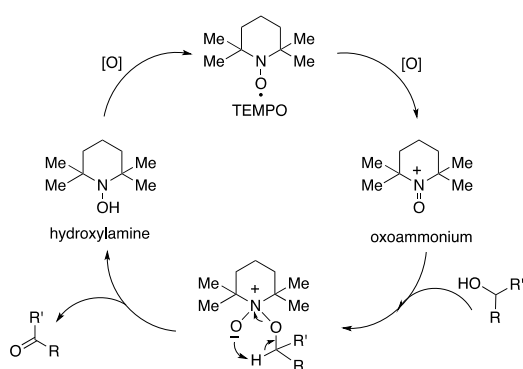# Chemoselective Oxidation by Electronically Tuned Nitroxyl Radical Catalysts**

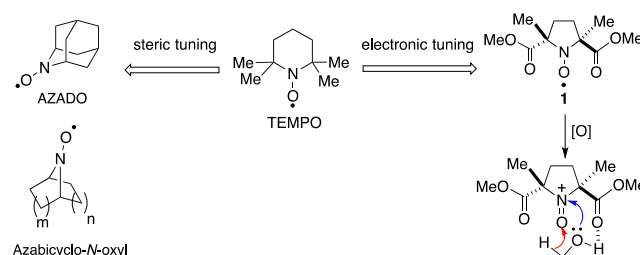*Shohei Hamada, Takumi Furuta, Yoshiyuki Wada, and Takeo Kawabata*

Metal-free processes for the oxidation of alcohols to the corresponding carbonyl compounds have been receiving increasing attention in current organic synthesis. Especially, 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) has been widely employed as a catalyst for the oxidation of alcohols under environmentally benign conditions.[1] Although TEMPO has been known to be useful for the selective oxidation of primary alcohols in the presence of secondary alcohols,[2] it has difficulties in catalyzing oxidation of sterically hindered secondary alcohols. The difficulty in the oxidation of secondary alcohols by TEMPO is associated with its steric environment around the active site.[3]

Scheme 1. Catalytic cycle of TEMPO-catalyzed oxidation of alcohols.

While the reactions of the sterically hindered secondary alcohols with the catalytically active oxoammonium group may be retarded by the steric interaction with the adjacent tetrasubstituted carbons (Scheme 1), the tetrasubstituted carbons are indispensable for the stability of the catalyst.[4] Iwabuchi and co-workers have solved this problem by virtue of Bredt's rule in an adamantyl skeleton (Scheme 2). 2-Azaadanantane N-oxyl (AZADO) and the derivatives have been found to be powerful catalysts for the oxidation of sterically hindered secondary alcohols. This is ascribed to the more favourable accessibility of alcohols to the oxoammonium species derived from

AZADO because of the lack of the sterically demanding tetrasubstituted carbons adjacent to the N-oxyl group (Scheme 2, steric tuning).[5] A similar approach employing azbicyclo-N-oxyls was reported by Onomura and co-workers.[6] Enhancement of the catalytic activity may alternatively be achieved by the electronic activation of the oxoammonium species. We envisaged that the oxoammonium species derived from nitroxyl radical **1** might be much more reactive than those derived from TEMPO due to the electron-withdrawing ester groups adjacent to the oxoammonium group (Scheme 2, electronic tuning).[7,8] Under these conditions, secondary alcohols are expected to readily react with the highly

reactive oxoammonium species, irrespective of the steric congestion around the active site. In addition to the electronic activation, the ester carbonyl groups are expected to facilitate the approach of the alcohols via hydrogen bonding interaction.[9]

Scheme 2. Steric- and electronic tuning of the activities of nitroxyl radical oxidation catalysts.

