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Highly Enantioselective Organocatalytic Oxidative Kinetic Resolution of Secondary Alcohols Using Chiral Alkoxyamines as Precatalysts: Catalyst Structure, Active Species, and Substrate Scope

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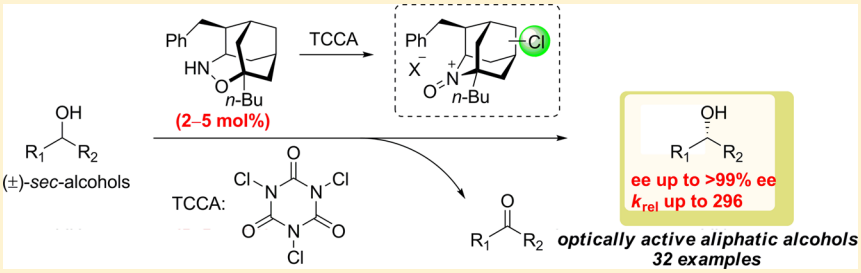
Supporting Information



ABSTRACT: The development and characterization of enantioselective organocatalytic oxidative kinetic resolution (OKR) of racemic secondary alcohols using chiral alkoxyamines as precatalysts are described. A number of chiral alkoxyamines have been synthesized, and their structure−enantioselectivity correlation study in OKR has led us to identify a promising precatalyst, namely, 7-benzyl-3-*n*-butyl-4-oxa-5-azahomoadamantane, which affords various chiral aliphatic secondary alcohols (ee up to >99%, k_{rel} up to 296). In a mechanistic study, chlorine-containing oxoammonium species were identified as the active species generated in situ from the alkoxyamine precatalyst, and it was revealed that the chlorine atom is crucial for high reactivity and enantioselectivity. The present OKR is the first successful example applicable to various unactivated aliphatic secondary alcohols, including heterocyclic alcohols with high enantioselectivity, the synthetic application of which is demonstrated by the synthesis of a bioactive compound.

INTRODUCTION

A chiral secondary alcohol is a ubiquitous but valuable structural motif in organic chemistry, being expressed in many biologically active natural products, synthetic intermediates, and reagents.[1] Chiral alcohols have been prepared via various approaches, such as the use of natural enantiopure materials, the resolution of enantiomers by chemical[2] or physical[3] means, and the enantioselective synthesis using asymmetric reagents or catalysts from prochiral substrates, e.g., the asymmetric reduction of ketones,[4] the enantioselective addition of a nucleophile to aldehydes,[5] and the asymmetric ring opening of epoxides.[6] Although these approaches have been extensively investigated, their scope is still limited. Thus, the investigation has continued to expand the applicability of each approach.

The oxidative kinetic resolution (OKR) of racemic secondary alcohols using asymmetric catalysts is a profitable method of choice to obtain chiral alcohols, offering chemists several attractive opportunities. For example, it shares the benefits of kinetic resolution, the racemic substrates for which are facile to design and synthesize and which could certainly yield chiral alcohols with high enantiopurity by controlling the reaction conversion. OKR is a convenient complement to other kinetic resolutions such as acylative ones[2h] and to the enantioselective reduction of ketones with inapplicable substrates. Additionally, the method furnishes a complementary set of chiral compounds when using substrates with multiple stereogenic centers.

Over the past decades, remarkable progress has been made in the OKR of racemic secondary alcohols, especially using transition-metal catalysts with chiral ligands.[7] Utilizing transition-metal/chiral ligand systems, various activated secondary alcohols, such as benzylic alcohols, allylic alcohols, and α-hydroxy acid derivatives, have been reliably resolved to high enantiomeric excesses. However, most of these systems have limitations in terms of substrate applicability, since reliable methods of resolving an unactivated class of alcohols have rarely been reported. As an exception, Katsuki and co-workers have most recently reported a highly enantioselective ruthenium-catalyzed OKR of not only activated but also unactivated secondary alcohols. The method was successfully applied to six examples of 1-alkyl-1-ethanols, and it exhibited good to high enantioselectivity.[8]

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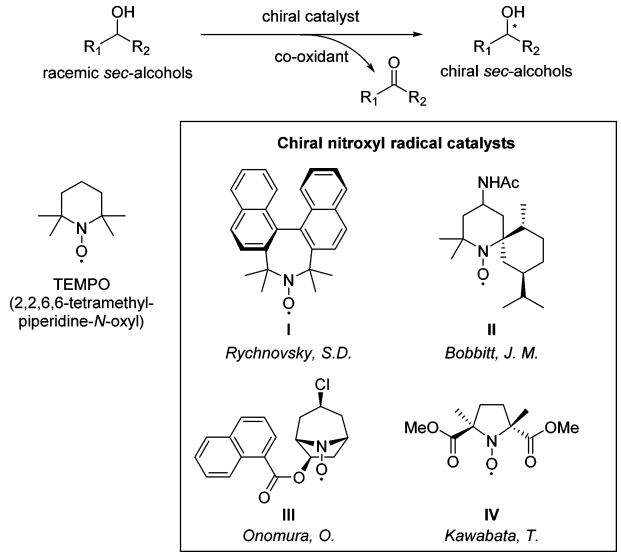
In recent years, asymmetric transformations using chiral organocatalysts have emerged as reliable approaches, other than those using transition-metal catalysts, the progress of which has been driven by their readily tunable and user-friendly characteristics.[9] Several nitroxyl-radical-type organocatalysts have been developed for the OKR of racemic secondary alcohols (Scheme 1).[10−13] One of the pioneering examples is

