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Oxidation

Highly Efficient Aerobic Oxidation of Alcohols by Using Less-Hindered Nitroxyl-Radical/Copper Catalysis: Optimum Catalyst Combinations and Their Substrate Scope

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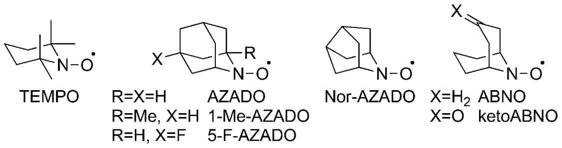
Abstract: The oxidation of alcohols into their corresponding carbonyl compounds is one of the most fundamental transformations in organic chemistry. In our recent report, 2-azaadamantane *N*-oxyl (AZADO)/copper catalysis promoted the highly chemoselective aerobic oxidation of unprotected amino alcohols into amino carbonyl compounds. Herein, we investigated the extension of the promising AZADO/copper-catalyzed aerobic oxidation of alcohols to other types of alcohol. During close optimization of the reaction conditions by using various alcohols, we found that the optimum combination of nitroxyl radical, copper salt, and solution concentration was dependent on the type of substrate. Various alcohols, including highly hindered and heteroatom-rich ones, were efficiently oxidized into their corresponding carbonyl compounds under mild conditions with lower amounts of the catalysts.

Introduction

The oxidation of alcohols into their corresponding carbonyl compounds is a ubiquitous but important transformation in organic chemistry; thus, numerous reagents for and methods of conducting this transformation in an efficient manner have been developed.[1] However, various aspects such as increased molecular size and complexity of the alcohol substrates, and sustainability demand more affordable and suitable methods for the alcohol-oxidation reactions.[2]

We have developed a series of highly active, nitroxyl-radical-type catalysts for oxidation reactions, namely, 2-azaadamantane *N*-oxyl (AZADO),[3] 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO),[4] 9-azanoradamantane *N*-oxyl (Nor-AZADO),[5] and their derivatives (Scheme 1),[6] and demonstrated their synthetic use.[7] These nitroxyl radicals, which featured a less-hindered structure, were capable of the highly efficient oxidation of alcohols into carbonyl compounds (in particular, the oxidation of highly sterically hindered alcohols), the one-pot oxidation of alcohols into carboxylic acids,[8] the one-pot oxidative cleavage of vicinal diols into (di)carboxylic acids,[9] and the oxidation of silyl enol ethers into diketones.[10] Notably, we have developed highly efficient and mild methods for the oxidation of alcohols into carbonyl compounds, namely, NO_x-mediated aerobic alcohol oxidation[6] and alcohol oxidation by using diisopropyl azodicarboxylate (DIAD) as a terminal oxidant.[11] These alcohol-oxidation methods had broad substrate scope and excellent functional-group tolerance. However, to our dissatisfaction, we encountered an issue: Most of these aforementioned methods failed to oxidize unprotected amino alcohols in an efficient manner. The selective oxidation of unprotected amino alcohols is recognized as an inherently highly challenging reaction.[12] The alcohol groups of amino alcohols are typically oxidized after the protection of amino groups as amides or carbamates.



Scheme 1. Structures of selected nitroxyl radicals.

To overcome this challenge of the chemoselective oxidation of alcohols in the presence of unprotected amino groups, we were interested in adapting another nitroxyl-radical-mediated method, namely, a combined catalytic system of a nitroxyl radical and copper.[13] Since the seminal work of Semmelhack et al., who used TEMPO/copper catalysis in the aerobic oxidation of benzylic and allylic alcohols in 1984,[14] this combination catalysis has been extensively investigated as a promising method for the oxidation of alcohols by using an ideal oxidant, that is, molecular oxygen. In 2011, Hoover and Stahl reported a highly practical aerobic oxidation reaction of alcohols by using TEMPO/copper catalysis, which efficiently oxidized unactivated aliphatic primary alcohols that contained various functional groups at room temperature in air.[15] Nitroxyl-radical/

