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An Expeditious Entry to 9-Azabicyclo[3.3.1]nonane *N*-Oxyl (ABNO): Another Highly Active Organocatalyst for Oxidation of Alcohols

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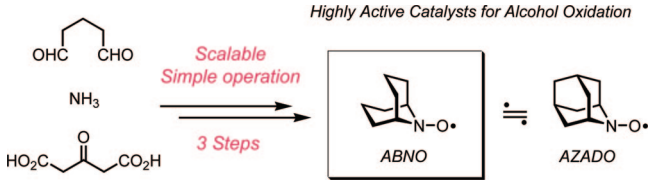
Received March 4, 2009



A practical, three-step synthetic route to 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO, **3**), an unhindered, stable class of nitroxyl radical, has been developed. ABNO exhibits a highly active nature compared with TEMPO in the catalytic oxidation of alcohols to their corresponding carbonyl compounds.

Since its discovery, the stable class of nitroxyl radicals, as exemplified by TEMPO (2,2,6,6-tetramethyl piperidinyl 1-oxyl (**1**); Figure 1), has been inspiring chemists to explore their novel uses in a wide range of molecular sciences.[1,2] The most dynamic behavior of nitroxyl radicals, their interconversion either to oxoammonium ions or to hydroxyl amines, is successfully exploited as a redox catalyst applicable to several synthetic transformations. In particular, TEMPO-catalyzed alcohol oxidations[3,4] have the highest priority in the contemporary pharmaceutical industry as efficient, mild, and environmentally acceptable methods.[5]

As part of our research program directed toward the development of novel organocatalysts for advanced organic synthesis, we recently reported that azaadamantane-type nitroxyl radicals, namely, 2-azaadamantane *N*-oxyl [AZADO (**2a**)] and 1-Me-AZADO (**2b**), are robust[6] alternatives to TEMPO with a markedly expanded substrate applicability (Figure 1).[7,8]

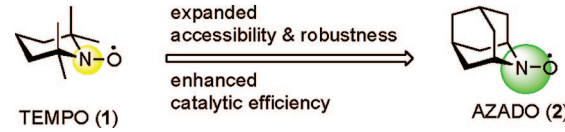


FIGURE 1. Design concept of AZADO.

We confirmed with some surprise that AZADOs exhibit extremely aggressive activities beyond our expectations and offer more than 20-fold higher catalytic efficiency in the oxidation of alcohols, including hindered secondary alcohols that TEMPO completely fails to efficiently oxidize to their corresponding products.[7] A preliminary structure−activity comparison between AZADO, 1-Me-AZADO, and 1,3-dimethyl-AZADO indicated that the steric effect near the active center exerts a critical impact on catalytic efficiency.[7]

Although we have developed gram-scale routes to AZADO (**2a**) and 1-Me-AZADO (**2b**) starting from commercially available 1,3-adamantanediol via a ten-step synthesis and a six-step synthesis, respectively,[7] we inquired into a more readily available alternative to AZADOs for the further development of nitroxyl radical-based methodologies in organic chemistry. As a logical extension, we were interested in bicyclic unhindered nitroxyl radicals,[9,10] such as 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO, **3**),[11] 8-azabicyclo[3.2.1]octane *N*-oxyl (ABOO, **4**),[11,12] and 7-azabicyclo[2.2.1]heptene *N*-oxyl (ABHO, **5**) (Figure 2).[12−14]

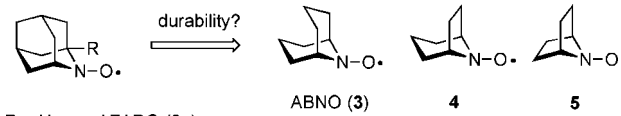


FIGURE 2. Bicyclic nitroxyl radicals.

With accumulated knowledge indicating the stability of bridged-bicyclo *N*-oxyls being in the order of ABNO > ABOO > ABHO,[14−16] we chose ABNO as the focus of this study.[17]

(1) Likhtenshtein, G. I.; Yamauchi, J.; Nakatsuji, S.; Smirnov, A. I.; Tamura, R. *Nitroxides*; Wiley-VCH, Weinheim, Germany, 2008.