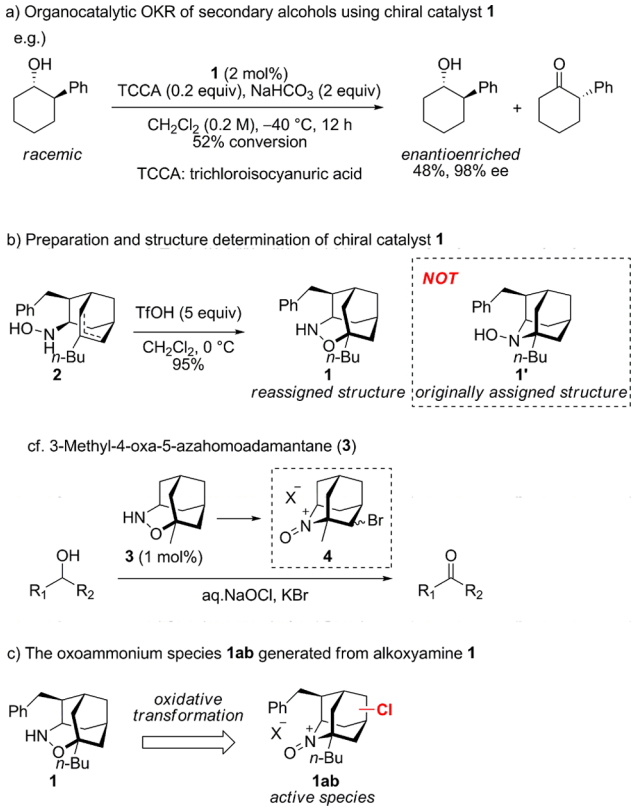
Scheme 1. TEMPO and Representative Chiral Nitroxyl Radical Catalysts for OKR of Secondary Alcohols



catalyst **I**, reported by Rychnovsky et al. in 1996, which exhibits moderate enantioselectivity for secondary benzylic alcohols.[10] Bobbitt and co-workers developed catalyst **II** for electrode OKR.[11] Unfortunately, these catalysts hardly achieve efficient enantioselective oxidation of unactivated secondary alcohols because of the steric bulkiness of the catalyst based on the structural motif of TEMPO. Onomura and co-workers developed a less-hindered azabicyclic type of catalyst **III**, which showed enhanced catalytic activity and enantioselectivity.[12] Kawabata and co-workers very recently reported that catalyst **IV**, which is converted to a highly electrophilic active species, exhibits high enantioselectivity on the OKR of some benzylic secondary alcohols.[13] Some other types of chiral organocatalysts for the OKR of racemic alcohols[14] and for the desymmetrization of meso-diols[15] have been reported. However, organocatalytic OKR suffers from almost the same limitation as transition-metal catalysis: OKR accommodating a wide range of unactivated aliphatic alcohols had never been developed until we reported OKR using chiral alkoxyamines.

In 2009, we communicated a highly enantioselective organocatalytic OKR of racemic secondary alcohols, which is the first successful example applicable to various unactivated aliphatic secondary alcohols, particularly carbocyclic alcohols (Scheme 2a).[16] The structure of the key chiral catalyst **1**, which is obtained by the treatment of the bicyclic hydroxylamine **2** with trifluoromethanesulfonic acid (TfOH), was originally assigned to the azaadamantane-type hydroxylamine **1′** (Scheme 2b).[16a] Very recently, we have found that the structure of the chiral catalyst should be reassigned to the homoadamantane-embedded alkoxyamine **1**,[16b] whose motif we have recently identified as an unprecedented type of organocatalyst for alcohol oxidation.[17] 3-Methyl-4-oxa-5-azahomoadamantane (**3**)

Scheme 2. Outline of This Work



exhibits high catalytic activity for alcohol oxidation via oxidative transformation into the oxoammonium active species **4**. In this paper, we describe a full account of the development of OKR catalyzed by chiral alkoxyamines. Their structures are unambiguously determined by detailed spectral analyses and X-ray single-crystal structural analysis. In a mechanistic study, the oxoammonium species **1ab** generated in situ from the alkoxyamine **1** is identified as an active species, and it is unexpectedly found that the chlorine atom in the oxoammonium species **1ab** plays a pivotal role in enhancing not only reactivity but also enantioselectivity (Scheme 2c). More detailed studies of the scope of OKR disclose the applicability of OKR to heterocyclic secondary alcohols, of which OKR affords useful chiral building blocks for the synthesis of various biologically active compounds of high enantiopurity.

RESULTS AND DISCUSSION

Design of Chiral Catalysts and Working Hypothesis for OKR of Racemic Secondary Alcohols. We previously developed highly active nitroxyl radical catalysts for alcohol oxidation, namely, 2-azaadamantane *N*-oxyl (AZADO) and 1-Me-AZADO.[18] Since AZADO and its derivatives have robust skeletons and a wider reaction space around the catalytic center to expand substrate accessibility, they exhibit markedly high catalytic activity in alcohol oxidation (Figure 1). For example, they can readily oxidize even bulky secondary alcohols that TEMPO fails to oxidize to give the corresponding ketones in high yield. In the light of the exceptionally high catalytic activity of AZADO as well as the inherent structural rigidity of the 2-azaadamantane skeleton, we envisaged that AZADO would serve as a reliable platform for chiral catalysts for the OKR of racemic secondary alcohols (Figure 1).

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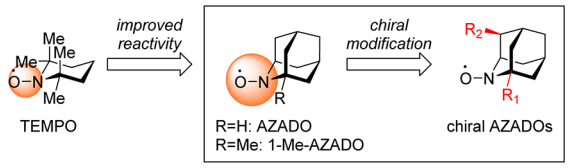

Figure 1. Design concept of chiral AZADOs.

Our design of chirally modified AZADO (chiral AZADO) stemmed logically from the mechanism of TEMPO-catalyzed alcohol oxidation proposed by Semmelhack and co-workers[19] and Bobbitt and co-workers,[20] in which the oxoammonium ion serves as the active species. We focused on the following two steps: (1) the addition of a substrate alcohol to the oxoammonium ion **A** and (2) the oxy-Cope-type elimination via a planar five-membered cyclic transition state (Figure 2a).

