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Cu-Catalyzed Aerobic Oxidation of Di-*tert*-butyl Hydrazodicarboxylate to Di-*tert*-butyl Azodicarboxylate and Its Application on Dehydrogenation of 1,2,3,4-Tetrahydroquinolines under Mild Conditions

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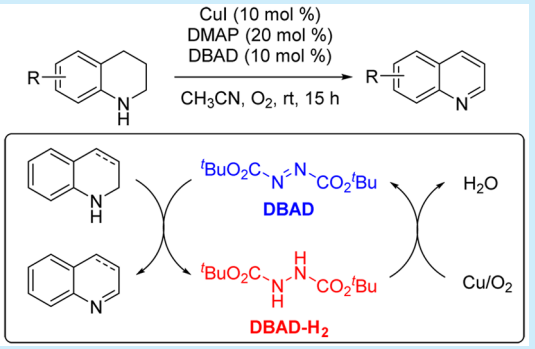
Supporting Information

ABSTRACT: A new class of co-catalytic system was developed with homogeneous CuI and di-*tert*-butyl azodicarboxylate for aerobic dehydrogenation of 1,2,3,4-tetrahydroquinolines under mild conditions. The developed co-catalytic system is consisting of di-*tert*-butyl azodicarboxylate-mediated dehydrogenation of 1,2,3,4-tetrahydroquinoline and aerobic oxidative regeneration of di-*tert*-butyl azodicarboxylate from di-*tert*-butyl hydrazodicarboxylate using molecular oxygen as a terminal oxidant. A variety of quinolines were efficiently synthesized by the developed Cu and di-*tert*-butyl azodicarboxylate co-catalytic system.



Azodicarboxylates such as diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), and di-*tert*-butyl azodicarboxylate (DBAD) are very versatile reagents in organic synthesis (Figure 1).[1] The representative utilization

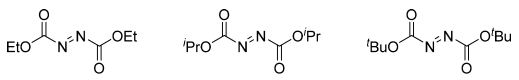


Figure 1. Representative azodicarboxylates.

of azodicarboxylates is Mitsunobu reaction.[2] The combination of DEAD and triphenylphosphine causes condensation reaction between carboxylic acids and alcohols to produce the corresponding esters.[3] In addition, azodicarboxylates have been used in electrophilic amination[4] as well as [4 + 2] cycloaddition[5] because they have an electron-deficient nitrogen−nitrogen double bond (N=N). It is also known that they are able to be utilized as carbon-centered radical traps.[6]

It is an interesting feature of azodicarboxylates that they serve as dehydrogenating reagents. Various molecules such as alcohols, thiols, and anilines underwent dehydrogenation in the presence of azodicarboxylates.[7] However, these dehydrogenations are less attractive from the viewpoint of sustainable and green chemistry because a stoichiometric amount of azodicarboxylate is required and the corresponding hydrazodicarboxylate is produced as a byproduct. To address these issues, we envisioned a co-catalytic system consisting of azodicarboxylate-mediated dehydrogenation and aerobic oxidative regeneration of azodicarboxylate from hydrazodicarboxylate using molecular oxygen as a terminal oxidant.[8] The suggested co-catalytic system requires a catalytic amount of azodicarboxylate and produces water as the sole byproduct. However, to the best of our knowledge, no aerobic oxidation of hydrazodicarboxylate to azodicarboxylate was reported, while anaerobic oxidative methods using fuming nitric acid, $PhI(OAc)_2$, *N*-bromosuccinimide (NBS), and Br_2/pyridine have been established.[9]

Taniguchi et al. have studied aerobic oxidation of hydrazine using Fe(Pc) (Pc = phthalocyanine) catalysis. They revealed that the Fe(Pc) catalyst facilitated the aerobic oxidation of carbazates and ethyl 2-phenylhydrazinecarboxylate.[10] However, iron catalysis was ineffective in the aerobic oxidation of diethyl hydrazodicarboxylate due to the two strongly electron-withdrawing groups.[11] Electrochemical studies supported these observations. For example, the oxidation potential of di-*tert*-butyl hydrazodicarboxylate (DBAD-H_2, 1.62 V) is higher than that of *tert*-butyl 2-phenylhydrazinecarboxylate (1.02 V).[12]