(2) For recent reviews, see: (a) Vogler, T.; Studer, A. *Synthesis* **2008**, 1979–1993. (b) Galli, C.; Gentili, P.; Lanzalunga, O. *Angew. Chem., Int. Ed.* **2008**, *47*, 4790–4796. (c) Sciannamea, V.; Jérôme, R.; Detrembleur, C. *Chem. Rev.* **2008**, *108*, 1104–1126. (d) Soule, B. P.; Hyodo, F.; Matsumoto, K.; Simone, N. L.; Cook, J. A.; Krishna, M. C.; Mitchell, J. B. *Free Radical Biol. Med.* **2007**, *42*, 1632.

(3) (a) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051–1071. (b) de Nooy, A. E.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1174.

(4) (a) Wang, X.; Liu, R.; Jin, Y.; Liang, X. *Chem.—Eur. J.* **2008**, *14*, 2679–2685. (b) Wang, N.; Liu, R.; Chen, J.; Liang, X. *Chem. Commun.* **2005**, 5322–5324. (c) Liu, R.; Liang, X.; Dong, C.; Hu, X. *J. Am. Chem. Soc.* **2004**, *126*, 4112–4113. (d) Miller, R. A.; Hoerner, R. S. *Org. Lett.* **2003**, *5*, 285–287. (e) Bolm, C.; Magnus, A. S.; Hildebrand, J. P. *Org. Lett.* **2000**, *2*, 1173–1475. (f) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977. (g) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J. L. *J. Org. Chem.* **1996**, *61*, 7452–7454. (h) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970–2972. (i) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559. (j) Semmelhack, M. F.; Schmid, C. R.; Cortés, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374–3376. (k) Cella, J. A.; Kelley, J. A.; Kenehan, E. F. *J. Org. Chem.* **1975**, *40*, 1860–1862.

(5) (a) Caron, S.; Drugger, S. G.; Ruggeri, S. G.; Ragan, J. A.; Brown Ripin, D. H. *Chem. Rev.* **2006**, *106*, 2943. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337. (c) Drugger, R. W.; Ragen, J. A.; Brown Ripin, D. H. *Org. Proc. Res. Dev.* **2005**, *9*, 253.

(6) Moad, G.; Rizzardo, E.; Solomon, D. H. *Tetrahedron Lett.* **1981**, *22*, 1165–1168.

(7) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412–8413.

(8) (a) Shibuya, M.; Sato, T.; Tomizawa, M.; Iwabuchi, Y. *Chem. Commun.* **2009**, 1739–1741. (b) Iwabuchi, Y. *J. Synth. Org. Chem. (Tokyo)* **2008**, *66*, 1076–1084. (c) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *Org. Lett.* **2008**, *10*, 4715–4718. (d) Shibuya, M.; Tomizawa, M.; Iwabuchi, Y. *J. Org. Chem.* **2008**, *73*, 4750–4752.

10.1021/jo900486w CCC: $40.75
Published on Web 05/28/2009

We herein report a scalable, three-step synthesis of ABNO and the scope of ABNO-catalyzed alcohol oxidations.[18]

With our vision of evolving a protecting group-free route to ABNO (**3**), we made a small modification of the historical Robinson−Schöpf reaction and observed marked improvement in the synthesis of norpseudopelletierine (**7**) (Scheme 1).[19−21] Thus, stirring a mixture of glutaraldehyde, acetonedicarboxylic acid (**6**), and 23% ammonia−water at rt for 35 h completed (monitored by NMR) not only the Robinson−Schöpf annulation,[19] but also the subsequent decarboxylation to give, after lyophilization, **7** as a yellow powder. Note that the "salt-free" conditions liberated us from laborious operations to isolate polar amine **7** from the reaction mixture. The Huang-Minlon modification of the Wolff−Kishner reduction of **7** was found to facilitate the expedient distillation of azabicyclononane (**8**) from the reaction mixture together with water.[22] The chloroform extracts of the distillate were dried over potassium carbonate, concentrated, and subjected to conventional oxidation conditions with cat. Na_2WO_4 and urea hydrogen peroxide (UHP) to furnish, after silica gel chromatography, ABNO (**3**) in an overall yield of 42%, thereby establishing the shortest synthesis route for ABNO.