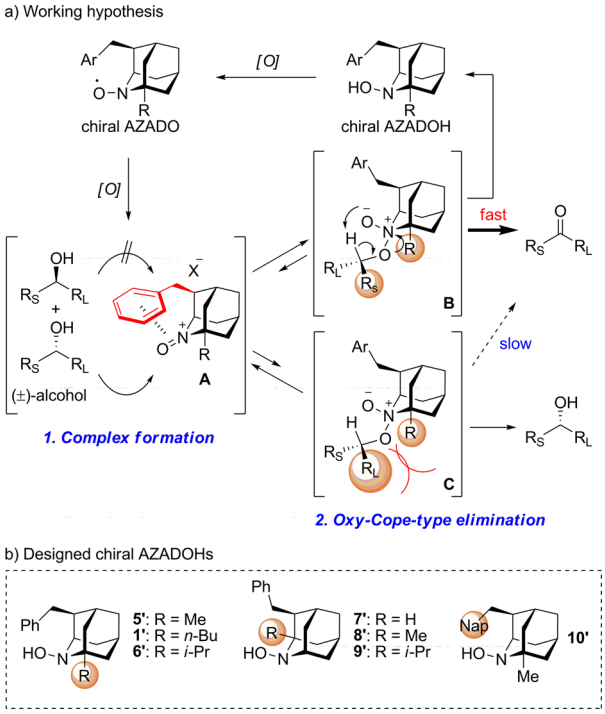

Figure 2. Working hypothesis of OKR catalyzed by chiral AZADOs and initial designs of chiral catalysts for OKR.

Thus, we assumed that the aromatic ring proximal to the catalytic center would shield one side of the oxoammonium ion by a cation−π interaction[21] in the first step, thereby preferentially forming two intermediates, **B** and **C**, by the diastereoselective attack of the racemic alcohol to the oxoammonium ion **A**.[22] The two diastereomers **B** and **C** should subsequently proceed to the crucial second step, namely, oxy-Cope-type elimination, where the alkyl group flanking the nearby catalytic center governs the enantiopreference of the oxidation. Although the intermediate **B** would easily collapse to the corresponding ketone and hydroxylamine (chiral AZADOH), the intermediate **C** would hardly collapse to the corresponding ketone, and thus, the chiral alcohol could be eventually recovered. On the basis of the working hypothesis, we designed a panel of chiral AZADOHs, **1′** and **5′**−**10′**, with different substituents, which we considered could be prepared more readily than the corresponding chiral AZADOs (Figure 2b).

Synthesis of Chiral Catalysts and Identification of Optimum Catalyst Structure. We attempted to synthesize chiral AZADOHs. As an example, the examination of the synthesis of the chiral AZADOH **1′** having benzyl (Bn) and *n*-butyl (*n*-Bu) groups is described (Scheme 3). The examination started with the preparation of the chiral aldol **12**. Simpkins' base-mediated asymmetric aldol reaction of the known bicyclic ketone **11**[18a] with benzaldehyde gave the aldol **12** with >99% ee after recrystallization.[23] The sequence of dehydration and hydrogenation afforded the chiral bicyclic ketone **13** in 90% yield in three steps. After the deprotection of the ketal group, the diketone underwent the addition of the *n*-Bu group under Imamoto's conditions using $CeCl_3$,[24] giving two isomers of *n*-Bu-substituted oxaadamantanols, **14a** and **14b**, which were separated by flash column chromatography. The mesylation of the oxaadamantanol **14a** followed by exposure to SiO_2 led to a Grob-type fragmentation to give the bicyclic ketone **15** as an inseparable mixture of two regioisomers.[25] The ketone **15** was converted to the hydroxylamine **2** via a two-step sequence consisting of oximation and partial reduction by $NaBH_3CN$. The treatment of **2** with 5 equiv of TfOH in CH_2Cl_2 at 0 °C gave a polar product in 95% yield. Previously, we reported that the structure of the polar product is the intended hydroxylamine **1′**, which was considered to catalyze the highly enantioselective OKR of racemic secondary alcohols.[16a] However, after detailed spectroscopic analysis along with our unexpected discovery of the synthesis of the homoadamantane-type alkoxyamine,[17] we found that the structure of the polar product should be reassigned to the alkoxyamine **1**. The spectroscopic data feature the 82.0 ppm peak on ^{13}C NMR, which indicates the connection of C3 not with nitrogen but with oxygen, and the sharp 3351 cm^{-1} peak on IR, which indicates not the O−H bond but the N−H bond. The structure of **1** was unambiguously determined by X-ray single-crystal structural analysis of the corresponding benzoate **16**. Therefore, it was concluded that the bicyclic hydroxylamine **2** underwent not protoamination but protoetherification by the action of the excess amount of TfOH to provide the homoadamantane-type alkoxyamine **2**. Other chiral alkoxyamines **5**−**10** were synthesized by a similar procedure throughout an asymmetric aldol reaction and TfOH-mediated protoetherification (Figure 3).[26]

According to our previous discovery of an alkoxyamine-type precatalyst for alcohol oxidation, the synthesized alkoxyamines **1** and **5**−**10** should be converted to the oxoammonium active species **1x** and **5x**−**10x** under the alcohol oxidation conditions (Figure 3).[17] Notably, the active species generated from the alkoxyamines share the same structural motif, namely, the oxoammonium ion, as those derived from the initially designed chiral AZADOs **1′** and **5′**−**10′** shown in Figure 2.

