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Selective Aerobic Oxidation of Primary Alcohols to Aldehydes

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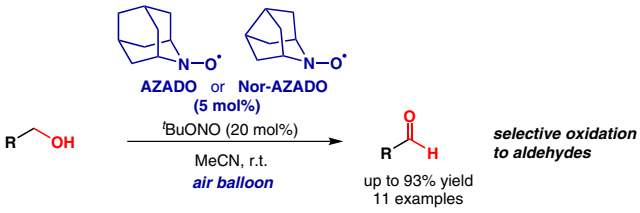

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Abstract The 2-azaadamantane-*N*-oxyl (AZADO)- and 9-azanoradamantane-*N*-oxyl (nor-AZADO)-catalyzed selective oxidation of primary alcohols to the corresponding aldehydes is described. The use of *tert*-butyl nitrite as the co-catalyst enables efficient aerobic oxidation in MeCN instead of previously reported AcOH; this is important for the selectivity of the reaction. The addition of a solution of saturated aqueous $NaHCO_3$ after the completion of the reaction was effective to suppress the overoxidation of the product to the corresponding carboxylic acid during the workup.

Key words oxidation, nitroxyl radical, primary alcohols, aldehydes, chemoselectivity

Oxidation of primary alcohols initially produces the corresponding aldehydes; subsequent oxidation of the aldehydes produces the corresponding carboxylic acids, often via the formation of hydrates (*gem*-diols).[1] Because aldehydes and carboxylic acids are not only essential components of various biologically active compounds, but also useful functional groups in organic synthesis, selective oxidation of primary alcohols to aldehydes or carboxylic acids is a valuable transformation.[2,3] Nitroxyl-radical-catalyzed oxidation has attracted much attention in synthetic organic chemistry owing to its safety and applicability to large-scale oxidation.[4] The pivotal 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, **1**) catalytically oxidizes alcohols to the corresponding carbonyl compounds in the presence of diverse co-oxidants.[5,6] The catalytic system using sodium hypochlorite (NaOCl) as the co-oxidant is widely used in academic organic synthesis as well as industrial organic synthesis, and primary alcohols are treated with an appropriate amount of NaOCl to afford the corresponding aldehydes, because further oxidation of aldehydes is relatively slow.[6b] The addition of excess NaOCl and a phase-transfer catalyst or, more efficiently, a stoichiometric amount of $NaClO_2$ facilitates further oxidation of aldehydes, affording the corresponding carboxylic acids.[6b,7] In anhydrous catalytic systems using $PhI(OAc)_2$ or trichloroisocyanuric acid (TCCA), the oxidation of primary alcohols to the corresponding aldehydes also proceeds selectively, because the aldehydes cannot form hydrates in the absence of water.[6,8] As aerobic oxidation is one of the most promising methods with a high economic efficiency and environmental sustainability, much effort has been devoted to its development.[9] Hu and Liang developed the first transition-metal-free aerobic oxidation method using TEMPO (**1**).[10a] Although several TEMPO-catalyzed aerobic oxidation methods have been developed, the substrate scope of these methods is rather limited.[10] We and others recently developed the substantially improved catalytic systems using highly active nitroxyl radical catalysts: 5-fluoro-2-azaadamantane *N*-oxyl (5-F-AZADO, **3**), 9-azanoradamantane *N*-oxyl (nor-AZADO, **4**), 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO, **5**) and keto-ABNO (**6**, Figure 1).[11–14] Using these catalytic systems, diverse secondary alcohols were efficiently oxidized to the corresponding ketones with a high compatibility for various functional groups. On the other hand, the oxidation of aliphatic primary alcohols has not been well studied using these catalytic systems. In our previous studies, the oxidation of primary alcohols afforded the corresponding aldehydes in moderate yields (<80% at the maximum) even after the optimization of the reaction conditions, because of the overoxidation of aldehydes to the corresponding carboxylic acids.[11a,b] Herein, we report the selective oxidation of primary alcohols to the corresponding aldehydes using AZADO (**2**) or nor-AZADO (**4**) as the catalyst.

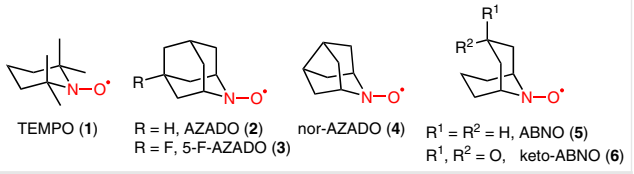


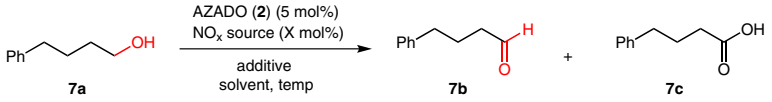
Figure 1 Structures of nitroxyl radicals