SCHEME 1. Three-Step Preparation Method of ABNO

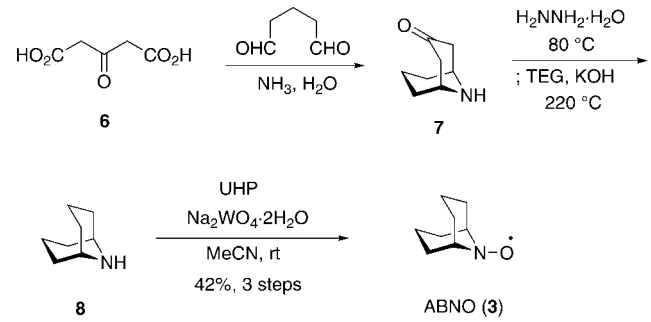
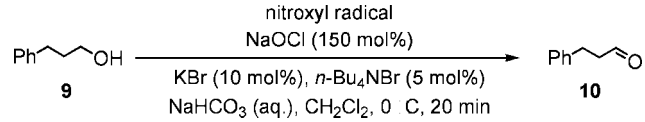


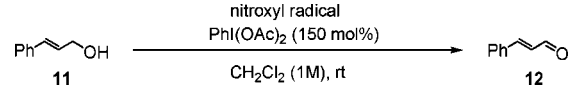
TABLE 1. Comparison of Catalytic Efficiencies of TEMPO and 1-Me-AZADO and ABNO Under Anelli's Condition



		yield (%)		
entry	mol %	TEMPO	1-Me-AZADO	ABNO
1	1	90	91	90
2	0.1	88	90	88
3	0.01	23	91	85
4	0.003		81[a]	41[a]
5	0.001		59[b]	28[b]
6	no catalyst			2

[a] Reaction time was 30 min. [b] Reaction time was 60 min.

TABLE 2. Comparison of Catalytic Efficiencies of TEMPO and 1-Me-AZADO and ABNO Under Margarita's Condition



		yield/reaction time		
entry	mol %	TEMPO	1-Me-AZADO	ABNO
1	10	95%/90 min	95%/<5min	92%/<5 min
2	1	43%/360 min	93%/40min	91%/30 min

Having established a markedly improved synthesis of ABNO, we evaluated the reactivity of ABNO by comparing it with those of TEMPO and 1-Me-AZADO. We first examined the applicability of Anelli's conditions using NaOCl as the bulk oxidant,[4h,i] which has acquired general popularity in TEMPO oxidations for its practicality.[7] Although apparently the same results were obtained for the catalytic oxidation of 3-phenypropanol (**9**) when catalysts were loaded either in 1 or 0.1 mol % (Table 1, entries 1 and 2, respectively), significant differences were ascertained when the catalyst loadings were decreased to 0.01 mol %: TEMPO showed a decline, whereas ABNO and 1-Me-AZADO maintained their performances, demonstrating the reactive nature of the unhindered class of nitroxyl radicals (Table 1, entry 3). Note that 1-Me-AZADO gave apparently better results than ABNO under conditions with a catalyst loading below 0.003 mol %, indicating the robustness of the 2-azaadamantane skeleton over the 9-azabicyclo[3.3.1]nonane.[23,24]

We next examined Margarita's conditions using $PhI(OAc)_2$ as the co-oxidant,[4f] which is useful for oxidations of substrates

(9) Hindrance around a nitroxyl radical center was believed to be an essential requirement for a nitroxyl radical to be stable, because simple nitroxyl radicals with an α-hydrogen underwent rapid disproportionation to their corresponding nitrone and hydroxyl amine.

(10) Dupeyre and Rassat reported the synthesis of norpseudopelletierine *N*-oxyl {9-azabicyclo[3.3.1]nonane-3-one *N*-oxyl} as the first stable unhindered nitroxyl radical, in which any nitrone formation would be prohibited by Bredt's rule. Since then, a panel of bridged-bicyclic unhindered nitroxyl radicals have been synthesized. (a) Dupeyre, R. M.; Rassat, A. *Tetrahedron Lett.* **1975**, *16*, 1839–1840. (b) Dupeyre, R. M.; Rassat, A. *J. Am. Chem. Soc.* **1966**, *88*, 3180–3181.

(11) Mendenhall, G. D.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 6395–6400.

(12) Aurich, H. G.; Czepluch, H. *Tetrahedron Lett.* **1978**, *19*, 1187–1190.