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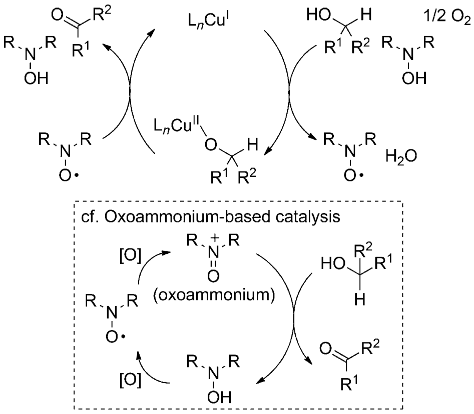
copper catalysis generate a copper-complex-type active species, thereby distinguishing itself from other nitroxyl-radical-mediated catalyses, which generate an oxoammonium-ion-type active species (Scheme 2).[16] We expected that a nitroxyl-radical/copper catalytic system that contained an active species other than an oxoammonium ion could achieve the chemoselective oxidation of unprotected amino alcohols. Gratifyingly, we found that AZADO/copper catalysis successfully oxidized alcohols with unprotected tertiary, secondary, and even primary amines into their corresponding amino carbonyl compounds at room temperature in open air.[17]



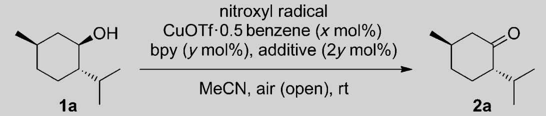
Scheme 2. Simplified mechanism of the alcohol-oxidation reaction by using nitroxyl-radical/copper catalysis compared with that using oxoammonium-based catalysis.

During our aforementioned studies, we expected that AZADO/copper catalysis would efficiently oxidize not only unprotected amino alcohols but also other various secondary alcohols. In fact, Steves and Stahl recently reported that ABNO/copper catalysis oxidized several secondary alcohols.[18] However, the ABNO/copper system required a rather high catalyst loading compared to our AZADO/copper system and heating to oxidize sterically demanding substrates. We envisaged that the judicious combination of an AZADO-type nitroxyl radical, a copper salt, and an additive(s) would realize a highly efficient aerobic alcohol oxidation with broad substrate applicability on the basis of the following key observations: 1) slight differences in the steric and electronic properties of AZADO-type nitroxyl radicals often exert marked effects on their catalytic activities[4–6,17,19] and 2) the AZADO/copper system has a different optimum combination of a copper salt and an amine additive to the TEMPO/copper and ABNO/copper systems.[17]

Herein, we report a highly efficient aerobic alcohol-oxidation reaction with broad substrate scope by using AZADO/copper catalysis. Optimization of the reaction conditions by using various alcohols led us to determine several optimal combinations of a nitroxyl radical and a copper salt, depending on the structure and characteristics of the alcohol substrate. The optimum catalyst combinations efficiently oxidized various alcohols, including highly hindered and heteroatom-rich substrates, in air at or below room temperature.

Results and Discussion

Table 1. Optimization of the reaction conditions.



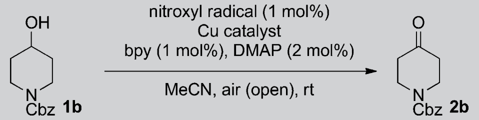
Entry	Nitroxyl radical [mol %]	x/y	Additive	MeCN [M]	t [h]	Conversion [%][a]
1	AZADO (3)	6:3	NMI	0.2	4	100
2	Nor-AZADO (3)	6:3	NMI	0.2	3	100
3	ABNO (3)	6:3	NMI	0.2	5	100
4	1-Me-AZADO (3)	6:3	NMI	0.2	12	96
5	TEMPO (3)	6:3	NMI	0.2	12	0
6	5-F-AZADO (3)	6:3	NMI	0.2	5	100
7	ketoABNO (3)	6:3	NMI	0.2	7	100
8	Nor-AZADO (1)	6:3	NMI	0.2	4	100
9	Nor-AZADO (1)	1:1	NMI	1	10	100
10	Nor-AZADO (1)	1:1	DMAP	1	6	100
11	AZADO (1)	1:1	DMAP	1	24	100
12	ABNO (1)	1:1	DMAP	1	48	98
13	Nor-AZADO (0.1)	1:1	DMAP	1	48	100
14[b]	Nor-AZADO (1)	1:1	DMAP	1	6	64

[a] Determined by gas chromatography. [b] CuCl was used instead of CuOTf. Tf = trifluoromethanesulfonyl, TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxy radical.