In 1996, Markó and co-workers reported that the combination of Cu, 1,10-phenanthroline, and DBAD could catalyze the aerobic oxidation of alcohol to aldehyde.[13] They proposed that the Cu/DBAD complex was generated by the hydrogen abstraction of the hydrazino-copper species. In addition to Markó's result, the Jiao group demonstrated that the combination of CuBr and pyridine facilitated aerobic oxidation of hydrazobenzene to azobenzene efficiently.[14] These interesting results prompted us to investigate aerobic oxidation of hydrazodicarboxylate to azodicarboxylate using copper catalyst. Herein, we describe the first Cu-catalyzed aerobic

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oxidation of hydrazodicarboxylate to azodicarboxylate using oxygen as an oxidant. By using this method, we could develop a Cu and azodicarboxylate co-catalytic system for the aerobic dehydrogenation of 1,2,3,4-tetrahydroquinoline under mild conditions.[15]

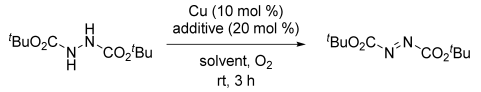
First, we screened the Cu source, additive, and solvent using DBAD-H_2 as a model substrate (Table 1). The aerobic oxidation of DBAD-H_2 did not occur under Markó's oxidation conditions (entry 1).[13] Gratifyingly, the aerobic oxidation of DBAD-H_2 in toluene with CuBr and pyridine, which was a competent catalyst system in Jiao's conditions,[14] showed a promising result to produce DBAD in moderate yield (entry 2). The use of polar solvents such as acetonitrile and dichloromethane gave higher yields than toluene (entries 3 and 4). Among the copper sources screened with pyridine, CuCl showed the best result, while the aerobic oxidation of DBAD-H_2 using CuI or $Cu(CH_3CN)_4PF_6$ was sluggish (entries 5−7). The use of a Cu^{II} catalyst such as $CuBr_2$ showed a moderate yield of DBAD (entry 8). Interestingly, the choice of copper source and additive was crucial for the successful aerobic oxidation of DBAD-H_2. We screened various combinations of copper source and additive (entries 8−11) and observed that the use of CuI with 4-(dimethylamino)pyridine (DMAP) gave full conversion of DBAD-H_2 to DBAD (entry 10). It is the first observation of aerobic oxidation of DBAD-H_2 to DBAD using an inexpensive copper catalyst with DMAP at room temperature. In the case of DIAD-H_2 oxidation, the use of 4-methoxypyridine (4-OMepy) instead of DMAP showed a good result to produce DIAD in 78% yield.[16] Unfortunately, the aerobic oxidation of DEAD-H_2 to DEAD showed poor conversions and low yields under copper systems.[16]

Quinoline is an important moiety in both biologically active compounds and natural products.[17] In 2011, Stone reported that the dehydrogenation of 1,2,3,4-tetrahydroquinolines with 2.4 equiv of DIAD provided a facile route for the synthesis of quinolines.[18] We felt that the dehydrogenation of 1,2,3,4-tetrahydroquinoline with azodicarboxylate is a suitable reaction to realize our proposed co-catalytic system, consisting of dehydrogenation with catalytic amount of DBAD and Cu-catalyzed aerobic oxidative regeneration of DBAD from DBAD-H_2.

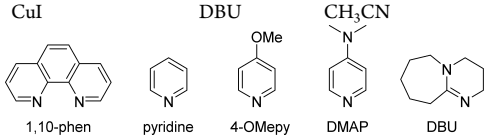
We tested DBAD-mediated dehydrogenation of 1,2,3,4-tetrahydroquinoline **1a** using 2.4 equiv of DBAD at room temperature. Similar to Stone's result using DIAD, the use of DBAD facilitated the dehydrogenation to produce parent quinoline **2a** in high yield (98%) (eq 1). We then investigated the cooperation between DBAD-mediated dehydrogenation of **1a** and the newly developed CuI/DMAP-catalyzed aerobic oxidative regeneration of DBAD from DBAD-H_2. Gratifyingly, it was observed that **2a** was produced in 92% yield even with a catalytic amount of DBAD in the presence of CuI, DMAP, and oxygen (eq 2). We were convinced that the developed aerobic dehydrogenation supplied a practical route for quinoline synthesis because inexpensive copper catalyst and oxygen as a terminal oxidant were employed under mild conditions.[19,20] Although a good yield of **2a** was observed in a shorter reaction time (85% in 9 h), we decided to retain 15 h for full conversion. The use of a catalytic amount of DBAD-H_2, instead of DBAD, caused a good conversion of **1a** to **2a** and showed 93% yield of the product (eq 3).

