Chemoselectivity

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Highly Chemoselective Aerobic Oxidation of Amino Alcohols into Amino Carbonyl Compounds**

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Abstract: *The direct oxidation of unprotected amino alcohols to their corresponding amino carbonyl compounds has often posed serious challenges in organic synthesis and has constrained chemists to adopting an indirect route, such as a protection/deprotection strategy, to attain their goal. Described herein is a highly chemoselective aerobic oxidation of unprotected amino alcohols to their amino carbonyl compounds in which 2-azaadamantane N-oxyl (AZADO)/copper catalysis is used. The catalytic system developed leads to the alcohol-selective oxidation of various unprotected amino alcohols, carrying a primary, secondary, or tertiary amino group, in good to high yield at ambient temperature with exposure to air, thus offering flexibility in the synthesis of nitrogen-containing compounds.*

The oxidation of alcohols into their corresponding carbonyl compounds is one of the most fundamental transformations in organic chemistry, and thus numerous selective alcohol oxidation methods have been developed.[1] Nevertheless, the direct oxidation of alcohols, having unprotected amino groups, into their corresponding amino carbonyl compounds often suffers from poor yield owing to either the nonproductive or destructive interaction between an electron-rich amino group and the oxidant, and reflects weak state-of-the-art alcohol oxidation:[2] alcohol moieties of amino alcohols are typically oxidized after the amino groups are protected as amides or carbamates, thus reducing synthetic efficiency.[3] Recently, the direct synthesis of amides from alcohols and amines by dehydrogenative condensation using ruthenium catalysts has been reported, and has achieved the selective oxidation of alcohols and hemiaminals in the presence of amines.[4] However, the general procedure for the selective oxidation of unprotected amino alcohols to their amino carbonyl compounds has not yet been reported.

We sought to develop mild and widely applicable methods for alcohol oxidation using nitroxyl radical catalysts, in which the corresponding oxoammonium ions serve as active species (Figure 1 a).[5] We focused on less sterically hindered oxoammonium ions, which are generated by the oxidation of 2-azaadamantane *N*-oxyl (AZADO) and related nitroxyl radicals (Figure 2).[6] AZADO and its relatives exhibit high catalytic activities for alcohol oxidation with a markedly broad substrate scope by using various mild or environ-

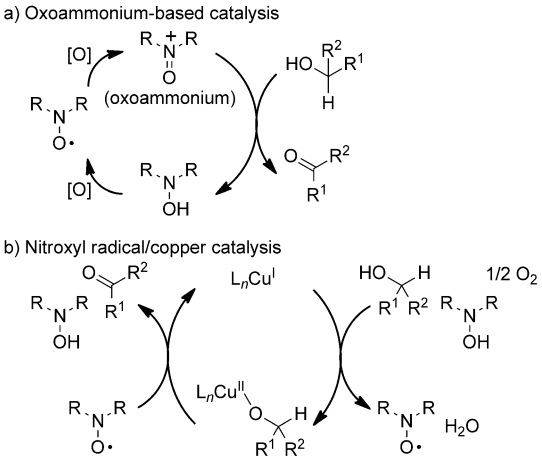

Figure 1. Simplified reaction mechanisms of nitroxyl-radical-catalyzed alcohol oxidation.

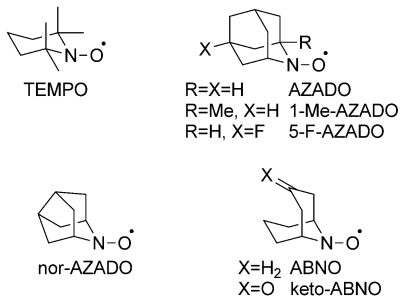

Figure 2. Structure of nitroxyl radicals.

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mentally benign terminal oxidants, such as NaOCl, PhI(OAc)$_2$, NO$_x$-O$_2$,[7] and diisopropyl azodicarboxylate.[8] Unfortunately, most of these methods fail to oxidize unprotected amino alcohols efficiently owing to the conceivable nonproductive interaction between oxoammonium ions and amines (Figure 3a).