We began by optimizing the reaction conditions for the oxidation of menthol (**1a**), a highly sterically hindered secondary alcohol, which required elevated temperatures and an O_2 atmosphere under ABNO/copper catalysis (Table 1).[18] The catalytic activities of various nitroxyl radicals were compared under the modified reaction conditions reported by Hoover and Stahl, who employed TEMPO, CuOTf, 2,2′-bipyridyl (bpy), and *N*-methylimidazole (NMI) as catalysts in MeCN at ambient temperature in air (Table 1, entries 1–7).[15] Catalytic activity was higher when a less sterically hindered nitroxyl radical was used. Thus, Nor-AZADO-oxidized-menthol (**1a**) afforded quantitative conversion within only 3 h (Table 1, entries 1–5). Notably, sterically hindered nitroxyl radical TEMPO did not oxidize menthol (**1a**), and the electron-deficient nitroxyl radicals 5-F-AZADO[6] and ketoABNO[20] showed lower activities than AZADO and ABNO, respectively (Table 1, entries 5–7). Decreasing the amount of the catalysts was examined by using Nor-AZADO as the nitroxyl radical (Table 1, entries 8–11). Lowering the amount of Nor-AZADO to 1 mol% had a negligible effect on the reaction efficiency (Table 1, entry 8). Although lowering the amounts of CuOTf (1 mol%), bpy (1 mol%), and NMI (2 mol%) significantly slowed the reaction rate, a concentrated (1 M) solution minimized the deceleration to oxidize the alcohol in quantitative yield within 10 h (Table 1, entry 9). After several alternative additives to NMI were examined, 4-dimethylaminopyridine (DMAP) was found to catalyze the reaction more efficiently (Table 1, entry 10).[21] Re-comparison of the catalytic efficiencies of Nor-AZADO, AZADO, and ABNO revealed that slight steric differences between these nitroxyl radicals led to considerable differences between their reaction efficiencies (Table 1, entries 10–12). Notably, even 0.1 mol% Nor-AZADO was sufficient to oxidize menthol (**1a**) in quantitative yield, although the reaction time was prolonged to 48 h (Table 1, entry 13). CuCl, which has shown good activity for oxidizing amino alcohols,[17] was not suitable for the oxidation of menthol (**1a**; Table 1, entry 14). Although several ligands, including 4,4′-dimethoxy-2,2′-bipyridyl,[18,21b,22] and solvents were also examined, bpy and MeCN gave the best results.[23]

Next, we optimized the reaction conditions for the oxidation of benzylcarbamate-containing piperidinol **1b**, which might coordinate copper catalysts to attenuate the catalytic activity, was examined (Table 2). The optimal reaction conditions for menthol (**1a**) promoted the oxidation of piperidinol **1b** in only 45% conversion (Table 2, entry 1). Interestingly, inexpensive CuCl showed a higher activity than CuOTf, and dilute (0.2 M) conditions suppressed the deactivation of copper catalysis to improve the conversion to 79% (Table 2, entries 2 and 3). Quantitative oxidation of piperidinol **1b** was achieved by increasing the amount of CuCl to 2 mol% (Table 2, entry 4). AZADO, ABNO, and 1-Me-AZADO showed almost the same catalytic activity as Nor-AZADO, owing to the small steric hindrance of compound **1b** (Table 2, entries 5–7).

Table 2. Optimization of the reaction conditions.



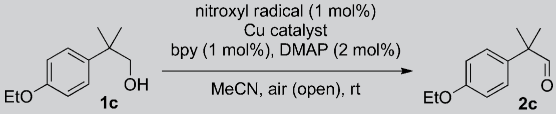
Entry	Nitroxyl radical	Cu catalyst [mol%]	MeCN [M]	*t* [h]	Conversion [%][a]
1	Nor-AZADO	CuOTf (1)[b]	1	6	45
2	Nor-AZADO	CuCl (1)	1	6	70
3	Nor-AZADO	CuCl (1)	0.2	9	79
4	Nor-AZADO	CuCl (2)	0.2	4	100
5	AZADO	CuCl (2)	0.2	4	100
6	ABNO	CuCl (2)	0.2	4	100
7	1-Me-AZADO	CuCl (2)	0.2	4	100

[a] Determined by gas chromatography. The conversion did not increase after an extended reaction time. [b] CuOTf·0.5 benzene was used as the CuOTf source. Cbz = benzyloxycarbonyl.

