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Highly Enantioselective Organocatalytic Oxidative Kinetic Resolution of Secondary Alcohols Using Chirally Modified AZADOs

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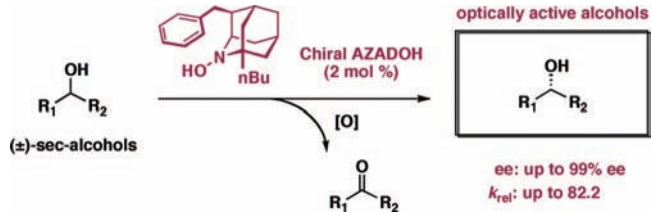
ABSTRACT



A highly enantioselective organocatalytic oxidative kinetic resolution (OKR) of racemic secondary alcohols has been accomplished using asymmetric organocatalysis. A panel of chirally modified 2-azaadamantane *N*-oxyls (AZADOs) exhibit superior catalytic activity and high enantioselectivity, allowing us to obtain optically active secondary alcohols with a k_{rel} value up to 82.2.

Enantioselective oxidation of racemic secondary alcohols offers chemists an attractive strategy for delivering optically active alcohols, which should play indispensable roles in the synthesis of various biologically active compounds.[1] In recent years, remarkable progress has been made, especially in transition-metal-catalyzed oxidation systems in the presence of asymmetric ligands.[2] Meanwhile, the development of non-transition-metal-catalyzed systems has attracted attention as a significant challenge because of their environmentally benign and user-friendly characteristics. Although many endeavors employing asymmetric organocatalysts, especially based on the chirally modified nitroxyl radicals,[3] have been carried out, the design of catalysts capable of applying a wide range of substrates with satisfactory selectivity has remained elusive. Our own interest in this field stems from our development of the azaadamantane-type of organocatalysts, AZADO and 1-Me-AZADO, which served as powerful oxidation catalysts for a wide range of secondary alcohols.[4] In this paper, we disclose the highly enantioselective organocatalytic oxidative kinetic resolution (OKR) of secondary alcohols using chirally modified AZADOs. The method reported here demonstrates the successful example of an

(1) For reviews on the preparation of optically active alcohols, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (b) Kagan, H. B.; Flaud, J. C. Kinetic Resolution. *Top. Stereochem.* **1988**, *18*, 249–330. (c) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974–4001.

(2) For selective examples of transition-metal-catalyzed OKR, see: (a) Hashiguchi, S.; Fujii, A.; Haak, K.-J.; Matsumoto, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *44*, 288–289. (b) Masutani, K.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 5119–5123. (c) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475–7476. (d) Ferrcira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725–7726. (e) Radosevich, A. T.; Musich, C.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 1090–1091. (f) Weng, S.-S.; Shen, M.-W.; Kao, J.-Q.; Munot, Y.-S.; Chen, C.-T. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 3522–3527. (g) Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 2447–2449, and references therein.

(3) For selective examples of chiral nitroxyl-radical-catalyzed OKR, see: (a) Ma, Z.; Huang, Q.; Bobbitt, J. M. *J. Org. Chem.* **1993**, *58*, 4837–4843. (b) Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.* **1996**, *61*, 1194–1195. (c) Kashiwagi, Y.; Kurashima, F.; Chiba, S.; Anzai, J.; Osa, T.; Bobbitt, J. M. *Chem. Commun.* **2003**, 114–115. (d) Rychnovsky, S.; Leu, W.-H.; Farmer, P.; Lin, R. *Tetrahedron: Asymmetry* **2005**, *16*, 3584–3598. (e) Shiigi, H.; Mori, H.; Tanaka, T.; Demizu, Y.; Onomura, O. *Tetrahedron Lett.* **2008**, *49*, 5247–5249.