(13) Rychnovsky and Farmer et al. demonstrated for the first time that unhindered nitroxyl radicals indeed worked as catalysts in alcohol oxidations. However, since their research interest was focused on the development of enantioselective catalysts, the catalytic efficiency of the elaborated C2-symmetric derivative of ABNO was not further examined. Graetz, B.; Rychnovsky, S.; Leu, W.-H.; Farmer, P.; Lin, R. *Tetrahedron: Asymmetry* **2005**, *16*, 3584–3598.

(14) In 2008, Onomura et al. reported the synthesis of a panel of azabicyclo *N*-oxyls and preliminary results on the electrochemical oxidation of alcohols using them as mediators to confirm their potential for the electrochemical oxidation of hindered secondary alcohols. However, they offer few comments on the efficiency of azabicyclo nitroxyl radicals toward oxidation of various alcohols under chemical conditions. (a) Demizu, Y.; Shiigi, H.; Oda, T.; Matsumura, Y.; Onomura, O. *Tetrahedron Lett.* **2008**, *49*, 48–52. (b) Shiigi, H.; Mori, H.; Tanaka, T.; Demizu, Y.; Onomura, O. *Tetrahedron Lett.* **2008**, *49*, 5247–5251.

(15) Ingold et al. reported that the decomposition rate of 9-azabiclo[3.3.1]nonane *N*-oxyl (ABNO) (**3**) was very slow, while 8-azabicylo[3.2.1]octane *N*-oxyl (**4**) dimerized irreversibly.[11]

(16) Rychnovsky et al. also reported that 2,5-dimethylbicyclo[2.2.1]heptane *N*-oxyl (**5**) was too unstable to isolate.

(17) We also synthesized 8-azabicyclo[3.2.1]octane and 7-azabicyclo[2.2.1]heptane and attemped their oxidation to the corresponding nitroxyl radicals. However, we failed to isolate these nitroxyl radicals; instead, the corresponding hydroxylamines were recovered.

(18) Iwabuchi, Y.; Shibuya, M.; Tomizawa, M. U.S. 20080221331, JP 20082128532.

(19) (a) Cope, A. C.; Dryden, H. L., Jr.; Howell, C. F. *Organic Synthesis*; Wiley: New York, 1963; Collect Vol. IV, p 816. (b) Cope, A. C.; Dryden, H. L., Jr.; Overberger, C. G.; D'Addieco, A. A. *J. Am. Chem. Soc.* **1951**, *73*, 3416–3418. (c) Menzies, R. C.; Robinson, R. *J. Chem. Soc.* **1924**, *191*, 2163. (d) Schöpf, C.; Lehmann, G. *Ann.* **1935**, *618*, 1.

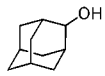
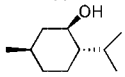
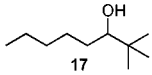
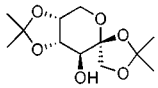
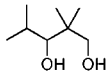
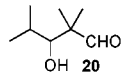
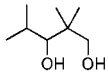
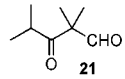
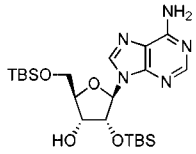
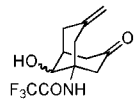
(20) (a) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4992–4996. (b) Nelsen, S. F.; Petillo, P. A.; Rumack, D. T. *J. Am. Chem. Soc.* **1990**, *112*, 7144–7147. (c) Nelsen, S. F.; Kessel, C. R.; Brien, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 702–711.

(21) (a) Hamada, Y.; Okamoto, N.; Hara, O. *Heterocycles* **2000**, *52*, 929–934. (b) Momose, T.; Toshima, M.; Toyooka, N.; Hirai, Y.; Eugster, C. H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1307–1313.

(22) Huang-Minlon, *J. Am. Chem. Soc.* **1949**, *71*, 3301.

(23) We speculate that the difference came from the stability of the oxoammonium ion generated in the catalytic cycle. For notes on the instability of 9-oxo-9-azabicyclo[3.3.1]nonane oxoammonium ion, see ref 20c.