We also optimized the reaction conditions for the oxidation of sterically hindered primary alcohol **1c**, which contained a *para*-ethoxyphenyl group (Table 3). The optimal reaction conditions for menthol (**1a**) oxidized compound **1c** in 65% conversion (Table 3, entry 1). Comparison of the catalytic activities of nitroxyl radicals identified 1-Me-AZADO as a suitable catalyst (Table 3, entries 2–5). After optimization of the copper salt and the solution concentration, we found that 3 mol% CuCl in 0.2 M MeCN solution gave almost-quantitative conversion of the substrate (Table 3, entries 6–9).

Based on our optimization of the reaction conditions for the oxidation of these three alcohols, we concluded that the optimal reaction conditions were determined by the type of substrate, as shown below:

Table 3. Optimization of the reaction conditions.

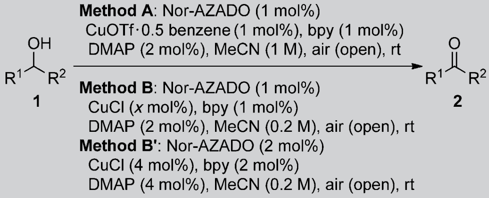


Entry	Nitroxyl radical	Cu catalyst [mol%]	MeCN [M]	*t* [h]	Conversion [%][a]
1	Nor-AZADO	CuOTf (1)[b]	1	6	65
2	AZADO	CuOTf (1)[b]	1	6	67
3	ABNO	CuOTf (1)[b]	1	6	69
4	1-Me-AZADO	CuOTf (1)[b]	1	6	78
5	TEMPO	CuOTf (1)[b]	1	12	11
6	1-Me-AZADO	CuCl (1)	1	6	79
7	1-Me-AZADO	CuCl (1)	0.2	9	93
8	1-Me-AZADO	CuCl (2)	0.2	9	97
9	1-Me-AZADO	CuCl (3)	0.2	6	>99

[a] Determined by gas chromatography. The conversion only increased slightly after an extended reaction time. [b] CuOTf·0.5 benzene was used as the CuOTf source.

1) The optimum combination of copper salt and solution concentration depends on the presence or absence of coordinating groups in the substrate. CuOTf in a concentrated solution should be used for alcohols without coordinating groups (Table 4, Method A), whereas CuCl in a dilute solution should be used for alcohols that contain coordinating groups (Table 4, Method B).

Table 4. Substrate scope.



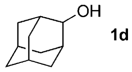
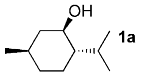
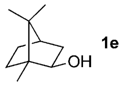
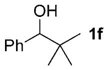
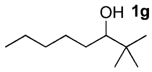
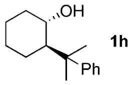
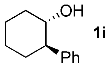
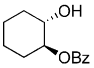
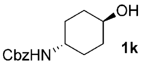
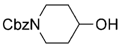
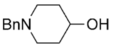
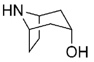
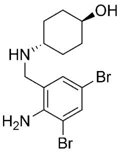
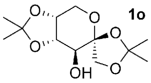
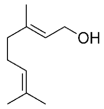
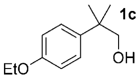
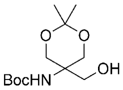
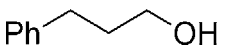
Entry	Substrate	Method	*t* [h]	Yield [%][a]
1	 **1d**	A[b]	13	96
2	 **1a**	A	9	87
3	 **1e**	A	7	85
4	 **1f**	A	6	98
5	 **1g**	A	22	85
6	 **1h**	A	12	98
7	 **1i**	A	6	(73[c])
8		B (x = 1)	8	97