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

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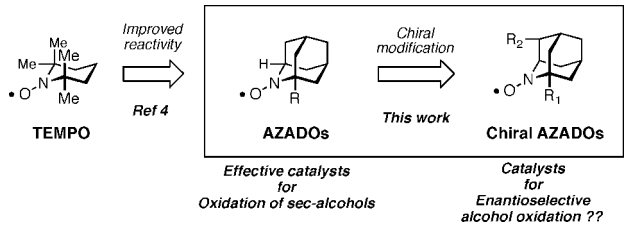
organocatalysts with a high level of enantioselectivity comparable to that of transition-metal-mediated systems, enabling the highly enantioselective OKR of a wide range of racemic secondary alcohols even under mild chemical conditions.[5]



The designed motif, namely, 4-aryl-1-alkyl-AZADO, relies on the generally accepted mechanism of TEMPO-catalyzed alcohol oxidation proposed by Semmelhack[6a] and Bobbitt,[6c] in which the key feature of the concept consists of the following two steps: (1) addition of the substrate to the oxoammonium species and (2) H-abstraction via a Cope-like planar five-membered cyclic transition state. Thus, we expected that in the first stage the cation-π interaction between N^+═O and the aryl group effectively shielded one side of the oxoammonium moiety to exhibit face selectivity,[7,8] and the alkyl group flanking the nearby catalytic center played an important role in the discrimination of racemic alcohols during the course of the oxidation (Figure 1).

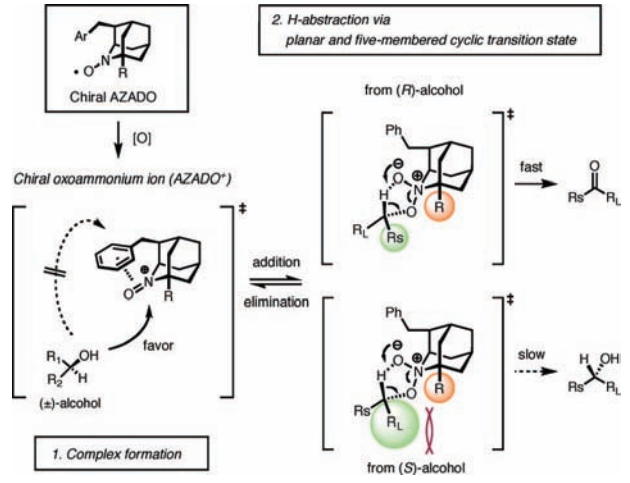


Figure 1. Working hypothesis of OKR catalyzed by chiral AZADO.

To assess our hypothesis, we synthesized a panel of chiral AZADOs and their corresponding hydroxylamine catalysts (see Supporting Information)[9] and evaluated their selectivity in OKR using *trans*-2-phenyl-cyclohexanol **8** as a substrate (Figure 2,

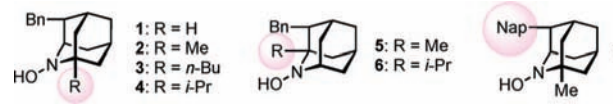
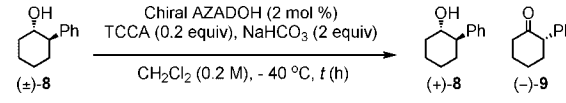


Figure 2. Panel of chiral AZADOs.

Table 1).[10] An initial attempt carried out using catalyst **1**, which has no substituent group, with TCCA[11] under −40 °C in CH_2Cl_2

Table 1. OKR of (±)-**8** Using a Panel of Chiral AZADOs



entry	catalyst	t [h]	convn [%][a]	ee [%][b]	config (alcohol)[b]	k_{rel}
1	**1**	3	52	8	*S*	1.2
2	**2**	3	55	96	*S*	32.0
3	**3**	3	52	98	*S*	82.2
4	**4**	3	38	41	*S*	7.8
5	**5**	24	50	−70	*R*	11.7
6	**6**	24	29	−23	*R*	4.5
7	**7**	3	55	98	*S*	32.8

[a] Conversion was estimated from isolated yields of alcohols. [b] Determined by chiral HPLC analysis.