With a panel of chiral alkoxyamines in hand, a comparative evaluation of their enantioselectivity was carried out using the (±)-*trans*-2-phenylcyclohexanol **17** as the substrate (Table 1). In the preliminary experiments, it was confirmed that the 7-Bn-3-Me-4-oxa-5-azahomoadamantane (**5**) showed a high enantioselectivity ($k_{fast}/k_{slow} = k_{rel}^{27} = 32.0$) using trichloroisocyanuric acid (TCCA)[28] as the co-oxidant in the presence of $NaHCO_3$ in CH_2Cl_2 solution at −40 °C (entry 1).[29] The catalyst **1** having an *n*-Bu group, which is more sterically effective than the Me group, exhibited excellent enantioselectivity at 52% conversion (k_{rel} = 82.2, entry 2). The more sterically congested *i*-Pr group of the catalyst **6** decreased its catalytic activity and enantioselectivity, suggesting that the flexibility of the *n*-Bu

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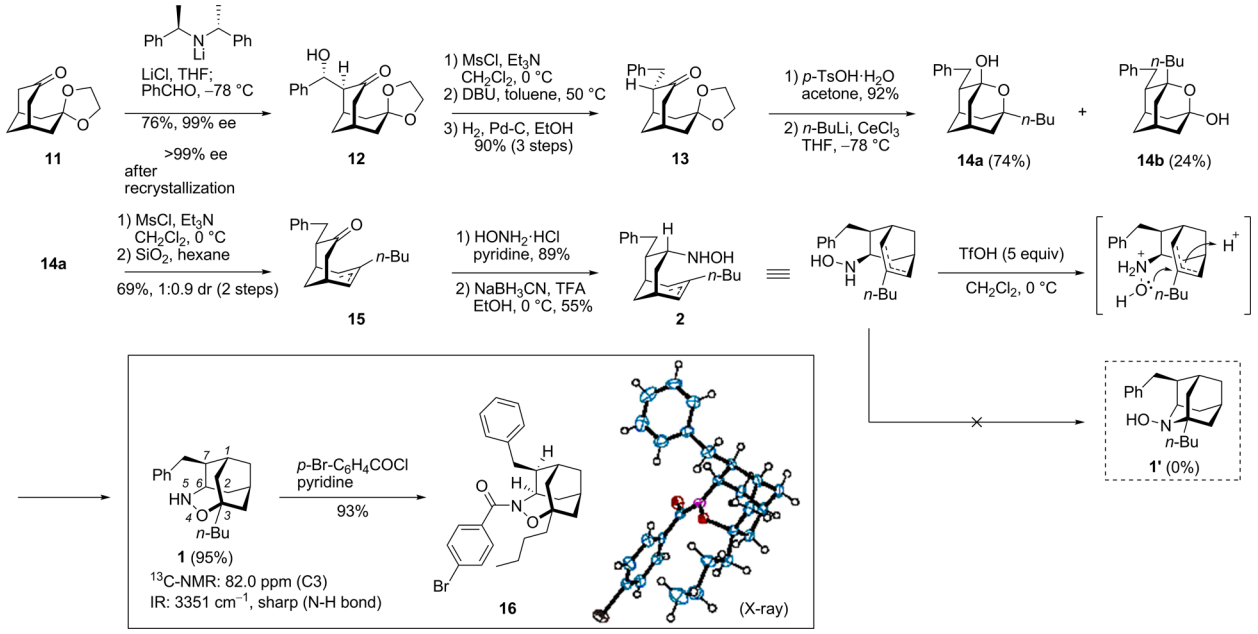
Scheme 3. Synthesis and Structure Elucidation of the Chiral Catalyst 1



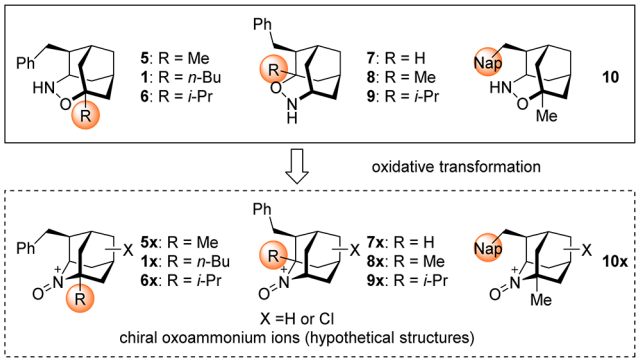
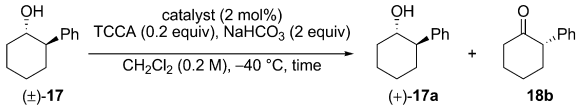


Figure 3. Structure of chiral alkoxyamines and chiral oxoammonium ions.

Table 1. Catalytic Activities of Chiral Alkoxyamines



				alcohol		
entry	catalyst	time (h)	conv (%)[a]	ee (%)[b]	config	k_{rel}[c]
1	**5**	3	55	96	*S*	32.0
2	**1**	3	52	98	*S*	82.2
3	**6**	24	38	41	*S*	7.8
4	**7**	3	52	8	*S*	1.2
5	**8**	3	50	–70	*R*	11.7
6	**9**	24	29	–23	*R*	4.5
7	**10**	3	56	98	*S*	32.8

[a]Conversion was calculated from the yield of alcohol isolated. [b]Determined by chiral HPLC. [c]$k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C is the conversion and ee is the enantiomeric excess of alcohol.

group near the catalytic center is essential for accommodating the asymmetric reaction space (entry 3). The catalyst **7**, which has no alkyl group, brought about a rapid oxidation with poor enantioselectivity (entry 4). Additionally, the configuration of the recovered alcohol depended on the position of the alkyl substituent group (entries 5 and 6). These results indicate that the alkyl substituents near the catalytic center are essential for the enantio-discrimination of the substrates. The catalyst **10**, which has an α-Nap group, showed almost the same enantioselectivity as the catalyst **6** (entry 7). The results shown in Table 1 showed good agreement with our working hypothesis shown in Figure 2. The 7-Bn-3-*n*-Bu-4-oxa-5-azahomoadamantane (**1**) was determined as the ideal precatalyst, generating the most effective chiral oxoammonium ion.

Mechanistic Studies. After confirming that the chiral alkoxyamines exhibit excellent enantioselectivity for the OKR of racemic secondary alcohols as reliable precursors of chiral oxoammonium ions, we were interested in the activity of chiral AZADOs, which we initially considered precursors of chiral oxoammonium ions (Figure 4). We envisaged that chiral

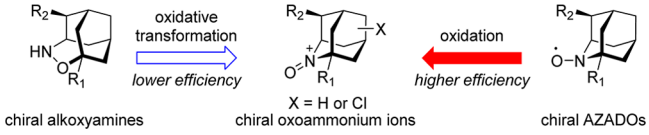


Figure 4. Chiral oxoammonium ions generated from chiral alkoxyamines and chiral AZADOs.