Table 4. (Continued)

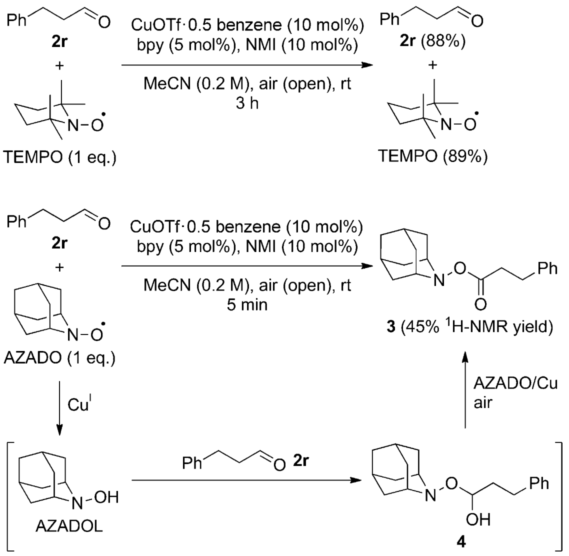
Entry	Substrate	Method	*t* [h]	Yield [%][a]
9	 **1j**	A	12	(13[d])
10		B (x=2)	4	97
11	 **1k**	B (x=1)	4	98
12	 **1b**	B (x=2)	5	99
13	 **1l**	B (x=2)	3	95
14	 **1m**	B′	1	90[e]
15	 **1n**	B′	2	99
16	 **1o**	B′[f]	4	98
17	 **1p**	B (x=1)[f,g,h]	3	93
18	 **1c**	B (x=3)[g]	7	95
19	 **1q**	B′[g,i]	2	79
20	 **1r**	A[g]	3	20[j]
21		B (x=2)[g]	2.5	60[j]

[a] Yield of isolated product. [b] MeCN (0.5 M) was used. [c] Conversion determined by gas chromatography. [d] Conversion determined by ^{1}H NMR spectroscopy. [e] The product was isolated after in situ Boc protection of the amino group; see Ref. [17]. [f] The reaction was performed at 0 °C. [g] 1-Me-AZADO was used instead of Nor-AZADO. [h] MeCN (1 M) was used. [i] MeCN (0.1 M) was used. [j] Yield determined by ^{1}H NMR spectroscopy; 1,3,5-trimethoxybenzene was used as the internal standard. Bz = benzoyl, Boc = *tert*-butoxycarbonyl.

2) The optimum nitroxyl radical depends on whether the substrate is a primary or secondary alcohol. Nor-AZADO should be used for secondary alcohols, especially sterically hindered substrates, whereas 1-Me-AZADO should be used for primary alcohols.

With sets of optimum conditions (i.e., Methods A and B and their 1-Me-AZADO variants) in hand, we applied them to examine the substrate scope (Table 4). Secondary alcohols **1a** and **1d**–**1h**, which didn't contain coordinating groups, were oxidized by using Method A in high yield, including the highly sterically hindered *trans*-2-(α-cumyl)cyclohexanol (**1h**; Table 4, entries 1–6). Cyclohexanols **1i** and **1j**, which contained coordinative phenyl and benzoyloxy groups at the β positions, were efficiently oxidized by using Method B, but not by Method A (Table 4, entries 7–10). Secondary alcohols **1k**, **1b**, and **1l**, which contained benzyl carbamate and benzyl amine substituents, were also oxidized in high yields (Table 4, entries 11–13). AZADO/copper catalysis even efficiently oxidized highly polar alcohol **1m**, which contained an unprotected secondary amine, as well as heteroatom-rich alcohols **1n** and **1o**, although higher amounts of the catalysts were needed (Table 4, entries 14–16). This catalysis tolerated trisubstituted olefins, which were sensitive to oxidative conditions (Table 4, entry 17). Notably, a lower temperature (0 °C) was effective for oxidizing alcohols **1o** and **1p**, possibly owing to the suppressed deactivation of the copper catalysis.[23] Sterically hindered primary alcohols **1c** and **1q** were also oxidized in good-to-high yields (Table 4, entries 18 and 19). Disappointingly, AZADO/copper catalysis did not efficiently oxidize 3-phenylpropanol (**1r**), which was readily oxidized by TEMPO/copper catalysis (Table 4, entries 20 and 21).[15]