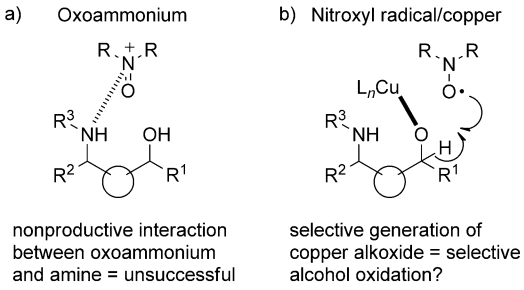
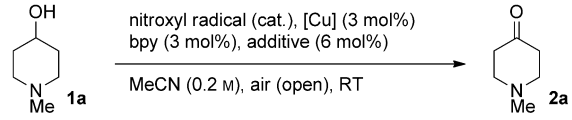


Figure 3. Working hypothesis: oxidation of amino alcohols by oxoammonium or nitroxyl radical/copper.

Herein, we focus on another type of nitroxyl-radical-catalyzed oxidation method, namely, nitroxyl radical/copper catalysis with molecular oxygen as the terminal oxidant (Figure 1b).[9] Since the pioneering work by Semmelhack et al. published in 1984, in which TEMPO and CuCl catalysts were used for the aerobic oxidation of benzylic/allylic alcohols to aldehydes,[10] the scope of nitroxyl radical/copper catalysis has grown,[11] especially from the contribution of the groups of Sheldon,[11g] Koskinen,[11c] and Stahl,[11a] thus enabling the methodology to lead to highly practical alcohol oxidations by judicious choice in the copper salt, ligand, and additives. The applicability of this catalysis has expanded to the synthesis of imines,[12] nitriles,[13] and nitrogen-containing heterocycles[14] by oxidizing not only alcohols but also amines. Most recently, Steves and Stahl have disclosed ABNO/copper catalysis which displays excellent reactivity with functional-group tolerance for primary and secondary aliphatic alcohols to give carbonyl compounds.[15] However, the selectivity of such catalysis toward the oxidation of unprotected amino alcohols has barely been addressed.[16] We envisaged that nitroxyl radical/copper catalysis could achieve the selective oxidation of amino alcohols into amino carbonyl compounds because a copper alkoxide intermediate would be more readily generated than a copper amide intermediate (Figure 3b). We report herein the highly chemoselective aerobic oxidation of unprotected amino alcohols into amino carbonyl compounds using AZADO and copper catalysts.

This study commenced with the comparison of the catalytic efficiencies of TEMPO and AZADO by using *N*-methyl-4-piperidinol (**1a**) as the model substrate under the reaction conditions reported by Hoover and Stahl who employed a nitroxyl radical, CuOTf, 2,2-bipyridyl (bpy), and *N*-methylimidazole (NMI) as the catalysts in MeCN at ambient temperature in open air.[11a] The result shows that 1 mol% AZADO oxidized **1a** to its corresponding ketone **2a** in 80% conversion, whereas 5 mol% TEMPO oxidized **1a** in only 25% conversion (Table 1, entries 1 and 2). The screening of copper salts indicated that halide salts of Cu^{I} showed higher

Table 1: Optimization of the reaction conditions for secondary alcohols.



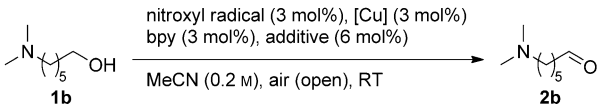
Entry	Nitroxyl radical (mol%)	[Cu]	Additive	*t* [h]	Conv. [%][a]
1[b]	TEMPO (5)	CuOTf[c]	NMI	24	25
2	AZADO (1)	CuOTf[c]	NMI	24	80
3	AZADO (1)	CuCl	NMI	4	100
4	AZADO (1)	CuBr	NMI	3	100
5	AZADO (1)	CuI	NMI	5	100
6	AZADO (1)	$CuBr_2$	NMI	12	56
7	AZADO (1)	CuCl	DMAP	2	100
8	5-F-AZADO (1)	CuCl	DMAP	3	98
9	nor-AZADO (1)	CuCl	DMAP	2	100
10	1-Me-AZADO (1)	CuCl	DMAP	3	100
11	ABNO (1)	CuCl	DMAP	6	93
12	keto-ABNO (1)	CuCl	DMAP	6	50
13	TEMPO (1)	CuCl	DMAP	3	0

[a] Determined by GC. [b] [Cu] (10 mol%), bpy (5 mol%), additive (10 mol%). [c] $(CuOTf)_2$·benzene was used as the CuOTf source. DMAP = 4-(*N*,*N*-dimethylamino)pyridine, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, Tf = trifuoromethanesulfonyl.