AZADOs are robust alternatives to chiral alkoxyamines because adamantane-skeletal nitroxyl radicals are converted to the corresponding oxoammonium ions more efficiently than homoadamantane-skeletal alkoxyamines. We have confirmed that AZADOs were smoothly converted to oxoammonium ions and recovered in almost quantitative yield, whereas the alkoxyamine was less efficiently converted to the active species, which was recovered in only ca. 30% yield after alcohol oxidation, accompanied by the formation of an inactive dimer and partial decomposition.[17]

To examine the catalytic activity and enantioselectivity of the chiral AZADO for the OKR of racemic secondary alcohols, we

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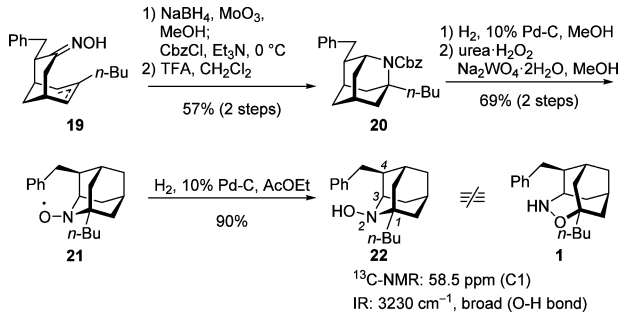
synthesized 4-Bn-1-*n*-Bu-AZADO (**21**), corresponding to the best chiral alkoxyamine **1** (Scheme 4). The chiral AZADO **21**

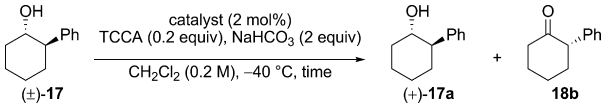
Scheme 4. Synthesis of 4-Bn-1-*n*-Bu-AZADO (21)

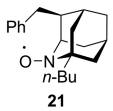
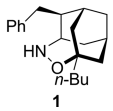


was prepared from the synthetic intermediate **19** of the alkoxyamines by adopting the synthetic procedure of 1-Me-AZADO.[18a] The reduction of the bicyclic oxime **19** followed by the in situ protection of the amine to give carbamate and then protoamination by trifluoroacetic acid afforded the *N*-Cbz-2-azaadamantane **20**. After the hydrogenolysis of the Cbz group, the resulting amine was oxidized by treatment with urea hydrogen peroxide to produce the chiral AZADO **21**. The structure of the nitroxyl radical **21** was supported by the result of the spectroscopic analysis of the corresponding hydoroxylamine **22**, the spectroscopic data of which were confirmed to be different from those of the chiral alkoxyamine **1**.

The catalytic activity and enantioselectivity of 4-Bn-1-*n*-Bu-AZADO (**21**) were evaluated using the racemic alcohol **17** as the substrate (Table 2). Unexpectedly, the chiral AZADO **21**

Table 2. Comparison of Catalytic Activities of Chiral AZADO and Chiral Alkoxyamine



entry	catalyst	time (h)	conv (%)[a]	alcohol ee (%)[b]	k_{rel}[c]
1	 **21**	24	53	85	21.6
2	 **1**	12	52	98	82.2

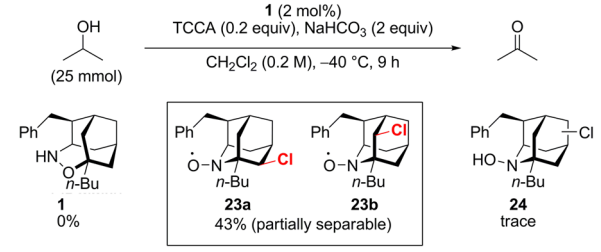
[a]Conversion was calculated from the yield of alcohol isolated. [b]Determined by chiral HPLC. [c]k_{rel} = ln[(1 − *C*)(1 − ee)]/ln[(1 − *C*)(1 + ee)], where *C* is the conversion and ee is the enantiomeric excess of alcohol.

gave a lower rate and a considerably lower enantioselectivity than the chiral alkoxyamine **1**. The higher reactivity and enantioselectivity of **1** suggested the involvement of another catalytically active species, which is different from the oxoammonium species derived from **21**.

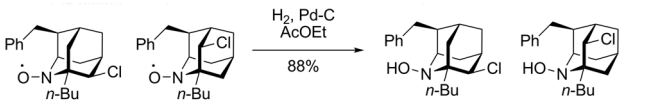
To identify the *real* active species generated from the chiral alkoxyamine **1** and to gain mechanistic insights into the OKR, we attempted to isolate products derived from **1** after the alcohol oxidation. We conducted a large-scale oxidation of 2-propanol (25 mmol) with the general OKR conditions (0.2 equiv of TCCA: 0.6 equiv of Cl^+) to isolate products derived from **1** after chromatographic purification (Scheme 5a). Two

Scheme 5. Experiments for Identifying Active Species of OKR

a) Isolation of products from catalyst **1**



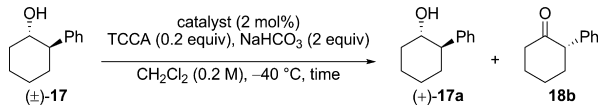
b) Determination of structure of chiral AZADOs **23a** and **23b**

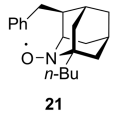
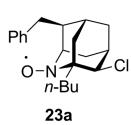
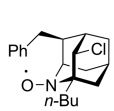


chiral chlorine-containing AZADOs (chiral Cl-AZADOs), **23a** and **23b**, were isolated as the major products, while neither **1**, chiral AZADO **21**, nor the corresponding hydoroxylamine **22** was isolated. The structure and yield of **23a** and **23b** were determined after reduction to the corresponding hydroxylamines **24a** and **24b** (Scheme 5b).