To explain why AZADO/copper catalysis did not efficiently oxidize simple primary alcohol **1r**, we compared the reactivities of AZADO and TEMPO. Equimolar mixtures of TEMPO/AZADO and aldehyde **2r** were subjected to copper-catalyzed aerobic oxidation (Scheme 3). When TEMPO was used, almost no reaction was observed, with recovery of compound **2r** and TEMPO in high yields. On the other hand, AZADO and compound **2r** reacted rapidly to afford ester **3** as the major product, along with several other unidentified minor products. Ester **3** was most likely generated by oxidation of hemiacetal **4**, which in turn was formed by the addition of the corresponding hydroxylamine of AZADO (AZADOL) to aldehyde **2r**. Based on these results, it was clear that less-sterically hindered nitroxyl radicals were deactivated by simple aldehydes to form esters, although highly hindered TEMPO survived.



Scheme 3. Reactivities of the nitroxyl radicals with aldehyde **2r**.

Conclusion

Encouraged by the exceptional chemoselectivity of AZADO/copper catalysis in the oxidation of amino alcohols, we examined the applicability of AZADO/copper catalysis to the oxidation of other alcohols. During detailed optimization of the reaction conditions for various alcohols, we found that tailor-made combinations of the AZADO-type nitroxyl radical, copper salt, and solution concentration afforded highly efficient aerobic oxidation of the alcohol substrates. The efficient oxidation of highly sterically hindered secondary alcohols was achieved by employing the least-hindered nitroxyl radical, Nor-AZADO. Alcohols that contained coordinative groups, which may attenuate the activity of the copper catalysis, were efficiently oxidized by CuCl instead of CuOTf under dilute conditions. These findings successfully expanded the substrate scope of the aerobic oxidation reaction of alcohols by using AZADO/copper catalysis: The optimized conditions efficiently oxidized various alcohols, including highly hindered and heteroatom-rich substrates, under mild conditions with smaller amounts of catalysts. In addition, a deactivation pathway of AZADO was identified. Notably, all of the catalysts employed herein, even Nor-AZADO and 1-Me-AZADO, are currently commercially available. This study should make the aerobic oxidation of alcohols using nitroxyl-radical/copper catalysis a practical "method of choice". We expect that this reaction will be employed as a powerful tool for the synthesis of natural products and fine chemicals.

Experimental Section

General

The reactions were monitored by thin-layer chromatography (TLC) on Merck Silica Gel 60 F_{254} TLC plates (0.25 mm), or by gas chromatography (GC) on an Agilent 7890A GC system with an Agilent J&W HP-5 GC column (30 m, 0.32 mm, 0.25 μm). Column chromatography was performed on Kanto Silica Gel 60 N (spherical, neutral, particle size: 0.063–0.210 mm) or Kanto Silica Gel 60 N (spherical, neutral, particle size: 0.040–0.050 mm). ^{1}H NMR spectra were recorded on a JEOL JNM-AL400 (400 MHz) spectrometer. Chemical shifts are reported relative to tetramethylsilane ($\delta = 0.00$ ppm). Multiplicities are described as follows: s singlet, d doublet, t triplet, q quartet, m multiplet, br broad. ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 (100 MHz) spectrometer. Chemical shifts are reported relative to $^{13}CDCl_3$ ($\delta = 77.0$ ppm). IR spectra were recorded on a JASCO FTIR-410 Fourier-transform infrared spectrophotometer. Low-resolution mass spectra were recorded on a JEOL JMS-DX303 mass spectrometer. High-resolution mass spectra were recorded on a JEOL JMS-700 mass spectrometer.

General Procedure for Aerobic Alcohol Oxidation by Using AZADO/Copper Catalysis (Method A)

CuOTf•0.5 benzene (2.52 mg, 10.0 μmol) was added to a solution of the alcohol (1.00 mmol), Nor-AZADO (1.38 mg, 10.0 μmol), bpy (1.56 mg, 10.0 μmol), and DMAP (2.44 mg, 20.0 μmol) in MeCN (1.0 mL) at RT. The mixture was stirred in air at RT until the alcohol was no longer detectable (TLC), and the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (3.0 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Et_2O/*n*-hexane) to afford the corresponding carbonyl compound.

