposed mechanism).

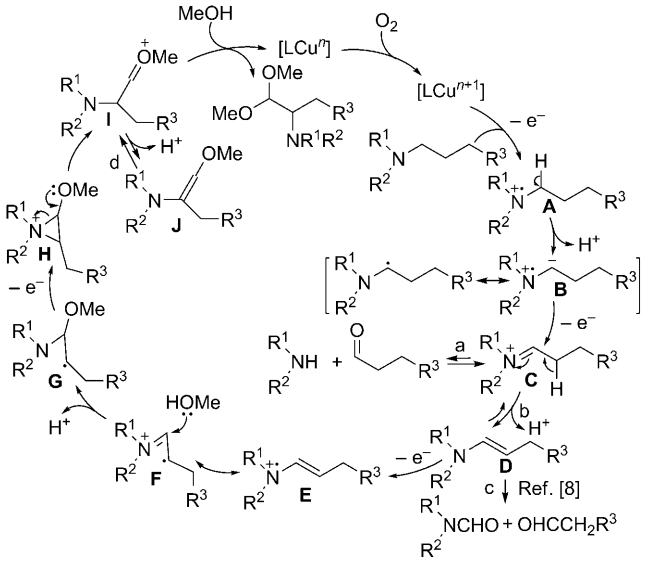
not oxidized in the reaction. Under the standard reaction conditions, compound **1n** gave product **2r** in about 48% yield. Of particular interest was the observation at 74% intensity of the hydrogen atom indicated in bold in **2r** in the $^1$H NMR spectrum. Similar results were observed for the experiments shown in Equations (4) and (5) in Scheme 3. The reason for H/D exchange may be due to deprotonation and protonation in the reversible steps b and d in the reaction mechanism (Scheme 5).

When compound **2a** was treated with $CD_3OD$ under similar reaction conditions, only 67% of **2a** was recovered, and the three expected by-products were produced, albeit in very low yield (Scheme 4). This result showed that most steps in this oxidative rearrangement were reversible, which may be one of the reasons why these by-products were produced.




***Scheme 4.*** Deuterium-labeling experiment.

A possible rationalization of this rearrangement on the basis of the trapping, control, and isotope-labeling experiments is shown in Scheme 5.[10] In this proposed mechanism, a series of copper–dioxygen species function as one-electron oxidizing agents toward the tertiary amine, enamine **D**, and intermediates **B** and **G**. Initially, the copper species [$LCu^{n+1}$] is formed in the catalytic system composed of the copper salt, molecular oxygen, and the bidentate ligand TMEDA.[3,4] After electron-transfer, deprotonation, and electron-transfer processes, iminium ion **C** is produced. Iminium ion **C** is then converted into enamine **D** by deprotonation. Next, electron transfer yields the cationic radical species **E** and **F**. Nucleophilic attack by methanol on intermediate **F** and subsequent electron transfer give the corresponding aziridinium ion **H**. Following opening of the three-membered ring to form oxocarbenium ion **I**, attack by an additional methanol molecule generates the observed product.




***Scheme 5.*** Proposed mechanism for the oxidative rearrangement of tertiary amines.

In conclusion, we have described a novel rearrangement of tertiary amines through the oxidation of aliphatic C–H bonds with a dioxygen–copper catalytic system for the direct synthesis of synthetically useful α-amino acetals. In comparison with the use of expensive metal catalysts and stoichiometric metal oxidants in traditional methods for C–H bond oxidation, this catalytic system has the clear advantages of mild reaction conditions and the use of air or oxygen as the oxidant. The development of other methods for the direct synthesis of α-amino acetals from secondary amines and aliphatic aldehydes or enamines, as well as further studies on the scope and mechanism of this reaction, the development of an asymmetric version, and the application of this methodology to the synthesis of complex molecules, are in progress.

## *Experimental Section*

Typical procedure: *N*,*N*-Dicyclohexyl-*n*-butylamine (**1a**; 0.118 g, 0.5 mmol) was added to a mixture of $CuBr_2$ (28 mg, 0.125 mmol) and TMEDA (29 mg, 0.25 mmol) in methanol (0.5 mL)/acetonitrile (2.0 mL) in air at room temperature. The mixture was stirred at 40 °C under an $O_2$ atmosphere (1 atm) until the conversion of **1a** was complete (TLC). The reaction mixture was then mixed with a small amount of silica gel and concentrated. Purification of the crude product by flash column chromatography (silica gel; triethylamine/ethyl acetate/hexane 0.1:1:100, v/v/v) afforded **2a** (98 mg, 66%).

Received: June 15, 2010
Revised: August 25, 2010
Published online: September 28, 2010

**Keywords:** α-amino acetals · copper · oxidative rearrangement · oxygen · tertiary amines

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