resulted in rapid oxidation with no selectivity (entry 1, k_R/k_S[12] = 1.2). On the other hand, for catalyst **2** with a methyl group, good selectivity was observed under the same reaction conditions (entry 2), and with the more sterically effective *n*-Bu type of catalyst **3** the oxidation proceeded in 52% conversion with excellent selectivity (entry 3, k_R/k_S = 82.2). Additionally, the configuration of recovered alcohols depended on the position of the alkyl substituent group (entries 5 and 6), suggesting that the α-substituent group of chiral AZADO is essential for the

(5) Osa and Bobbitt reported a highly enantioselective OKR using a chiral TEMPO (1-azaspiro[5.5]undecane *N*-oxyl radical) modified electrode system; however, the chiral TEMPO itself is not applicable to simple chemical conditions.[3c,e]

(6) (a) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. S. *Tetrahedron Lett.* **1986**, *27*, 1119–1122. (b) de Nooy, A. E. J.; Basemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1174. (c) Bobbitt, J. M.; Wiberg, K. B. *J. Org. Chem.* **2007**, *72*, 4504–4509, and references therein.

(7) For examples of cation-π interaction, see: (a) Kawabata, T; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169–3170. (b) Li, X.; Liu, P.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2008**, *130*, 13836–13837. (c) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303–1324.

(8) An interesting paper, in which the effects on the π-facial diastereoselectivity of the substituent in the 4-position of adamantin-2-one were investigated, has been reported; see:(a) Barboni, L.; Filippi, A.; Fraschetti, C.; Giuli, S.; Marcolini, M.; Marcantoni, E. *Tetrahedron Lett.* **2008**, *49*, 6065–6067.

(9) In preliminary experiments, chiral AZADO and chiral AZADOH (its corresponding hydroxylamine), which is a synthetic precursor of chiral AZADO, afforded similar k_R/k_S values for OKR. In view of its availability, we chose the chiral AZADOH catalyst for further study.

(10) See Supporting Information for details of the preparation of the catalysts and screening for reaction conditions in OKR.

(11) (a) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041–3044. (b) Luca, L. D.; Giacomelli, G.; Masala, S.; Porcheddu, A. *J. Org. Chem.* **2003**, *68*, 4999–5001.

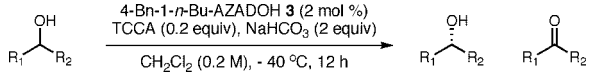
(12) For details of k_R/k_S values, see: (a) Kagan, H. B.; Flaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Ed.; Wiley & Sons: New York, 1988; Vol. 18, pp 249−330. (b) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974–4001.

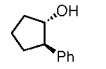
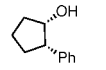
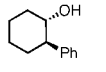
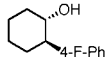
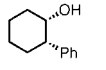
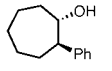
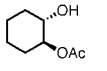
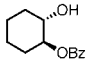
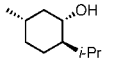
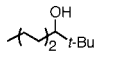
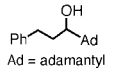
(13) The sterically congested *i*-Pr group of the catalyst decreased catalytic activity and enantioselectivity. We consider that flexibility of the substituent group as normal butyl group is essential for the generation of broad asymmetric reaction space. This assumption was supported by the fact that catalyst **2** with a Me group gave low selectivity with other secondary alcohols (see Supporting Information).

enantiodiscrimination of the substrates.[13] These results strongly support the validity of our working hypothesis and provide useful experimental insight into the proposed mechanism of nitroxyl radical mediated alcohol oxidation.[6]

Having developed the optimal catalyst, we investigated the substrate scope of the oxidative kinetic resolution. As described in Table 2, **3**/TCCA systems attained good to excellent levels