First, primary alcohol **7a** was subjected to the previously reported reaction conditions using easily available AZADO (**2**, 5 mol%) instead of 5-F-AZADO (**3**),[11] yielding a small amount of aldehyde **7b** and carboxylic acid **7c** together with dimeric ester **7d** and unreacted **7a** (Table 1, entry 1). To suppress the overoxidation by controlling the hydrate formation, the conditions for aerobic oxidation in an anhydrous solvent were investigated; the use of *tert*-butyl nitrite (TBN) instead of $NaNO_2$ was effective for the oxidation in MeCN under O_2 atmosphere (balloon).[10e] The production of **7d** was suppressed, and **7b** was obtained in a good yield. However, **7c** was produced in 21% yield (Table 1, entry 2). Considering that **7c** was produced by the oxidation of the hydrate formed from the reaction of **7b** with the H_2O produced from O_2, the reaction was repeated in the presence of dehydrating agents such as MS 3A and $MgSO_4$. From these trials, no significant positive result was obtained: The addition of MS 3A was detrimental to the reaction, and that of $MgSO_4$ slightly improved the yield of the desired product (Table 1, entries 3 and 4). Here, we noticed that most of the product **7c** was produced during the workup of the reaction: After the reaction mixture was concentrated using a rotary evaporator after the completion of the reaction, the yield of **7c** substantially increased. We assumed that the oxidation of **7b** to **7c** was caused by HNO_3 generated from NO_x during workup. Because the oxidation did not proceed in the presence of Et_3N (Table 1, entry 5), saturated aqueous $NaHCO_3$ was added to the reaction mixture after the completion of the reaction to neutralize the acidity of HNO_3 (Table 1, entry 6). Thus, the production of **7c** was suppressed, and **7b** was isolated in 92% yield. The oxidation efficiently proceeded under an air atmosphere instead of an O_2 atmosphere (Table 1, entry 7). The oxidation also proceeded at room temperature, affording **7b** in 93% yield, even though the reaction time was extended to ten hours (Table 1, entry 8). TEMPO-catalyzed oxidation was slow, affording **7b** in 25% yield even after 24 hours (Table 1, entry 9)

With the optimal conditions in hand, the selective oxidation of a variety of primary alcohols was investigated (Table 2).[15] Not only simple straight-chain alcohols were selectively oxidized to the corresponding aldehydes in high yields, but also hindered neopentyl alcohols were selectively oxidized (Table 2, entries 1–7). Because the oxidation of **15a**–**17a** afforded the desired products in low-to-moderate yields, nor-AZADO (**4**) was used as the catalyst instead of AZADO (**2**).

Nor-AZADO (**4**) efficiently catalyzed the aerobic oxidation of these alcohols, providing the corresponding alde-

Table 1 Optimization of Reaction Conditions



Entry	NO_x (mol%)	Additive	Oxidant	Solvent	Temp (°C)	Time (h)	**7b** (%)[a]	**7c** (%)[a]
1	$NaNO_2$ (10)	none	air	AcOH	r.t.	12	9	22
2	TBN (20)	none	O_2	MeCN	50	2	77	21
3	TBN (20)	MS 3A	O_2	MeCN	50	6	10	trace
4	TBN (20)	$MgSO_4$	O_2	MeCN	50	2	83	10
5	TBN (20)	Et_3N	O_2	MeCN	50	2	0	0
6	TBN (20)	none[b]	O_2	MeCN	50	2	92	trace
7	TBN (20)	none[b]	air	MeCN	50	2	88	trace
8	TBN (20)	none[b]	air	MeCN	r.t.	10	93	trace
9[c]	TBN (20)	none[b]	air	MeCN	r.t.	24	25	0

[a] Isolated yield.
[b] Saturated aqueous $NaHCO_3$ was added after the reaction.
[c] 5 mol% TEMPO was used as a catalyst.

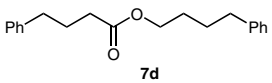
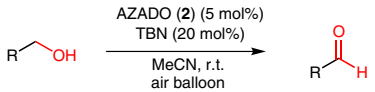
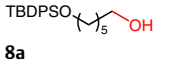
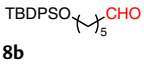
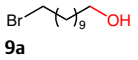
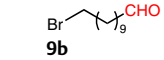
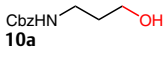
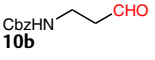
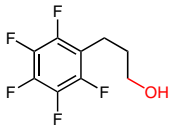
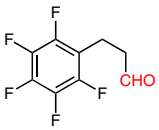
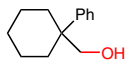
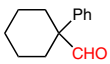
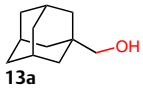
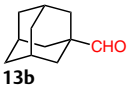
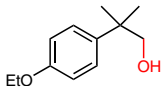
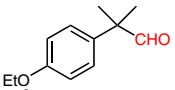
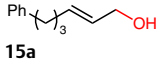
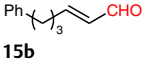
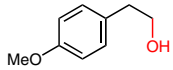
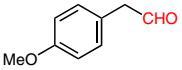
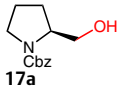
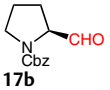
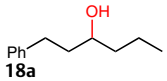
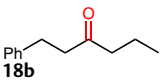