reactivity than CuOTf, and that the reaction proceeded in quantitative conversion within 5 hours (entries 3–6). After screening amine-base types of additives, DMAP was found to accelerate the reaction (entry 7).[11h] Thus, other nitroxyl radicals were examined (entries 8–13), and 5-F-AZADO and nor-AZADO, which showed higher reactivity than AZADO in the NO$_x$-mediated aerobic oxidation of alcohols, showed the same activity as AZADO or lower in this case (entries 8 and 9).[6c,7] ABNO and keto-ABNO, which were reported as catalysts for the copper-mediated aerobic oxidation of alcohols and amines, respectively, worked less efficiently than AZADO (entries 11 and 12).[12c,15] Although many ligands and solvents were also examined, bpy and MeCN gave the best results.[17]

Next, we determined the optimum reaction conditions for the oxidation of amino primary alcohols using 6-dimethyl-amino-1-hexanol (**1b**) as the model substrate (Table 2).

Table 2: Optimization of the reaction conditions for primary alcohols.



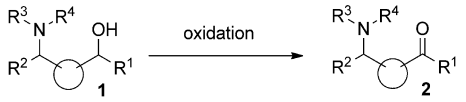
Entry	Nitroxyl radical	[Cu]	Additive	*t* [h]	Conv. [%][a]
1	TEMPO	CuOTf[b]	NMI	1	10
2	AZADO	CuOTf[b]	NMI	1	29
3	AZADO	CuCl	DMAP	1	42
4	5-F-AZADO	CuCl	DMAP	1	36
5	nor-AZADO	CuCl	DMAP	1	36
6	1-Me-AZADO	CuCl	DMAP	2	67
7	ABNO	CuCl	DMAP	1	39
8	TEMPO	CuCl	DMAP	0.5	7

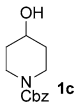
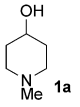
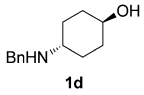
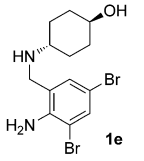
[a] Determined by GC. Conversions did not increase after an extended reaction time. [b] $(CuOTf)_2$·benzene was used as the CuOTf source.

AZADO showed superior catalytic activity to TEMPO in the oxidation of **1b** to give the aldehyde **2b** in 29% conversion under the standard reaction conditions reported by Hoover and Stahl (entries 1 and 2). The combination of CuCl and DMAP gave better conversion than that of CuOTf and NMI (entry 3). After screening nitroxyl radical catalysts, it was found that the more bulky 1-Me-AZADO showed higher activity than AZADO (entries 4–8). Previous structure–activity relationship studies showed that less sterically hindered nitroxyl radicals exhibited higher reactivity.[6c,d]

With the optimum reaction conditions in hand, we compared the reactivity of AZADO/copper catalysis with that of conventional selective alcohol oxidation methods, namely, PCC oxidation,[18] Swern oxidation,[19] Dess–Martin oxidation,[20] and TPAP oxidation,[21] by oxidizing secondary alcohols with tertiary and secondary amines (Table 3). In the control experiments, it was confirmed that all the methods efficiently oxidized the N-Cbz-protected piperidinol **1c** in high yield. In contrast, the oxidation of the amino alcohols **1a**, **1d**, and **1e** was ineffective in the cases of the conventional methods, thereby giving the ketones in low or modest yield. AZADO/copper catalysis exhibited excellent activities for all the amino alcohols, including the highly functionalized amino alcohol **1e**, to give the amino ketones in high yields and it worked well even on a 50 mmol scale. Notably, imino ketones or imino alcohols were not obtained in the oxidation of the benzylamino alcohol **1d** or **1e** even though nitroxyl radical/copper catalysis can oxidize benzylic amines to imines.[12c,22]

Table 3: Comparison of known methods and AZADO/copper catalysis of amino alcohol oxidation.[a]

