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Radical Reactions

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Chemoselective Oxidation by Electronically Tuned Nitroxyl Radical Catalysts**

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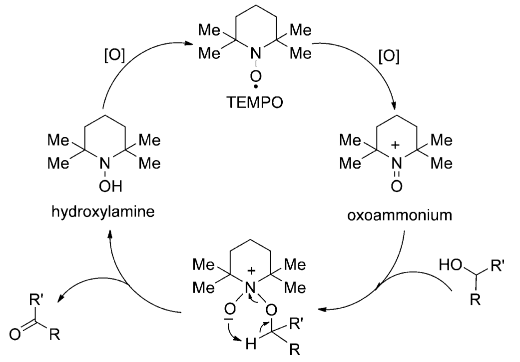
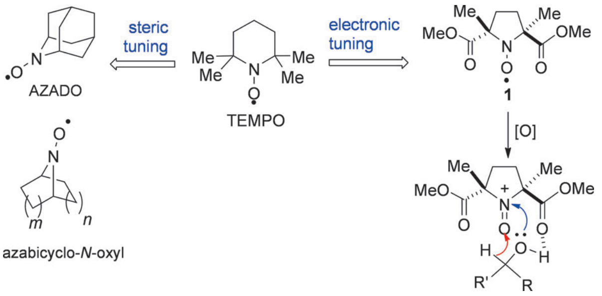
Metal-free processes for the oxidation of alcohols to the corresponding carbonyl compounds have been receiving increasing attention in organic synthesis. Specifically, 2,2,6,6-tetramethylpiperidyl-1-oxyl (TEMPO) has been widely employed as a catalyst for the oxidation of alcohols under environmentally 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 the steric environment around the active site.[3]

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 carbon atoms (Scheme 1), the tetrasubstituted carbon atoms 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 its derivatives have been found to be powerful catalysts for the oxidation of sterically hindered secondary alcohols. This ability is ascribed to the more favorable accessibility of alcohols to the oxoammonium species derived from AZADO because of the lack of the sterically demanding tetrasubstituted carbon atoms adjacent to the N-oxyl group (Scheme 2, left).[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 the nitroxyl radical **1** might be much more reactive than those derived from TEMPO because of the electron-withdrawing ester groups adjacent to the oxoammonium group (Scheme 2, right).[7,8] Under these reaction 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 through a hydrogen-bonding interaction.[9]



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



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

The 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. The racemic **1** was prepared according to the procedure reported by Einhorn and co-workers, and the racemic nitoxyl radical **2**, possessing an ester group, was also prepared for estimating the effects of the electron-withdrawing ester group (Figure 1; for the preparation of **2** see the Supporting Information). The redox potentials of the 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] With this information in

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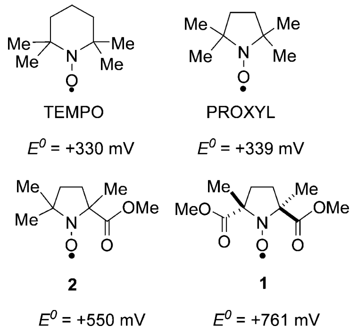
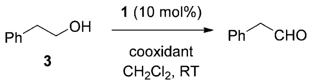


Figure 1. Redox potentials of nitroxyl radicals.

mind, the properties of the nitroxyl radicals **1**, **2**, and PROXYL as oxidation catalysts were investigated.

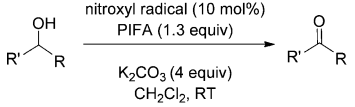
To investigate the catalytic properties of **1**, we began with the search for a cooxidant in the oxidation of 2-phenylethanol (**3**) catalyzed by **1** (Scheme 3). After examining various oxidants, including phenyl iodonium diacetate (PIDA), phenyl iodonium bis(trifluoroacetate) (PIFA), NaOCl, *m*CPBA, NCS, NIS, trichloroisocyanuric acid (TCCA), and the Koser reagent (TsOI(OH)Ph), PIFA was found to be most suitable for this purpose (see the Supporting Information). Treatment of **3** with 10 mol % of **1**, 1.3 equivalents of PIFA, and 4 equivalents of K_2CO_3 in CH_2Cl_2 at room temperature for 50 minutes gave phenylacetaldehyde in 72 % yield.