Nitroxyl radical **1** and its *meso*-isomer were prepared by Einhorn and co-workers in 2000.[10] To the best of our knowledge, however, the catalytic properties as an oxidation catalyst have never been reported. Racemic **1** was prepared according to the procedure reported by Einhorn and co-workers. Racemic nitoxyl radical **2** possessing a ester group was also prepared for estimating the effects of the electron-withdrawing ester group (Figure 1) (For the preparation of **2**, see Supporting Information). The redox potentials of nitroxyl radicals **1**, **2**, PROXYL, and TEMPO were measured by cyclic voltammetry, and found to be +761 mV, +550 mV, +339 mV, and +330 mV, respectively.[11] The increase in the number of electron-withdrawing ester groups resulted in the increase of the oxidation potentials. Thus, the nitroxyl radical with the higher oxidation potential would generate the more reactive oxoammonium species toward reductants (Scheme 2, red arrow) and Lewis bases (Scheme 2, blue arrow).[12] These backgrounds in mind, the properties of nitroxyl radicals **1**, **2**, and PROXYL as oxidation catalysts were investigated.
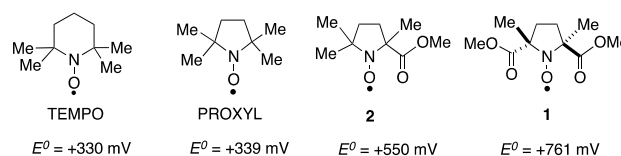
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E^0 = +330 mV E^0 = +339 mV E^0 = +550 mV E^0 = +761 mV

Figure 1. Redox potentials of nitroxyl radicals.

To investigate the catalytic properties of **1**, we began with the search for the cooxidant in the oxidation of 2-phenylethanol (**3**)

Scheme 3. Screening of the cooxidant in the oxidation of **3** catalyzed by **1**.
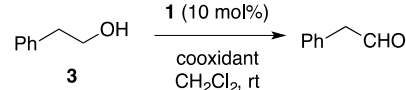
catalyzed by nitroxyl radical **1** (Scheme 3). After examining various oxidants including phenyl iodonium diacetate (PIDA), phenyl iodonium bis(trifluoroacetate) (PIFA), NaOCl, *m*CPBA, NCS, NIS, Trichloroisocyanuric acid (TCCA), and Koser reagent (TsOI(OH)Ph), PIFA was found to be most suitable for this purpose (For the details, see Supporting information). Treatment of **3** with 10 mol% of **1**, 1.3 equivalents of PIFA, and 4 equivalents of K$_2$CO$_3$ in CH$_2$Cl$_2$ at room temperature for 50 min gave phenylacetaldehyde in 72 % yield.

We then examined the properties of nitroxyl radicals **1**, **2**, PROXYL, and TEMPO as oxidation catalysts for various secondary alcohols using PIFA as a cooxidant (Table 1). Treatment of **4** with 1.3 equivalents of PIFA and 4 equivalents of K$_2$CO$_3$ in the presence of 10 mol% of **1** in CH$_2$Cl$_2$ at room temperature for 25 min gave bicyclo[2,2,1]hepta-2-one in a quantitative yield (entry 1). TEMPO, PROXYL, and **2** were used instead of **1** under the identical conditions for the transformation of **4**, except for the source of nitroxyl radical, to give the corresponding ketone in 20, 10, and 62% yield, respectively (entry 1). The catalytic activities were also found to be in the increasing order of TEMPO ~ PROXYL < **2** < **1** for the oxidation of secondary alcohols **5**-**7** (entries 2-4). The corresponding ketones were obtained in almost quantitative yields from the oxidation reactions of **5**-**7** catalyzed by **1**. While the desired ketones were obtained only in moderate yields (38~61%) by the oxidation of **8** and **9** catalyzed by **1**, the similar tendency of the catalytic activity was also observed (entries 5 and 6). Kinetic studies for the oxidation of **7** in the presence of nitroxyl radicals, PROXYL, **2**, and **1**, were performed under pseudo-first-order conditions using 10 equivalents of PIFA. The relative rates for the oxidation of **7** in the presence of PROXYL, **2**, and **1** were found to be ~0 : 1.0 : 2.7, respectively (For the details, see Supporting information). All of these data indicate that the catalytic efficiency of the nitroxyl radicals was parallel to their oxidation potentials, which is consistent with the electronic tuning hypothesis that nitroxyl radicals with the adjacent electron-withdrawing groups would generate the oxoammonium species with enhanced reactivity (Scheme 2).