The isolated chiral Cl-AZADOs **23a** and **23b** were employed as catalysts for the OKR of the racemic alcohol **17**, for comparison with 4-Bn-1-*n*-Bu-AZADO (**21**) (Table 3). Interestingly, the chiral Cl-AZADOs **23a** and **23b** gave a higher reaction rate and a higher enantioselectivity than 4-Bn-1-

Table 3. Catalytic Activity of Chiral AZADOs



entry	catalyst	time (h)	conv (%)[a]	alcohol ee (%)[b]	k_{rel}[c]
1	 **21**	24	53	85	21.6
2	 **23a**	12	55	>99	>79.3
3	 **23b**	12	52	95	55.7

[a]Conversion was calculated from the yield of alcohol isolated. [b]Determined by chiral HPLC. [c]k_{rel} = ln[(1 − *C*)(1 − ee)]/ln[(1 − *C*)(1 + ee)], where *C* is the conversion and ee is the enantiomeric excess of alcohol.

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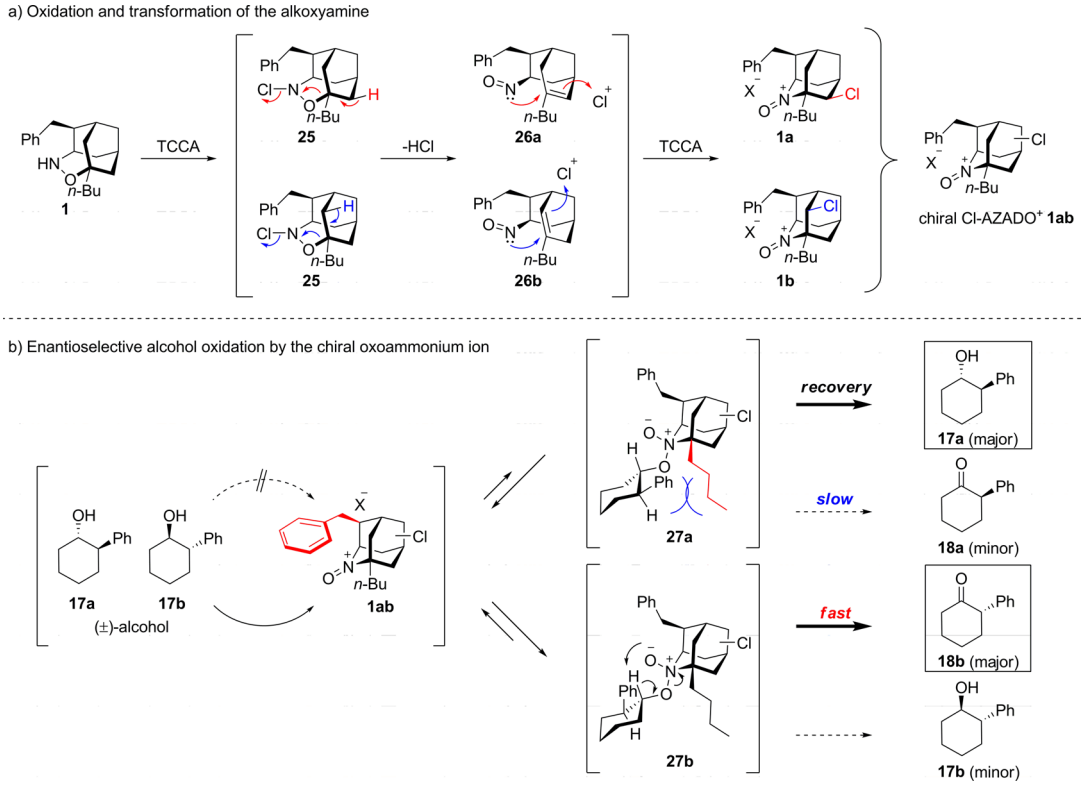

Figure 5. A plausible mechanism.

n-Bu-AZADO (**21**). Notably, the chiral Cl-AZADO **23a** especially smoothly oxidized the alcohol with excellent enantioselectivity (entry 2, k_{rel} > 79.3). These results suggest that introducing a chlorine atom into the azaadamantane skeleton is essential for highly enantioselective OKR and that even the position of the chlorine atom affects catalytic activities.

On the basis of all the aforementioned results, the proposed mechanism of OKR is shown in Figure 5. First, the chiral alkoxyamine **1** is chlorinated by TCCA to give the chloroamine **25** (Figure 5a). **25** is converted to the nitorosoalkenes **26a** and **26b** as transient intermediates by the heterolytic cleavage of C−O bond with deprotonation, and then **26a** and **26b** immediately undergo chloroamination to give oxoammonium ions (the chiral Cl-AZADO$^+$ **1a** and the chiral Cl-AZADO$^+$ **1b**) as the active species. Next, the racemic alcohol (±)-**17** approaches the chiral AZADO$^+$ **1ab** (Figure 5b). In this stage, the Bn group effectively shields one side of the oxoammonium moiety; thus, (±)-**17** attacks oxoammonium ions diastereoselectively to form the intermediates **27a** and **27b**.[19,20] The enantiomer **17b** is easily oxidized via the intermediate **27b** to afford the corresponding ketone **18b**. On the other hand, the other enantiomer **17a** is difficult to oxidize because the oxy-Cope-type elimination of the intermediate **27a** is prevented by the steric repulsion between the *n*-Bu group on the catalyst and the Ph group on the alcohol. For the difference in the oxidation rate, the chiral alcohol **17a** is eventually recovered with high enantioselectivity. Although the effect of the chlorine atom is still unclear, we consider that the chlorine atom would exert an electronic effect on reactivity and a steric effect on enantioselectivity. Thus, an electron-withdrawing chlorine atom would enhance the electrophilicity of the oxoammonium ion **1ab**, which would increase the reaction rate,[30,31] and the bulky chlorine atom would subtly affect the conformation of the *n*-Bu group on the catalyst, which would enhance enantioselectivity.[32]

Although it was revealed that the chiral Cl-AZADOs **23a** and **23b** exhibited excellent enantioselectivity in the OKR of racemic secondary alcohols, we consider that the use of the precatalyst **1** instead of **23a** or **23b** is preferable for the following two reasons: (1) **1** could be prepared much more readily than **23a** and **23b**, and **1** exhibited adequate enanitioselectivity; (2) **1** was stable during long-term storage, whereas **23a** and **23b** gradually decomposed during storage.