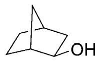
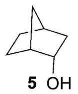
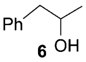
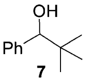
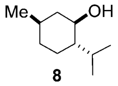
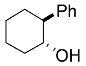


Scheme 3. Screening of the cooxidant in the oxidation of **3** catalyzed by **1**.

We then examined the properties of the 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_2CO_3 in the presence of 10 mol % of **1** in CH_2Cl_2 at room temperature for 25 minutes 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 reaction conditions for the transformation of **4**, except for the source of the nitroxyl radical, to give the corresponding ketone in 20, 10, and 62 % yield, respectively (entry 1). The catalytic activities were also found to increase in the order of TEMPO $\approx$ PROXYL $<$ **2** $<$ **1** for the oxidation of the 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**, a 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 about 0:1.0:2.7, respectively (see the Supporting information). All of these data indicate that the catalytic efficiency of the nitroxyl radicals parallels their oxidation potentials, and are consistent with the electronic tuning hypothesis that nitroxyl radicals with an adjacent electron-withdrawing group 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]

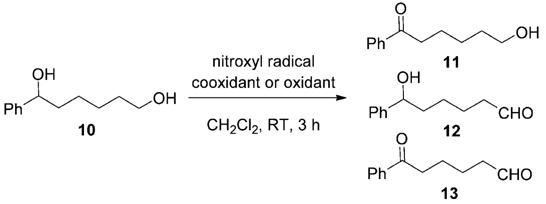


Entry	Substrate	*t*	Yield [%][b]			
			TEMPO	PROXYL	**2**	**1**
1	 **4**	25 min	20	10	62	100
2	 **5**	25 min	44	29	93	100
3	 **6**	45 min	11	10	85	94
4	 **7**	45 min	0	0	53	100
5	 **8**	18 h	4	1	31	38
6	 **9**	18 h	20	18	36	61

[a] The reactions were run at the substrate concentration of 0.09 M.
[b] Yields determined by ^{1}H NMR analysis of the crude reaction mixture using 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 the aldehyde **12** exclusively for the monooxidation products (71 %), by the oxidation of the primary hydroxy group, with concomitant formation of the 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 (entry 2). AZADO showed the similar chemoselectivity to that of TEMPO in the oxidation of **10** (entries 3 and 4). In contrast, **1** showed totally different chemoselectivity. The product **11** from the oxidation of bezylic secondary hydroxy group of **10** was obtained exclusively for the monooxidation products (77 %) with concomitant formation of **13** (6 %; entry 5). Reaction at the lower temperature (−15 °C) slightly improved the mono/dioxidation ratio (81:4), maintaining the predominant oxidation 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 che-

Table 2: Chemoselectivity in the oxidation of **10**.[a]



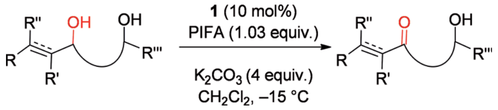
Entry	Nitroxyl radical (10 mol%)	Cooxidant or oxidant (1.03 equiv)	**11** and **12** Yield [%][b,c]	**13** Yield [%][b]
1	TEMPO	PIDA	71 (<1:>99)	5
2	TEMPO	PIFA[d]	52 (29:71)	14
3	AZADO	PIDA	63 (9:91)	14
4	AZADO	PIFA[d]	53 (50:50)	16
5	**1**	PIFA[d]	77 (>99:<1)	6
6[e]	**1**	PIFA[d]	81 (>99:<1)	4
7	–	PIFA[d]	<5 (–)	<5
8	–	DMP[f]	55 (75:25)	24

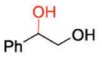
[a] Reactions were run at a substrate concentration of 0.05 M. [b] Yields determined by ^1H NMR analysis of the crude reaction mixture using sorbic acid as an internal standard. [c] Ratio of **11** to **12** given within parentheses. [d] K_2CO_3 (4 equiv) was added. [e] Run at −15 °C for 4 h. [f] Dess–Martin periodinate.

moselective oxidation of **10** to give **11** preferentially with moderate selectivity and yield (entry 8).