TABLE 3. The Scope of ABNO

entry	substrate	method[a]	yield (%)[b] TEMPO	1-Me-AZADO	**ABNO**
1	 **13**	A	83	94	93
2	 **14**	A	16	99	100
3	 **15**	A	trace	95	94
4	 **16**	A	13	95	93
5	 **17**	A	15	93	95
6	 **18**	A	8	99	98
7	 **19**	A[c] (NaOCl 125 mol%)	25	 **20** 96	72[d]
8	 **19**	A[e] (NaOCl 300 mol%)	57[f]	 **21** 87	82
9	 **22**	B	12	100	91
10[g]	 **23**	B	ND[h]	36[i]	98

[a] Method A: Reactions were catalyzed by 1 mol % nitroxyl radicals with NaOCl (150 mol %), KBr (10 mol %), nBu$_4$NBr (5 mol %), aq NaHCO$_3$ in H_2Cl_2 at 0 °C for 20 min. Method B: Reactions were catalyzed by 5 mol % nitroxyl radicals with 330 mol % of PhI(OAc)$_2$ in CH_2Cl_2 (0.1 M) for 14 h at rt. [b] Isolated yield. [c] 125 mol %of NaOCl was used. [d] 8% of **21** was also produced. [e] 300 mol % of NaOCl was used. [f] Yield of **20**. [g] Reaction was catalyzed by 10 mol % of nitroxyl racial with 200 mol % of PhI(OAc)$_2$ in CH_2Cl_2 (0.3 M) for 2 h at room temperature. [h] Not determined. [i] Reaction time was 24 h.

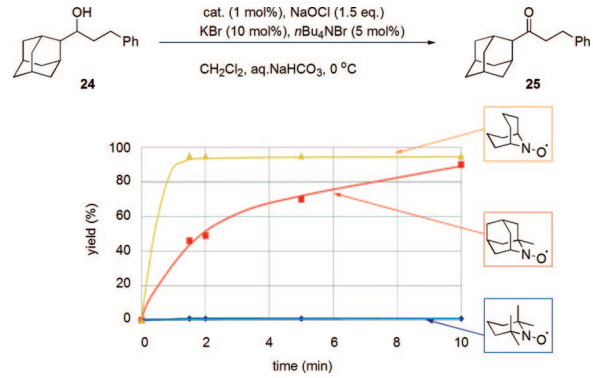
containing electron-rich moieties, such as alkenes and aromatic rings. We confirmed a similar tendency in catalytic efficiencies: TEMPO < ABNO ≈ 1-Me-AZADO.[7]

We then explored the scope of ABNO chemistry, which is summarized in Table 3. The use of 1 mol % of ABNO gives similar results to 1-Me-AZADO under Anelli's conditions (Method A, Table 3, entries 1−6). It is interesting to point out that both 1-Me-AZADO and ABNO exhibited marked preference on oxidation of primary alcohol over secondary alcohol: in the case of oxidation of diol **19** carrying a primary and secondary alcohol moiety employing a slight excess (125 mol %) NaOCl, both 1-Me-AZADO and ABNO catalyzed selective oxidation of the primary alcohol moiety to afford aldol **20** in 96% and 72% yield, respectively (Table 3, entry 7). In the case of using 300 mol % NaOCl, 1-Me-AZADO and ABNO rapidly oxidized both the alcohol portions to give keto-aldehyde **21** in 87% and 82% yield, respectively (Table 3, entry 8).

Nucleic derivative **22** was also effectively oxidized under Margarita's conditions (Method B, Table 3, entry 9). Notably, ABNO oxidized the congested bicyclic substrate **23** with marked efficiency while 1-Me-AZADO completely failed to oxidize it (Table 3, entry 10).

During the above-mentioned experiments, we noticed some kinetic superiority of ABNO compared with 1-Me-AZADO (Table 2, entry 2; Table 3, entries 4 and 5) that led us to conduct a close comparison of the catalytic efficiencies of ABNO and 1-Me-AZADO using a designed substrate, **24**, for analysis. It was found that ABNO completely consumed the alcohol immediately after the addition of the bulk oxidant, while 1-Me-AZADO took 10 min to complete the reaction (Scheme 2).

SCHEME 2. Comparison of the Catalytic Efficiency



This result strongly suggests that ABNO could be advantageous in the oxidation of substrates that are challenging because of structural complexity.