Table 1. Catalytic properties of nitroxyl radicals TEMPO, PROXYL, **2**, and **1** for the oxidation of secondary alcohols with PIFA as a cooxidant.[a]

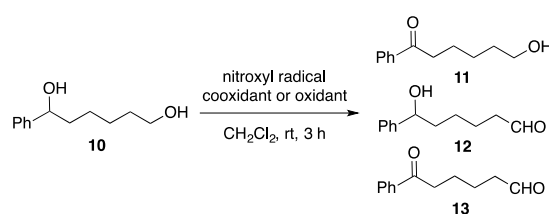| Entry	Substrate	Time	TEMPO	PROXYL	2	1
			Yield [%][b]			
1	**4**	25 min	20	10	62	100
2	**5**	25 min	44	29	93	100
3	**6**	45 min	11	10	85	94
4	**7**	45 min	0	0	53	100
5	**8**	18 h	4	1	31	38
6	**9**	18 h	20	18	36	61

[a] The reactions were run at the substrate concentration of 0.09 M.
[b] Yields determined by ^{1}H NMR of the crude reaction residue with sorbic acid as an internal standard.

Chemoselective oxidation of **10**, possessing a benzylic secondary hydroxy group and an aliphatic primary hydroxy group, was then examined (Table 2). Reaction of **10** with a TEMPO/PIDA system gave aldehyde **12** exclusively (>99 % ratio) among monooxidation products (71%) by the oxidation of the primary hydroxy group with concomitant formation of dioxidation product **13** (5%) (entry 1). Use of PIFA as a cooxidant increased the ratio of the oxidation of the benzylic hydroxy group, while the oxidation of the aliphatic primary hydroxy group was still predominant (71% ratio, entry 2). AZADO showed the similar chemoselectivity to that of TEMPO in the oxidation of **10** (entries 3 and 4). On the other hand, **1** showed totally different chemoselectivity. Product **11** from the oxidation of bezylic secondary hydroxy group of **10** was obtained exclusively (>99 % ratio) among the monooxidation products (77%) with concomitant formation of dioxidation product **13** (6%) (entry 5). Reaction at the lower temperature (−15 °C) slightly improved the mono/dioxidation ratio (81/4) maintaining the predominant oxidation (>99 % ratio) of the benzylic hydroxy group (entry 6). Although it has been known that hypervalent iodine reagents could promote chemoselective oxidation of benzylic alcohols in the presence of aliphatic alcohols,[13,14] PIFA itself did not promote oxidation of **10** in the absence of nitroxyl radical catalysts (entry 7). Dess-Martin periodinate promoted chemoselective oxidation of **10** to give **11** preferentially with moderate selectivity and yield (**11**:**12**=75:25, 55% yield for monooxidation, entry 8).
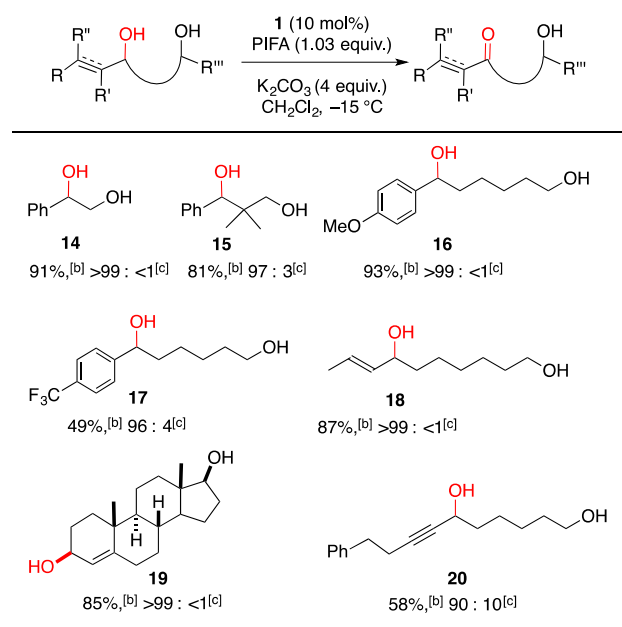
Table 2. Chemoselectivity in the oxidation of **10**. [a]