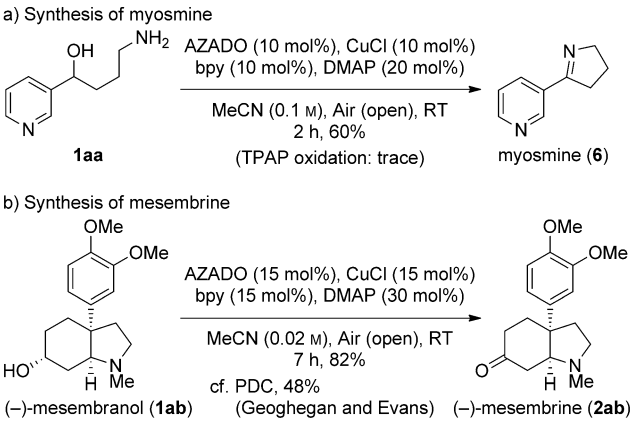


Amino alcohol	PCC[b]	Swern[b]	DMP[b]	TPAP[b]	AZADO/Cu[c]
 **1c**	92% /2 h	95% /0.75 h	97% /2 h	90% /0.75 h	97% /1.5 h
 **1a**	16% /1.5 h	65% /1 h (10%)	20% /3 h (17%)	32% /3 h (29%)	96% /3 h[d]
 **1d**	26% /1 h (<5%)	32% /1.2 h	0% /4 h (<29%)	68% /4 h (13%)	92% /2 h
 **1e**	14% /2 h (29%)	10% /2 h (3%)	Dec. /1 h	<1% /12 h (72%)	97% /2 h 99% /3.5 h[e]

[a] Reaction conditions: PCC: PCC (1.5 equiv), 4 Å M.S. (500 mg/1 mmol substrate), CH_2Cl_2 (0.2 M), RT; Swern: $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2 (0.17 M), −78 °C to RT; DMP: Dess–Martin periodinane (1.5 equiv), CH_2Cl_2 (0.2 M),RT; TPAP: TPAP (5 mol%), NMO (1.5 equiv), 4 Å M.S. (500 mg/1 mmol substrate), CH_2Cl_2 (0.1 M), RT; AZADO/Cu: AZADO (3 mol%), CuCl (3 mol%), bpy (3 mol%), DMAP (6 mol%), MeCN (0.2 M), air (open), RT. Yields of product/time (remaining substrate) are shown. [b] Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [c] Yield of isolated product. [d] 1 mol% AZADO was used. [e] 50 mmol scale. Cbz = benzyloxycarbonyl.

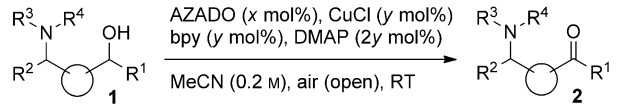
Encouraged by the promising results, we applied the optimum reaction conditions to examine the substrate scope (Table 4 and Table 5). Note that the yields of amino carbonyl products with aliphatic secondary and primary amines were determined by isolating the Boc-protected products, because of the difficulty in isolating the highly polar unprotected products (Table 5). The benzylic alcohol **1f** and the allylic alcohol **1g** were efficiently oxidized with 1 mol% AZADO (Table 4, entries 1 and 2). The examination of the functional-group tolerance indicated that AZADO/copper catalysis tolerated benzylic and allylic amines, an ester, and N-heterocycles (entries 3–9). Furthermore, this catalysis selectively oxidized not only the sterically bulky secondary alcohols **1o** and **1p** but also the primary alcohol **1q** in good yields (entries 10–12). The oxidation of the chiral primary alcohols **1r** and **1s** proceeded with almost complete retention of their stereochemistry (entries 13 and 14). Notably, 5-benzylamino-1-pentanol (**1t**), which was converted into δ-valerolactam by ruthenium-catalyzed dehydrogenation,[23] was transformed into the enamine dimer **4** in good yield (entry 15). Unfortunately, the vicinal amino alcohol **1u** was not oxidized (entry 16). Secondary alcohols with aliphatic secondary and primary amines were efficiently oxidized into the amino ketones even in the case of the bulky alcohol **1w** with a nitrile group (Table 5, entries 1–4). The more challenging primary alcohol **1z**, having a secondary amine, was also selectively oxidized to give the aldehyde in moderate yield (entry 5).