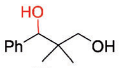
Since highly selective oxidation of the benzylic secondary hydroxy group of **10** was observed with a **1**/PIFA system, the reagent system was applied to the chemoselective oxidation of various diols containing either a secondary benzylic, or, allylic, or propargylic hydroxy group together with an aliphatic hydroxy group (Table 3). Highly chemoselective oxidation of the benzylic hydroxy group of the diols **14**–**17** proceeded in the presence of a primary aliphatic hydroxy group by treatment with the **1**/PIFA system in CH_2Cl_2 at −15 °C. Notably, the 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) for diols **18** and **19** in the presence of an aliphatic hydroxy group by treatment with the **1**/PIFA system. The diol **20** also underwent chemoselective oxidation of the propargylic hydroxy group (90:10).[16]

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

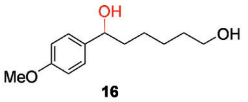




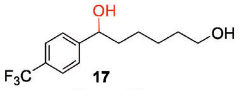
14
91%,[b] >99 : <1[c]



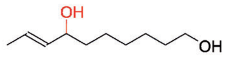
15
81%,[b] 97 : 3[c]



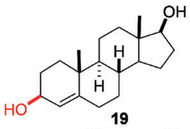
16
93%,[b] >99 : <1[c]



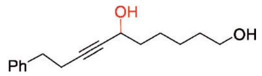
17
49%,[b] 96 : 4[c]



18
87%,[b] >99 : <1[c]



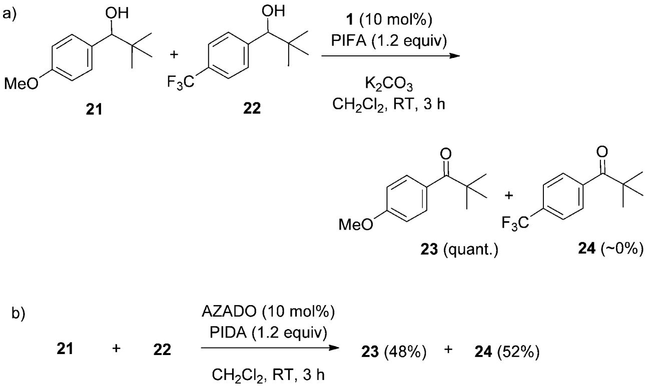
19
85%,[b] >99 : <1[c]



20
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 ^1H NMR spectroscopy of the crude reaction mixture using 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 result from 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**, and resulted in quantitative formation of the ketone **23** as the sole oxidation product (Scheme 4a). In contrast, oxidation by an AZADO/PIDA system afforded a mixture of almost equal amounts of the ketones **23** and **24** (Scheme 4b). These contrasting results indicate that **1** promotes oxidation by discrimination of the electronic nature of the substrate, while AZADO does so by 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 **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 $k_H/k_D = 4.3$ (see the 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 (see the Supporting information). A linear relationship was observed in both cases between $\log(k_X/k_H)$ 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 negative and large reaction constants indicate that the benzylic position is positively charged at