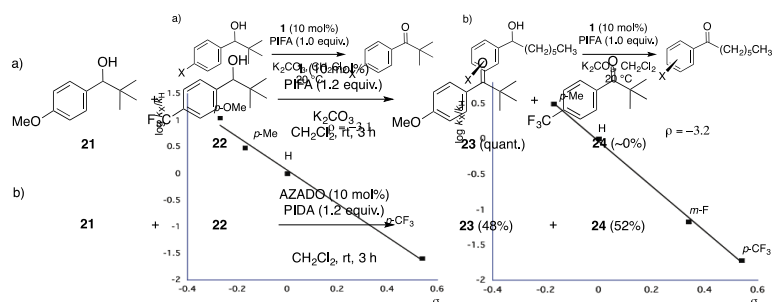| Entry	Nitroxyl radical (10 mol%)	Cooxidant or oxidant (1.03 equiv.)	Combined yield (%) of **11** and **12**[b] (**11:12** ratio)	Yield (%) of **13**[b]
1	TEMPO	PIDA	71 (<1 : >99)	5
2	TEMPO	PIFA[c]	52 (29 : 71)	14
3	AZADO	PIDA	63 (9 : 91)	14
4	AZADO	PIFA[c]	53 (50 : 50)	16
5	**1**	PIFA[c]	77 (>99 : <1)	6
6[d]	**1**	PIFA[c]	81 (>99 : <1)	4
7	–	PIFA[c]	<5 (-)	<5

| 8 | – | DMP[e] | 55 (75 : 25) | 24 |

Since highly selective oxidation of the benzylic secondary hydroxy group of **10** was observed with a **1**/PIFA system, the reagent system was applied to the chemoselective oxidation of various diols containing a secondary benzylic, allylic, or propargylic hydroxy group (Table 3). Highly chemoselective oxidation of the benzylic hydroxy group of diols **14**-**17** proceeded in the presence of a primary aliphatic hydroxy group by treatment with a **1**/PIFA system in CH_2Cl_2 at −15 °C (96:4->99:<1 ratio, 49-93% yield for monooxidation). It is worthy to note that diol **14** underwent chemoselective oxidation of the benzylic alcohol to give 2-hydroxy-1-phenylethanone without oxidative cleavage of the vicinal diol.[15] Allylic oxidation took place exclusively (>99:<1) in diols **18** and **19** in the presence of an aliphatic hydroxy group by treatment with a **1**/PIFA system. Diol **20** also underwent chemoselective oxidation of the propargylic hydroxy group (90:10).[16]

Table 3. Chemoselective oxidation of various diols.[a]

14	**15**	**16**
91%,[b] >99 : <1[c]	81%,[b] 97 : 3[c]	93%,[b] >99 : <1[c]

17	**18**
49%,[b] 96 : 4[c]	87%,[b] >99 : <1[c]

19	**20**
85%,[b] >99 : <1[c]	58%,[b] 90 : 10[c]