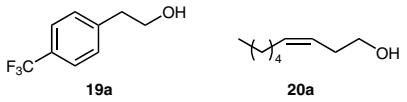
Table 2 Selective Aerobic Oxidation of Primary Alcohols with Catalytic Amounts of AZADO (**2**)/TBN or Nor-AZADO (**4**)/TBN in MeCN



Entry	Alcohol	Product	Time (h)	Yield (%)[a]
1	 **8a**	 **8b**	24	86
2	 **9a**	 **9b**	12	89
3	 **10a**	 **10b**	10	85
4	 **11a**	 **11b**	9	80
5	 **12a**	 **12b**	8	92
6	 **13a**	 **13b**	10	91
7	 **14a**	 **14b**	24	93
8	 **15a**	 **15b**	24 9	79 87[b]
9	 **16a**	 **16b**	9	86[b]
10	 **17a**	 **17b**	24 7	24 85[b]
11	 **18a**	 **18b**	6	90

[a] Isolated yield.
[b] 5 mol% of nor-AZADO (**4**) was used as the catalyst.

hydes **15b–17b** in high yields (Table 2, entries 8–10). It was also confirmed that the racemization of **17b** did not occur during the reaction. Secondary alcohol **18a** was also efficiently oxidized to ketone **18b** (Table 2, entry 11). However, in the oxidation of CF_3-susbstituted electron-deficient homobenzylic alcohol **19a** and homoallylic alcohol **20a**, a large amount of the starting material was recovered together with a small amount of unidentified products (Figure 2). Since **19b** and **20b** have an activated methylene, they might react with the catalyst, and lead to a deactivation of the reaction.[11b,c]



19a **20a**

Figure 2 Limitation of substrate scope

In conclusion, we developed a method for the chemoselective aerobic oxidation of primary alcohols to the corresponding aldehydes. The use of TBN as the cocatalyst enables the aerobic oxidation in an aprotic solvent such as MeCN, which is effective for the selective oxidation of primary alcohols to the corresponding aldehydes. The overoxidation to the corresponding carboxylic acids occurs during the workup, which was effectively suppressed by the addition of saturated aqueous $NaHCO_3$ after the completion of the reaction. In some cases, nor-AZADO catalyzed the oxidation reaction more efficiently than AZADO. These oxidation methods would expand the substrate scope of nitroxyl-radical-catalyzed aerobic oxidation.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588155.

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(15) **4-Phenylbutanal (7b); Typical Procedure**

To a solution of 4-phenylbutan-1-ol (**7a**, 45.8 mg, 0.305 mmol) and AZADO (**2**, 2.36 mg, 15.5 μmol) in MeCN (1.5 mL) was added TBN (92%, 7.9 μL, 61 μmol). The reaction mixture was stirred under an air atmosphere at r.t for 10 h. After the addition of a saturated aqueous $NaHCO_3$ solution (3 mL), the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane–EtOAc, 20:1) to give 4-phenylbutanal (**7b**) as a colorless oil; 42.0 mg (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.56 (t, *J* = 1.6 Hz, 1 H), 7.34–7.25 (m, 2 H), 7.24–7.16 (m, 3 H), 2.66 (t, *J* = 7.6 Hz, 2 H), 2.45 (dt, *J* = 7.6, 1.6 Hz, 2 H), 1.97 (quint, *J* = 7.6 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.3, 140.2, 127.5, 125.1, 42.2, 34.0, 22.7.

3-Pentafluorophenylpropanal (11b)

Colorless oil; 66.4 mg (80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 3.03 (t, *J* = 7.2 Hz, 2 H), 2.80 (t, *J* = 7.2 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4, 145.0 (dm, *J* = 245 Hz), 140.0 (dm, *J* = 243 Hz), 137.5 (dm, *J* = 251 Hz), 113.3 (td, *J* = 18.1, 3.8 Hz), 42.5, 15.1. HRMS (DART): *m/z* calcd for $C_{18}H_{14}F_{10}NO_3{\cdot}NH_4$ [2M + NH_4]$^+$: 466.0865; found: 466.0858.

4-Methoxyphenylacetaldehyde (16b)

Pale yellow oil; 56.8 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (t, *J* = 2.0 Hz, 1 H), 7.17–7.09 (m, 2 H), 6.95–6.85 (m, 2 H), 3.80 (s, 3 H), 3.62 (d, *J* = 2.0 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 158.9, 130.6, 123.7, 114.4, 55.2, 49.7.