Table 2. Scope of Substrates Employing the **3**/TCCA System

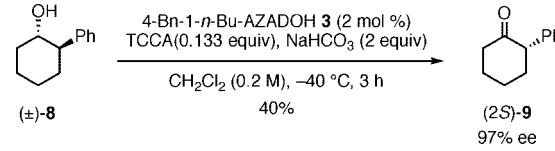


entry	substrate	convn [%][a]	ee [%][b]	config. (alcohol)[c]	k_{rel}
1		57	99	*S*	32.6
2		57[d]	97	*S*	26.2
3		52	98	*S*	82.2
4		53	99	*S*	80.1
5		53	99	*S*	80.1
6		58	60	*S*	4.5
7		57[d]	88	*S*	13.8
8		58[d]	90	*S*	14.0
9		52	63	*S*	6.8
10		54	46	---	3.5
11	 Ad = adamantyl	56	90	*S*	17.4

[a] Conversion was estimated from isolated yields of alcohols. [b] Determined by chiral HPLC analysis. [c] For etermination of the absolute configurations, see Supporting Information. [d] **3** (3 mol %), $PhI(OAc)_2$ (0.7 equiv), CH_2Cl_2, −5 °C.

of asymmetric induction with several nonactivated classes of alcohols. Cyclopentanol and cyclohexanol having an aryl substituent group serve especially well as substrates[14] for resolution, with selectivity factors as high as 82.2 (entries 1−5). Note that the OKR of **8** using **3** with 0.133 equiv of TCCA (0.4 equiv as Cl^+) afforded (2*S*)-ketone **9** in 40% yield and with excellent enantiopurity (97% ee), indicating that the **3**/TCCA system is mild enough to prevent an epimerization of ketone via enol formation, thus allowing easy access to enantiomerically enriched carbonyl compounds (Scheme 1).

Scheme 1. Preparation of Enantiomerically Enriched (2*S*)-Ketone **9**



(±)-**8** (2*S*)-**9** 97% ee

Unfortunately, a seven-membered ring substrate could not be resolved efficiently (entry 6). The resolution can also be accomplished with 2-alkyl- or 2-alkoxyl-substituted cyclohexanols in moderate to good selectivity (entries 7−9). On the other hand, the resolution of acyclic substrates resulted in low selectivity, although a substrate having a sterically congested adamantyl group affords a good result (entries 10 and 11), indicating importance of the steric interaction for enantioselectivity.[15]

In conclusion, we have disclosed the efficient kinetic resolution of racemic secondary alcohols catalyzed by chiral AZADOs and their corresponding hydroxylamine catalyst. Our catalytic system recorded the highest k_{rel} value comparable to that of the transition-metal-mediated process when α-substituted cyclopentanol and cyclohexanols were employed as the substrates. Even though limited substrates could be applicable to our system to date, this research provided useful insights for development of more efficient catalytic systems applicable to a wider range of substrates. Further studies are in progress to expand the scope of chirally modified AZADOs on the oxidative desymmetrization of *meso*-diols.

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 the Research Fellowship for Young Scientists (M.T.), Grant-in-Aid for Young Scientists (B) (No. 19790005), 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 and a research grant from Uehara Memorial Fundation for the Promotion of Life Science. We thank Dr. Chizuko Kabuto (Tohoku University) for her helpful discussion.

Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Optically active 2-substituted cyclohexanols and cyclohexane diol derivatives are reliable tools as chiral reagents, especially as auxiliaries, for asymmetric synthesis; see: (a) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953–964. (b) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656–4661. (c) Sakai, K.; Suemune, H. *Tetrahedron: Asymmetry* **1993**, *4*, 2109–2118. (d) Laumen, K.; Breitgoff, D.; Seemayer, R.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1989**, 148–150. (e) Tanyeli, C.; Turkut, E.; Akhmedov, I. M. *Tetrahedron: Asymmetry* **2004**, *15*, 1729–1733.

(15) The resolution of less hindered secondary alcohols such as 1-phenylethanol or indanol proceeds with low selectivity ($k_{rel} < 4$) and with rapid oxidation rate, indicating that substituent size at C-1 of chiral AZADO plays essential roles for the efficient resolution.