[a] The reactions were run at the substrate concentration of 0.05 M. [b] Combined yield of monooxidation products determined by ^{1}H NMR of the crude reaction residue with sorbic acid as an internal standard. [c] Ratio between the products from the oxidation of C-OH to that from C-OH.
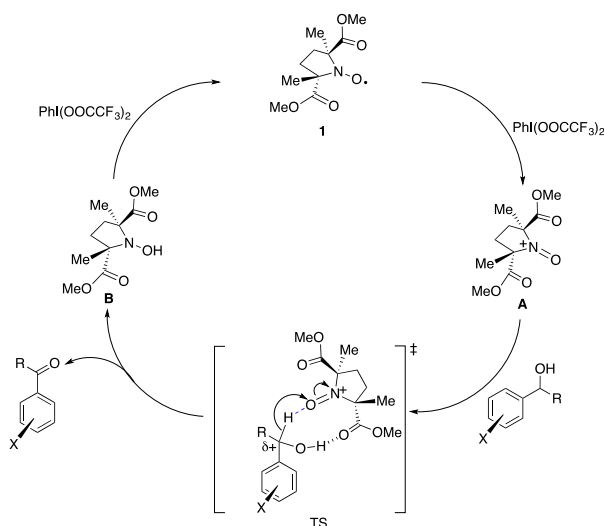
From the reaction scope in Table 3, the oxidation of **16** appeared to proceed faster than that of **17**. It seemed to be due to the different electronic nature of the aromatic rings. We then examined the competitive oxidation between **21** and **22** (Scheme 4). A 1:1 mixture of **21** and **22** was treated with 1.2 equivalents of PIFA in the presence of 10 mol% of **1** gave ketone **23** quantitatively as a sole oxidation product (Scheme 4a). On the other hand, oxidation by an AZADO/PIDA system afforded a mixture of almost equal amounts of ketones **23** and **24** (Scheme 4b). These contrastive results indicates that nitroxyl radical **1** promote oxidation via discrimination of the electronic nature of the substrate, while AZADO does via discrimination of the steric environment of the substrate. Thus, a **1**/PIFA system enables oxidative kinetic resolution of structurally similar but electronically distinct benzylic alcohols.

Scheme 4. a) Kinetic resolution of benzylic alcohols by chemoselective oxidation discriminating the electronic nature of the substrates.

Mechanistic aspects of the oxidation promoted by nitroxyl radical **1** were then investigated. Since **1** could promote the oxidation of benzylic alcohol in a highly chemoselective manner, mechanistic investigation was focused on the oxidation of benzylic alcohols. The kinetic isotope effect of the oxidation of benzylic alcohol **7** with a **1**/PIFA system was measured under pseudo-first-order conditions, and determined to be $k_H/k_D=4.3$ (for the detail, see Supporting information).[17] Hammett plots of the oxidation reactions of *tert*-butyl aryl carbinols (Figure 2a) and *n*-hexyl aryl carbinols (Figure 2b) catalyzed by **1** were performed (For the detail, see Supporting information). Linear relationship was observed in both cases between $\log(k_H/k_X)$ and substituent constants σ, and the reaction contants were found to be $\rho = -3.1$ and -3.2 for the former and the latter, respectively. The negatively large reaction constants indicate that the benzylic position is positively charged at the transition state. This indicates that the hydrogen atom α to the OH group is transferred as a hydride at the transition state.[18] Form these data, we propose the mechanism of the oxidation of benzylic secondary alcohols with a **1**/PIFA system (Scheme 5).

Due to the high oxidation potential of nitroxyl radical **1**, a strong oxidant, PIFA, is required for the generation of oxoammonium **A**. Since the oxoammonium group in **A** is expected to be highly electron deficient due to the adjacent ester groups, it readily suffers reductive transformation. Substrate approach may be assisted by the hydrogen-bonding interaction between the hydroxy group of the substrate alcohol and the ester carbonyl group of **A**. Hydride transfer from the benzylic C-H to the oxygen of the oxoammonium group in **A** would produce benzylic ketone and hydroxy amine **B**. Oxidation of **B** with PIFA would regenerate oxoammonium **A**. This mechanism seems limited only to the oxidation of secondary benzylic, allylic, and propargylic alcohols. At the moment, we have no definite view for the mechanism of the oxidation process of primary benzylic and aliphatic alcohols by a **1**/PIFA system.[19]

Scheme 5. A possible catalytic cycle for the oxidation of benzylic alcohols promoted by nitroxyl radical **1**.

Figure 2. Hammett plots for the oxidation of alkyl aryl carbinols.