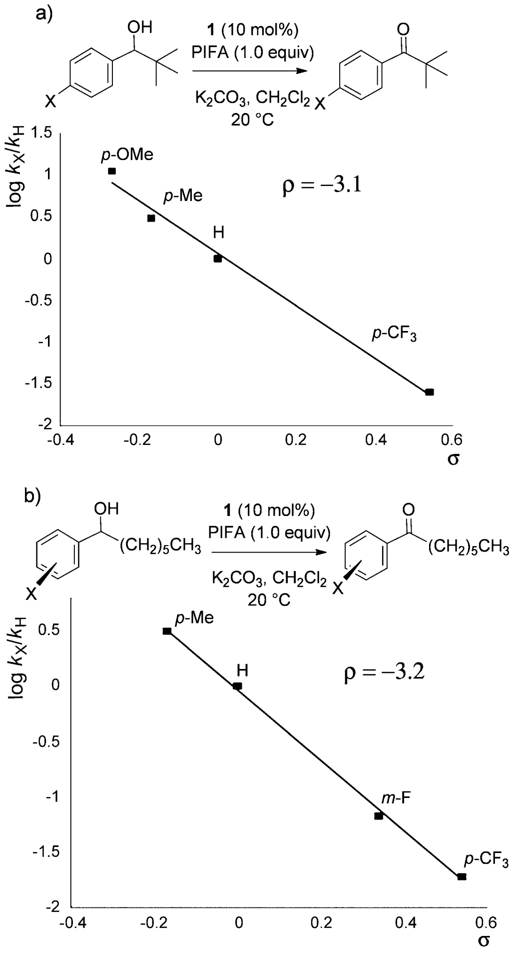
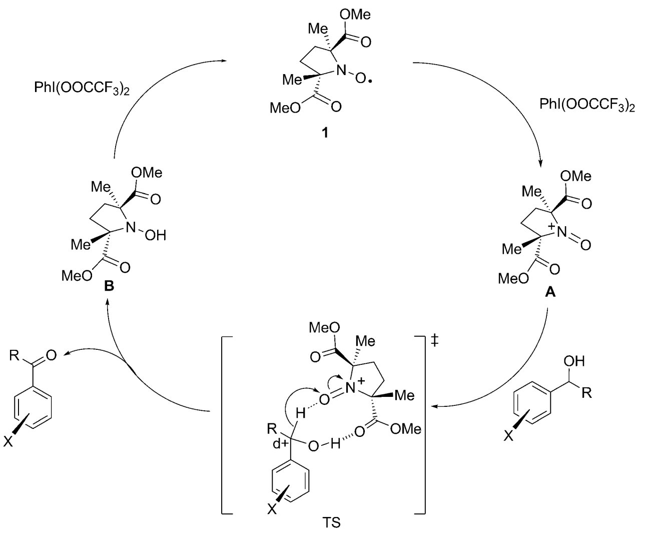


Figure 2. Hammett plots for the oxidation of alkyl aryl carbinols.

the transition state. This information indicates that the hydrogen atom α to the OH group is transferred as a hydride at the transition state.[18] From these data, we propose the mechanism of the oxidation of benzylic secondary alcohols with a **1**/PIFA system (Scheme 5).

Because of the high oxidation potential of **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 because of the adjacent ester groups, it readily undergoes 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 atom of the oxoammonium group in **A** would produce a benzylic ketone and hydroxy amine **B**. Oxidation of **B** with PIFA would regenerate **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 the **1**/PIFA system.[19]

In conclusion, we have disclosed intriguing catalytic properties of the nitroxyl radical **1** as an oxidation catalyst. Despite the steric congestion around the nitroxyl radical



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

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.

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[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 because of 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 because of 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 Ref. [5c].

[9] We have proposed a hydrogen-bonding interaction between the catalyst and the substrate as the key to 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. Synth. Catal.* **2012**, *354*, 3291 – 3298; c) K. Yoshida, T. Shigeta, T. Furuta, T. Kawabata, *Chem. Commun.* **2012**, *48*, 6981 – 6983.

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[11] The reference electrode was Ag/Ag^{+}. For details, see the Supporting information.

[12] Niroxyl radical catalysts such as TEMPO derivatives possessing OCOR group at the 4-position (Ref. [7]) and 5-F-AZADO (Ref. [8]) have been reported to be more active catalysts compared to the parent TEMPO and AZADO, respectively, because of the electron-withdrawing substituents. Because the electron-withdrawing substituents are located at a position remote 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 (Ref. [7]), AZADO and the 5-F-AZADO (Ref. [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.* **2000**, *112*, 1362 – 1364; *Angew. Chem. Int. Ed.* **2000**, *39*, 1306 – 1308; b) H. Tohma, Y. Kita, *Adv. Synth. 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, *Chin. J. Chem.* **2009**, *27*, 587 – 592.

[15] Vicinal diols have been known to undergo oxidative cleavage in the presence of I^{III} reagents, see: a) 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: 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 details see the Supporting Inforamtion).

[18] A hydride transfer mechanism has been proposed in TEMPO-mediated oxidation of alcohols based on computational studies: W. F. Bailey, J. M. Bobbitt, K. B. Wiberg, *J. Org. Chem.* **2007**, *72*, 4504 – 4509.

[19] The Hammet plot for the oxidation of benzylic primary alcohols ($ArCH_2OH$) did not show linearity.