In summary, we have disclosed a readily accessible, three-step synthesis of a less-hindered persistent class of nitroxyl radical ABNO and its scope as a highly aggressive catalyst for the oxidation of alcohols. Although ABNO showed a slight decline in terms of catalytic turnover compared with 1-Me-AZADO, the kinetically more efficient ABNO may find use in alcohol oxidations. The ready availability of ABNO will also inspire its novel application in many branches of material science.

Experimental Section

Synthesis of 9-Aza-bicyclo[3.3.1]nonane *N*-Oxyl (ABNO 3). To a solution of acetonedicarboxylic acid **6** (2.1 g, 14.4 mmol) in H_2O (50 mL) was slowly added 23% ammonia−water (4.5 mL) at 0 °C. Then glutaraldehyde (1.44 g, 14.4 mmol) in water (52.5 mL) was added over 1 h. After the solution was stirred for 35 h at rt, the solvent (H_2O) was removed under freeze-drying condition. The resulting yellow solid **7** was used in the next reaction without further purification.

(24) We have recently reported the synthesis of stable oxoammonium salts (1-Me-AZADO$^+$Cl$^-$ and 1-Me-AZADO$^+$BF$_4^-$) and their use in the efficient one-pot oxidation of primary alcohols to carboxylic acids.[8a]

The mixture of **7** and $H_2NNH_2 \cdot H_2O$ (2.2 mL, 43.1 mmol) was stirred at 80 °C for 2 h. To a solution of KOH (8.0 g, 144 mmol) in triethyleneglycol (21 mL) in a two-necked round-bottomed flask distillation apparatus, the solution of **7** and $H_2NNH_2 \cdot H_2O$ was added dropwise. After the mixture was stirred at 220 °C for 30 min, H_2O (50 mL) was added dropwise over 2 h at 220 °C. During the reaction, the product, amine **8**, was distillated with H_2O under azeotropic condition. The resulting aqueous solution was extracted with $CHCl_3$ and dried over K_2CO_3. Evaporation of the solvent afforded **8** as a colorless oil, which was used in the next reaction without further purification.

To a solution of the crude **8** in MeCN (14.4 mL) was added $Na_2WO_4 \cdot H_2O$ (0.95 g, 1.88 mmol) at ambient temperature and the mixture was stirred for 30 min. After the solution was cooled to 0 °C, urea hydrogen peroxide (2.7 g, 28.8 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h and at ambient temperature for 4 h. H_2O was added to the reaction mixture and the aqueous solution was extracted with $CHCl_3$. The organic layer was dried over K_2CO_3 and concentrated. The residue was purified by silica gel column chromatography to yield ABNO (**3**) (0.84 g, 6 mmol) as a red solid. An analytical sample was prepared by sublimation: phase change 50 and ca. 85 °C, mp 126−129 °C (lit.[11] phase change 53 and ca. 70 °C, mp 129−130 °C); IR (neat, cm^{-1}) 1484, 1453, 1352, 1292; EI-MS *m*/*z* 140 (M^+), 81 (100%); HRMS (EI) calcd for $C_8H_{14}NO$ 140.1075 (M^+), found 140.1052. Anal. Calcd for $C_8H_{14}NO$: C 68.58; H, 10.06; N, 9.99. Found: C, 68.39; H, 9.87; N, 9.83.

Representative Procedure for Oxidation of Alcohols under Anelli's Condition. To a solution of 2-phenyl-1-cyclohexanol (**14**) (300 mg, 1.7 mmol), KBr (20 mg, 0.17 mmol), and TBAB (27 mg, 0.085 mmol) in CH_2Cl_2-saturated aqueous $NaHCO_3$ (2:1v/v, 6.4 mL) was slowly added 2.5 M NaOCl (1 mL, 2.5 mmol) in saturated aqueous $NaHCO_3$ (2 mL) at 0 °C. After 20 min, the mixture was quenched with saturated aqueous Na_2SO_3 and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane−AcOEt (9:1 v/v)] to afford 2-phenyl-1-cyclohexanone (296 mg, 1.7 mmol, 100%) as a white solid.

Acknowledgment. This work was partly supported by a Grant-in-Aid for Scientific Research (B) (No. 17390002) from the Japan Society for the Promotion of Science, Grant-in-Aid for Young Scientists (B) (No. 17790005), and Grant-in-Aid for the Grobal COE Program for "International Center of Research & Education for Molecular Complex Chemistry" from Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available: The experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900486W