In conclusion, we have disclosed intriguing catalytic properties of nitroxyl radical **1** as an oxidation catalyst. Despite the steric congestion around the nitroxyl radical group of **1**, it was found to be an effective oxidation catalyst for various secondary alcohols. This was assumed to be due to the high reactivity of the oxoammonium species generated from **1** based on the electronic tuning effects. Chemoselective oxidation of benzylic alcohols in the presence of aliphatic alcohols and oxidative kinetic resolution of structurally similar benzylic alcohols with different electronic nature were also performed.

[1] For reviews, see: a) A. E. J. de Nooy, A. C. Besemer, H. van Bekkum, *Synthesis* **1996**, 1153-1174; b) R. A. Sheldon, I. W. C. E. Arends, *Adv. Synth. Catal*. **2004**, *346*, 1051-1071; c) L. Tebben, A. Studer, *Angew. Chem. Int. Ed*. **2011**, *50*, 5034-5068.

[2] a) M. F. Semmelhack, C. S. Chou, D. A. Cortes, *J. Am. Chem. Soc.* **1983**, *105*, 4492-4494; b) R. Siedlecka, J. Skarzewski, J. Mlochowski, *Tetrahedron Lett.* **1990**, *31*, 2177-2180; c) N. J. Davis, S. L. Flitsch, *Tetrahedron Lett.* **1993**, *34*, 1181-1184; d) A. E. J. de Nooy, A. C. Basemer, H. van Bekkum, *Tetrahedron* **1995**, *51*, 8023-8032; e) A. E. J. de Nooy, A. C. Basemer, H. van Bekkum, *Carbohydrate Res.* **1995**, *269*, 89-98; f) J. Einhorn, C. Einhorn, F. Ratajczak, J. -L. Pierre, *J. Org. Chem.* **1996**, *61*, 7452-7454; g) A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974-6977; h) L. De Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2001**, *3*, 3041-3043; h) J. M. Hoover, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 16901-16910.

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[4] a) K. Adamic, D. F. Bowman, T. Gillan, K. U. Ingold, *J. Am. Chem. Soc.* **1971**, *93*, 902-908. b) D. F. Bowman, T. Gillan, K. U. Ingold, *J. Am. Chem. Soc.* **1971**, *93*, 6555-6561; c) J. Martinie-Hombrouck, A. Rassat, *Tetrahedron* **1974**, *30*, 433-436.

[5] a) M. Shibuya, M. Tomizawa, I. Suzuki, Y. Iwabuchi, *J. Am. Chem. Soc.* **2006**, *128*, 8412-8413; b) M. Shibuya, T. Sato, M. Tomizawa, Y. Iwabuchi, *Chem. Commun.* **2009**, 1739-1741. c) M. Shibuya, Y. Osada, Y. Sasano, M. Tomizawa, Y. Iwabuchi, *J. Am. Chem. Soc.* **2011**, *133*, 6497-6500.

[6] Y. Demizu, H. Shiigi, T. Oda, Y. Matsumura, O. Onomura, *Tetrahedron Lett.* **2008**, *49*, 48-52.

[7] Inokuchi and co-workers developed TEMPO derivatives possessing the OCOR group at the 4-position. These derivatives were expected be more reactive catalysts than TEMPO due to the inductive effects of the remote 4-OCOR groups, and have been effectively used for the oxidation of secondary alcohols in the presence of stoichiometric amount of Py HBr$_3$. The difference in E^0 between TEMPO and the 4-OCOCF$_3$ derivative was reported to be 121 mV. See: Z-W. Mei, T. Omote, M. Mansour, H. Kawafuchi, Y. Takaguchi, A. Jutand, S. Tsuboi, T. Inokuchi, *Tetrahedron* **2008**, *64*, 10761-10766.

[8] 5-F-AZADO was claimed to be a more reactive catalyst than AZADO due to the presence of an electron-withdrawing F atom at the remote position. The difference in E^0 between AZADO and the 5-F-AZADO was reported to be 177 mV. See reference 5c.