In order to obtain mechanistic insight into the developed aerobic dehydrogenation, control reactions were carried out (Table 2). When the dehydrogenation of **1a** was carried out without DBAD, a poor yield of **2a** was observed (entry 2). This

Table 1. Optimization of Cu-Catalyzed Aerobic Oxidation of DBAD-H_2 to DBAD[a]



entry	Cu	additive	solvent	yield[b] (%)
1	CuCl	1,10-phen	fluorobenzene	<1
2	CuBr	pyridine	toluene	45
3	CuBr	pyridine	CH_3CN	84
4	CuBr	pyridine	CH_2Cl_2	80
5	CuCl	pyridine	CH_3CN	88
6	CuI	pyridine	CH_3CN	6
7	$Cu(CH_3CN)_4PF_6$	pyridine	CH_3CN	7
8	$CuBr_2$	pyridine	CH_3CN	65
9	CuI	4-OMepy	CH_3CN	50
10	CuI	DMAP	CH_3CN	94
11	CuI	DBU	CH_3CN	9



[a]Reaction conditions: DBAD-H_2 (0.5 mmol), copper (10 mol %), and additive (20 mol %) in solvent (1.0 mL) under an O_2 balloon at room temperature for 3 h. [b]Yield determined by ^1H NMR spectroscopy (internal standard: 1,1,2,2-tetrachloroethane).

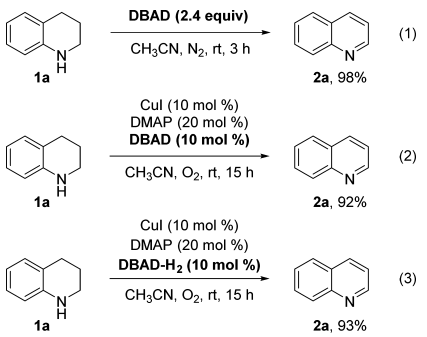
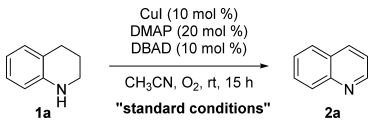


Table 2. Control Reactions of Cu-Catalyzed Aerobic Dehydrogenation of 1,2,3,4-Tetrahydroquinoline to Quinoline[a]



entry	change from the "standard conditions"	yield[b] (%)
1	none	92
2	no DBAD	20
3	no DBAD and CuI	0
4	no CuI	6
5	no DMAP	5
6	N_2 instead of O_2	7

[a]Reaction conditions: **1a** (0.5 mmol), CuI (10 mol %), DMAP (20 mol %), and DBAD (10 mol %) in CH_3CN (1.0 mL) under an O_2 balloon at room temperature for 15 h. [b]Yield determined by ^1H NMR spectroscopy (internal standard: 1,1,2,2-tetrachloroethane).

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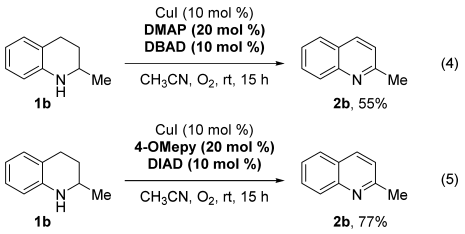
result implies that Cu-catalyzed direct amine oxidation was not a major pathway.[21] It was observed that the direct dehydrogenation of **1a** by O_2 did not occur (entry 3). When CuI, DMAP, or O_2 was eliminated from the standard conditions, only stoichiometric dehydrogenation of **1a** by DBAD (10 mol %) took place (entries 4–6).[22] These results indicate that our proposed co-catalytic mechanism, consisting of DBAD-mediated dehydrogenation of **1a** and Cu-catalyzed aerobic regeneration of DBAD, would be the most plausible pathway.[23]

The CuI/DMAP/DBAD system showed good reactivity in the aerobic dehydrogenation of **1a**; however, this catalytic system was not efficient in the aerobic dehydrogenation of substituted tetrahydroquinolines, probably due to steric hindrance between the tertiary butyl group of DBAD and substituents. For example, the aerobic dehydrogenation of 2-methyltetrahydroquinoline **1b** gave a 55% yield of 2-methylquinoline **2b** (eq 4). To address the steric issue, we



attempted to use a less sterically hindered azodicarboxylate such as DIAD instead of DBAD. Interestingly, CuI-catalyzed dehydrogenation of **1b** using DIAD and 4-OMepy, instead of DBAD and DMAP, increased the yield of **2b** (eq 5). On the basis of these results, we set up two reaction conditions. Method A is CuI/DMAP/DBAD-catalyzed aerobic dehydrogenation for simple 1,2,3,4-tetrahydroquinolines, and method B is CuI/4-OMepy/DIAD-catalyzed aerobic dehydrogenation for sterically hindered tetrahydroquinolines.