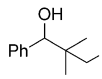
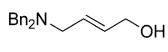
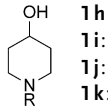
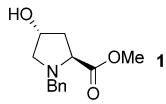
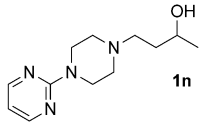
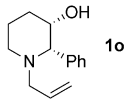
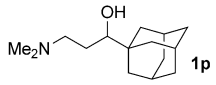
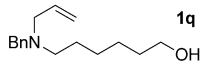
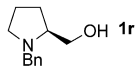
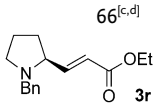
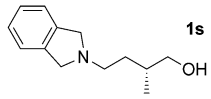
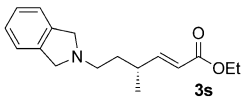
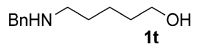
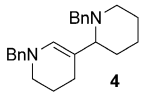
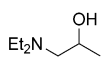
To demonstrate the utilization of the highly chemoselective alcohol oxidation, we applied AZADO/copper oxidation to the synthesis of nitrogen-containing natural products. The readily prepared pyridyl amino alcohol **1aa** was efficiently converted into myosmine (**6**) in 60% yield under the standard reaction conditions, whereas the TPAP oxidation of the alcohol **1aa** afforded only a trace amount of myosmine (**6**; Scheme 1a).[24] AZADO/copper catalysis also oxidized mesembranol (**1ab**) to (−)-mesembrine (**2ab**) in high yield. The reaction has recently been reported by Geoghegan and



Scheme 1. Application to synthesis of natural alkaloids.

Table 4: Oxidation of alcohols with tertiary and benzylic secondary amines.[a]

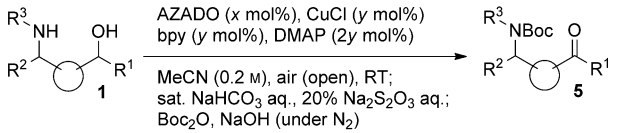


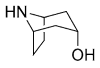
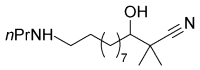
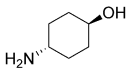
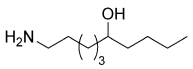
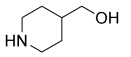
Entry	Amino alcohol	x/y	t [h]	Yield [%][a]
1	 **1f**	1/3	2.5	92
2	 **1g**	1/3	3	90
3	 **1h**: R = allyl	1/3	2.5	97
4	**1i**: R = Bn	1/3	2.5	97
5	**1j**: R = PMB	1/3	3	99
6	**1k**: R = geranyl	3/3	4.8	87
7	 **1l**	1/3	2	94
8	 **1m**	3/3	1.7	96
9	 **1n**	5/5	4.5	77
10	 **1o**	3/3	2	88
11	 **1p**	5/5	2.5	80
12[b]	 **1q**	5/5	1	74
13[b]	 **1r**	5/5	2.5	66[c,d]  **3r**
14[b]	 **1s**	5/5	1.5	64[c,e]  **3s**
15[b]	 **1t**	3/3	1.5	80[f]  **4**
16	 **1u**	3/3		0 (n.r.)

[a] Yield of isolated product. [b] 1-Me-AZADO was used instead of AZADO. [c] The aldehyde product was isolated as the ester **3** after treatment with a Wittig reagent. [d] > 99% *ee* of **3r** was given. [e] 99% *ee* of **3s** was given. [f] Yield of **4**. n.r. = no reaction, PMB = *para*-methoxybenzyl.

Evans as a formidable reaction for which PDC was identified as the best reagent to give mesembrine in 48% yield (Scheme 1b).[2a]

Table 5: Oxidation of alcohols with aliphatic secondary and primary amines.[a]



Entry	Amino alcohol		x/y	t [h]	Yield [%][a]
1		**1v**	3/3	4	89
2		**1w**	5/5	2.5	74
3		**1x**	3/3	1	88
4[b]		**1y**	5/5	2	72
5[b,c]		**1z**	5/5	1.5	61

[a] Yield of isolated product. [b] 0.1 M MeCN was used. [c] 1-Me-AZADO was used instead of AZADO. Boc = *tert*-butoxycarbonyl.

In summary, we have developed a highly efficient and chemoselective aerobic oxidation of amino alcohols to amino carbonyl compounds. The catalytic system consisting of AZADO and copper(I) oxidized not only alcohols with tertiary amino groups but also those with secondary and primary amines in good to high yield. Moreover, AZADO/copper catalysis could be utilized for the synthesis of nitrogen-containing natural products. Studies of the precise mechanism of this catalysis are under way.

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