[9] We have proposed hydrogen bonding interaction between the catalyst and the substrate as the key for regioselective acylation promoted by functionalized pyrrolidinopyridine catalysts. See: a) T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata, H. Schedel, *J. Am. Chem. Soc.* **2007**, *129*, 12890-12895; b) K. Yoshida, K. Mishiro, Y. Ueda, T. Shigeta, T. Furuta, T. Kawabata, *Adv. Syn. Catal.* **2012**, *354*, 3291-3298; c) K. Yoshida, T. Shigeta, T. Furuta, T. Kawabata, *Chem. Commun.* **2012**, *48*, 6981-6983.

[10] J. Einhorn, C. Einhorn, F. Ratajczak, J-L. Pierre, *Synth. Commun.* **2000**, *30*, 1837-1848.

[11] The reference electrode was Ag/Ag$^+$. For the detail, see Supporting information.

[12] Niroxyl radical catalysts such as TEMPO derivatives possessing OCOR group at the 4-position (reference 7) and 5-F-AZADO (reference 8) have been reported to be more active catalysts compared to parent TEMPO and AZADO, respectively, due to the electron-withdrawing substituents. Because the electron-withdrawing substituents are located at the remote position from the active site (nitroxyl group), the electronic effects in these catalysts seems to be much smaller than the present case. The extent of the electronic effects may be suggested by the difference in their redox potentials: The differences in E^0 between TEMPO and the 4-OCOCF$_3$ derivative (reference 7), AZADO and the 5-F-AZADO (reference 8), and PROXYL and **1** (this work) were 121 mV, 177 mV, and 422 mV, respectively.

[13] a) H. Tohma. S. Takizawa, T. Maegawa, Y. Kita, *Angew. Chem. Int. Ed.* **2000**, *39*, 1306-1308; b) H. Tohma. Y. Kita, *Adv. Syn. Catal.* **2004**, *346*, 111-124.

[14] For a recent example of chemoselective oxidation of benzylic alcohol in the presence of aliphatic alcohol, see: H. Ruijun, L. Ming, W. Hegeng, W. Yanguang, *Chinese J. Chem.* **2009**, *27*, 587-592.

[15] Vicinal diols have been known to undergo oxidative cleavage in the presence of I (III) reagents, see: K. C. Nicolaou, V. A. Adsool, C. R. H. Hale, *Org. Lett.* **2010**, *12*, 1552-1555; b) M. Shibuya, T. Shibuta, H. Fukuda, Y. Iwabuchi, *Org. Lett.* **2012**, *14*, 5010-5013.

[16] Recently, chemoselective oxidation of allylic and benzylic alcohols with an *N*-hydroxyindole-Cu(I)-air system has been reported, see: S. Shen, V. Kartika, Y. S. Tan, R. D. Webster, K. Narasaka, *Tetrahedron Lett.* **2012**, *53,* 986-990.

[17] The kinetic isotope effect of the oxidation of an aliphatic alcohol, 3-phenylpropanol, with a **1**/PIFA system was also measured under pseudo-first-order conditions, and determined to be $k_H/k_D=1.7$ (for the detaildetail, see Supporting inforamtion).

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[19] The Hammet plot for the oxidation of benzylic primary alcohols (ArCH$_2$OH) did not show linearlity.

Oxidation catalyst

Shohei Hamada, Takumi Furuta,
Yoshiyuki Wada, and Takeo Kawabata*

Chemoselective Oxidation by Electronically Tuned Nitroxyl Radical Catalysts

Electronic tuning: Nitroxyl radical **1** was disclosed to be an efficient catalyst for the oxidation of secondary alcohols. The oxoammonium generated from **1** was highly reactive due to the adjacent electron-withdrawing ester groups (electronic tuning effect), irrespective of the steric congestion around the active site. Catalyst **1** promoted highly chemoselective oxidation of benzylic alcohols in the presence of aliphatic alcohols. The oxidation of the benzylic alcohols was proposed to proceed via rate-determining hydride transfer.