General Procedure for Aerobic Alcohol Oxidation by Using AZADO/Copper Catalysis (Method B)

CuCl (10.0*x* μmol, *x* mol%) was added to a solution of the alcohol (1.00 mmol), Nor-AZADO (1.38 mg, 10.0 μmol), bpy (1.56 mg, 10.0 μmol), and DMAP (2.44 mg, 20.0 μmol) in MeCN (5.0 mL) at RT. The mixture was stirred in air at RT until the alcohol was no longer detectable (TLC), and the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (3.0 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Et_2O/*n*-hexane) to afford the corresponding carbonyl compound.

2-(4-Ethoxyphenyl)-2-methylpropanal (2c): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.44$ (s, 1H), 7.17 (dd, $J = 6.8$, 2.4 Hz, 2H), 6.89 (d, $J = 6.8$, 2.4 Hz, 2H), 4.02 (q, $J = 7.2$ Hz, 2H), 1.43 (s, 6H), 1.40 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.1$, 158.0, 132.7, 127.7, 114.7, 63.3, 49.6, 22.4, 14.7 ppm; IR (neat): $\tilde{\nu} = 1724\ cm^{-1}$; MS (EI): *m/z* 192 $[M]^+$, 163 (100%); HRMS (EI): *m/z* calcd for $C_{12}H_{16}O_2$: 192.1150 $[M]^+$; found: 192.1130.

Reaction of AZADO with Aldehyde 2r Under Copper-Catalyzed Aerobic Oxidation Conditions

CuOTf•0.5 benzene (8.00 mg, 31.8 μmol) was added to a solution of aldehyde **2r** (42.5 mg, 0.312 mmol), AZADO (47.7 mg, 0.313 mmol), bpy (2.74 mg, 17.5 μmol), and NMI (2.69 mg, 32.8 μmol) in MeCN (1.5 mL) at RT. After stirring for 5 min in air, a saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude product. The yield of *O*-acylhydroxylamine **3** was determined to be 45% by ^{1}H NMR analysis of the crude product by using 1,3,5-trimethoxybenzene as an internal standard. Compound **3** was partially isolated by flash column chromatography on silica gel (EtOAc/*n*-hexane, 1:8 v/v) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$–7.19 (m, 5H), 3.37 (s, 2H), 2.99 (t, $J = 7.8$ Hz, 2H), 2.65 (t, $J = 7.8$ Hz, 2H), 2.21–2.15 (m, 4H), 1.93–1.90 (m, 2H), 1.83–1.77 (m, 4H), 1.43–1.35 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.3$, 140.4, 128.5, 128.3, 126.3, 55.7, 36.6, 36.2, 35.0, 31.2, 30.3, 26.2, 25.8 ppm; IR (neat): $\tilde{\nu} = 1750\ cm^{-1}$; MS (EI): *m/z* 285 $[M]^+$, 153 (100%); HRMS (EI): *m/z* calcd for $C_{18}H_{23}NO_2$: 285.1729 $[M]^+$; found: 285.1736.

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[23] See the Supporting Information.

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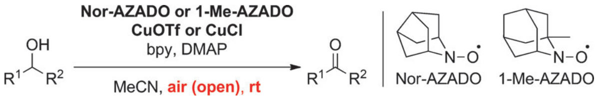
FULL PAPER



New radicals: A highly efficient aerobic oxidation of alcohols by using AZADO-type nitroxyl-radical/copper catalysis has been developed. The optimum combination of the nitroxyl radical, copper salt, and solution concentration was dependent on the type of substrate. The optimum conditions efficiently oxidized various alcohols, including highly hindered and heteroatom-rich alcohols, under mild conditions.

Oxidation

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Highly Efficient Aerobic Oxidation of Alcohols by Using Less-Hindered Nitroxyl-Radical/Copper Catalysis: Optimum Catalyst Combinations and Their Substrate Scope