Scope and Application of OKR of Racemic Secondary Alcohols Using Chiral Alkoxyamine 1/TCCA System. Having the **1**/TCCA system as an effective system for the OKR of racemic secondary alcohols, we investigated its substrate scope and application. First, unactivated aliphatic secondary alcohols with relatively simple functional groups were examined (Table 4). The cyclopentanols **28a** and **28b** and the cyclohexanols **28c** and **28d** with an aryl substituent group were efficiently resolved with high enantioselectivity (k_{rel} up to 82.2, entries 1−5). Unfortunately, the cycloheptanol **28e** was not resolved very efficiently (entry 6). The OKR also resolved the 2-alkoxy-substituted cyclohexanols **28f** and **28g** (protected cyclohexane-1,2-diols) and *d*/*l*-menthol **28h** with moderate to good selectivity (entries 7−9). Note that optically active 2-substituted cyclohexanol derivatives are often used as chiral auxiliaries for asymmetric synthesis.[33] Although the OKR of the acyclic substrate **28i** resulted in low selectivity, that of the substrate **28j** having a sterically congested adamantyl group resulted in good selectivity (entries 10 and 11). The OKR resolved isoborneol **28k** with good selectivity (entry 12). The OKR of activated secondary benzylic alcohols was also examined. Although 1-phenylethanol **28l** was resolved in poor selectivity, more sterically hindered alcohol **28m** was resolved in moderate selectivity (entries 13 and 14). Notably,

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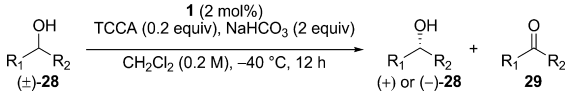
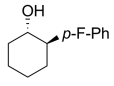
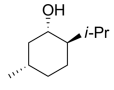
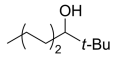
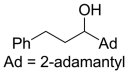
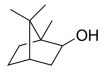
Table 4. Substrate Scope of OKR Using the Chiral Alkoxyamine 1/TCCA System

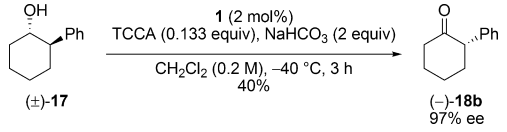


entry	(±)-alcohol		conv (%)[a]	alcohol ee (%)[b]	k_{rel}[c]
1		**28a**	57	99	32.6
2		**28b**	57	97	26.2
3		**17**	52	98	82.2
4		**28c**	53	99	80.1
5		**28d**	53	99	80.1
6		**28e**	58	60	4.5
7		**28f**	57[d]	88	13.8
8		**28g**	58[d]	90	14.0
9		**28h**	52	63	6.8
10		**28i**	54	46[e]	3.5
11		**28j**	55	90	17.4
12		**28k**	51	73[f]	11.8
13		**28l**	53	27	2.1
14		**28m**	56[g]	63	5.5

[a]Conversion was calculated from the yield of alcohol isolated. [b]Determined by chiral HPLC. [c]$k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C is the conversion and ee is the enantiomeric excess of alcohol. [d]Conditions: cat. (3 mol %), $PhI(OAc)_2$ (0.7 equiv), −5 °C, CH_2Cl_2. [e]The absolute configuration is not determined. [f]Determined by chiral GC. Absolute configuration *S*. [g]Condition: 24 h.

the optically active ketone **18** was obtained by the OKR of **17** using **1** with 0.133 equiv of TCCA (0.4 equiv of Cl^+) in 40% yield with excellent enantiopurity (97% ee), which means that the **1**/TCCA system is sufficiently mild to prevent the epimerization of ketones via enol formation and allows for easy access to enantiomerically enriched ketones (Scheme 6).

Scheme 6. Preparation of Enantiomerically Enriched Ketone 18b



Next, we further investigated the scope of the OKR using the **1**/TCCA system so as to develop its synthetic utility. We focused on heterocyclic alcohols, which are host structures of many natural products and biologically active compounds. For example, the compounds **30**[34] and **31** and **32**[35] have inhibitory activity against human renin,[36] and the compounds **33**[37] and **34** and **35**[38] are selective antagonists of the human neurokinin-1 (hNK1) receptor (Figure 6).

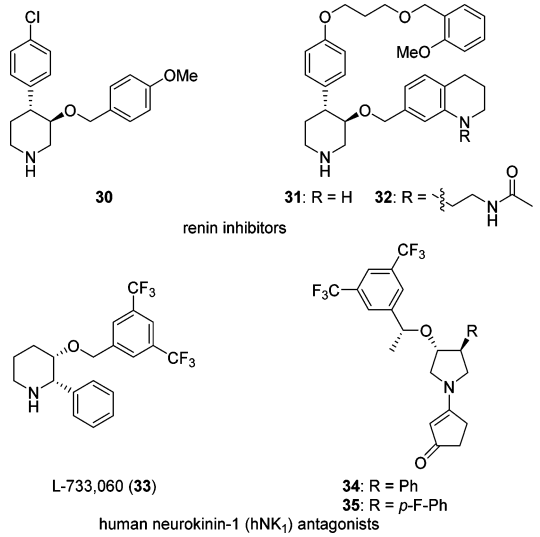


Figure 6. Biologically active compounds derived from chiral heterocyclic alcohols.