The substrate scope of 1,2,3,4-tetrahydroquinolines using two methods is elucidated in Figure 2. The parent quinoline **2a** was obtained in 92% yield using method A. The aerobic dehydrogenation of 2-substituted tetrahydroquinolines such as **1b** and **1c** caused moderate yields in method A (55% and 52%), but exposure of **1b** and **1c** to method B gave improved product yields (77% and 66%). The series of 4-phenyl-substituted tetrahydroquinolines, which were synthesized by reductive amination and cyclization,[24] were then tested (**2d–g**). Generally, method B showed better results than method A. The aerobic dehydrogenation of various 6-substituted tetrahydroquinolines was examined. Substrates having an electron-donating group, such as methoxy and methyl, underwent aerobic dehydrogenation in moderate and high yield, respectively (**2h** and **2i**). Halogen groups such as bromo and fluoro were tolerable in the present reaction conditions and led to good yields of quinoline products (**2j** and **2k**). Quinolines with a nitro or trifluoromethyl group at position 7 were easily synthesized from the corresponding 1,2,3,4-tetrahydroquinolines through the developed aerobic dehydrogenation (**2l** and **2m**). Pleasingly, acridine could be produced efficiently from 9,10-dihydroacridine using the present aerobic dehydrogenation (**2n**).

In conclusion, we revealed that CuI/DMAP was able to catalyze the aerobic oxidation of DBAD-H_2 to DBAD. By using this aerobic oxidation, we developed a CuI and DBAD co-catalytic system for the aerobic dehydrogenation of 1,2,3,4-tetrahydroquinolines to afford quinolines under mild conditions. A variety of 1,2,3,4-tetrahydroquinolines underwent dehydrogenation in the presence of a catalytic amount of CuI, DBAD, and DMAP to produce the corresponding quinolines; however, the use of DIAD and 4-methoxypyridine, instead of DBAD and DMAP, was effective for the dehydrogenation of sterically hindered substrates. Further mechanistic studies and other applications, especially for the Mitsunobu reaction using a catalytic amount of azodicarboxylate,[25] are now under investigation.

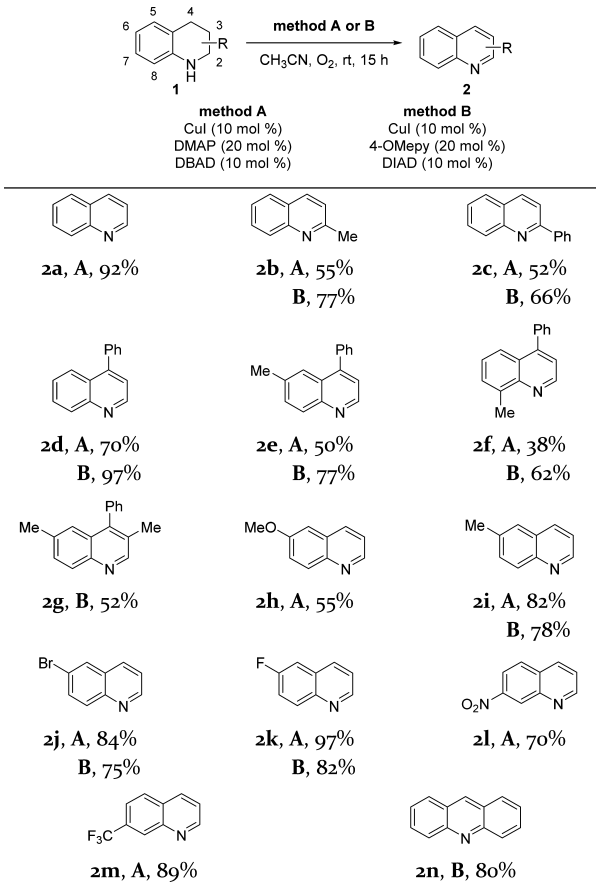


Figure 2. Substrate scope of aerobic dehydrogenation of 1,2,3,4-tetrahydroquinolines using two methods. Reaction conditions: method A, 1,2,3,4-tetrahydroquinoline (0.5 mmol), CuI (10 mol %), DMAP (20 mol %), and DBAD (10 mol %) in CH_3CN (1.0 mL) under an O_2 balloon at room temperature for 15 h; method B, 4-OMepy (20 mol %) and DIAD (10 mol %) were used instead of DMAP and DBAD. Isolated yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03166.

Detailed experimental procedure and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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