We examined the applicability of the OKR using the chiral alkoxyamine **1**/TCCA to aryl substituted heterocyclic alcohols (Table 5).[39] The OKR of *N*-Cbz-*trans*-3-phenyl-4-piperidinol (**36a**) with the **1**/TCCA system resulted in 57% conversion with excellent selectivity (entry 1). The *trans*-4-phenyl-3-piperidinol **36b** was also resolved with excellent enantioselectivity (entry 2). Additionally, the OKR of the *trans*-4-phenyl-3-piperidinol substrates **36c**−**36i** with an electron-donating (Me−) or electron-withdrawing (F−, Cl−, MsO−) group proceeded with high selectivity as well (entries 3−9). Unfortunately, the substrate **36f** with the highly electron rich *p*-methoxyphenyl group underwent decomposition under the oxidative conditions (entry 6). The OKR of the *cis*-2-phenyl-3-piperidinols **36j** and **36k** showed moderate selectivity (entries 10 and 11), although that of the *trans*-2-phenyl-3-piperidinol (**36l**) showed poor selectivity (entry 12). The OKR of the aryl-substituted pyrrolidinol substrates **36m**−**36p** afforded good selectivity (entries 13−16). Although the tetrahydropyran and tetrahydrofuran-type substrates **36q** and **36r** were slowly oxidized with rather attenuated selectivity compared with carbocyclic alcohols (entries 17 and 18), the substrates **36s** and **36t** with the acetonide group were efficiently resolved with high enantioselectivity (entries 19 and 20).

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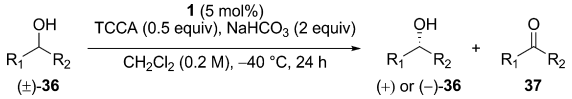
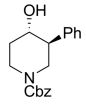
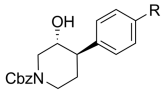
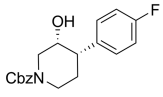
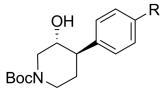
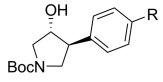
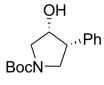
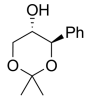
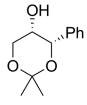
Table 5. Application of the OKR Using the Chiral Alkoxyamine 1/TCCA System to Heterocyclic Alcohols

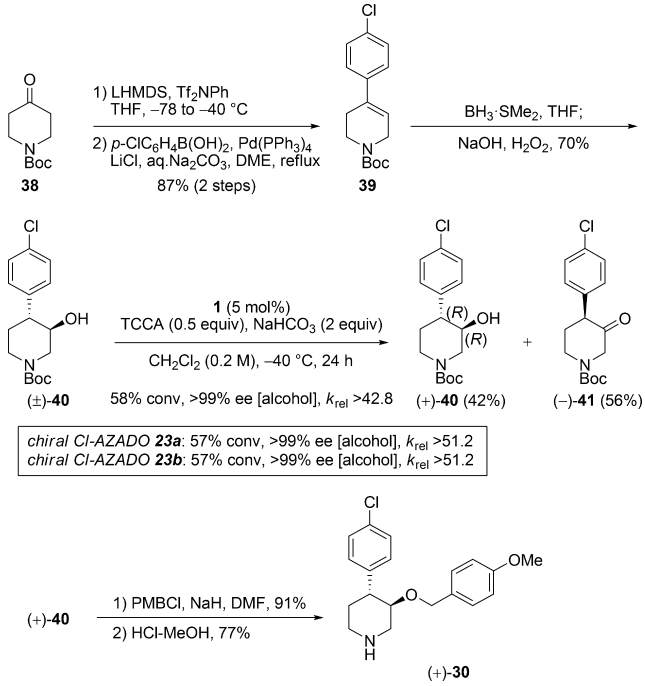


entry	(±)-alcohol		conv (%)[a]	alcohol ee (%)[b]	k_{rel}[c]
1		**36a**	57	99	51.2
2		**36b:** R = H	53	99	173
3		**36c:** R = F	57	98	29.9
4		**36d:** R = Cl	60	99	45.4
5		**36e:** R = Me	57	99	72.1
6		**36f:** R = OMe		decomposition	
7		**36g**	55	99	90.1
8		**36h:** R = H	51	99	297
9		**36i:** R = OMs	58	99	42.8
10		**36j:** R = Boc	59[d]	57	4.0
11		**36k:** R = Cbz	60[d]	43	2.6
12		**36l**	64[d]	3	1.9
13		**36m:** R = H	54[e]	73	7.8
14		**36n:** R = F	51[e]	70	10.4
15		**36o:** R = Me	52	40	3.1
16		**36p**	66[e]	64	3.7
17		**36q**	52	72	11.1
18		**36r**	56	23	1.8
19		**36s**	53[e]	90	26.8
20		**36t**	51[e]	94	67.6

[a]Conversion was calculated from the yield of alcohol isolated. [b]Determined by chiral HPLC. [c]$k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where C is the conversion and ee is the enantiomeric excess of alcohol. [d]Condition: 3 h. [e]Condition: TCCA (0.4 equiv).

Having confirmed the good enantioselectivity of the OKR for heterocyclic alcohols, we demonstrated the validity of our method by synthesizing the renin inhibitor **30**. The synthesis of **30** commenced with the preparation of enol triflate from *N*-Boc-4-piperidone **38** and the subsequent Suzuki–Miyaura coupling reaction with *p*-Cl-phenyl boronic acid to afford **39** (Scheme 7). The hydroboration of the olefin **39** followed by oxidation provided the aryl-substituted piperidinol (±)-**40**. The

Scheme 7. Synthesis of Renin Inhibitor 30



OKR of (±)-**40** employing the **1**/TCCA system exhibited excellent enantioselectivity to give (+)-**40** in 42% yield with >99% ee (and the corresponding ketone in 56% yield). The absolute configuration of the chiral alcohol **40** was determined to be 3*R*,4*R* by measuring the optical rotation [$[\alpha]_D^{22}$ +13.2 (*c* 0.21, AcOEt)] and comparing it with the reported value [lit.[40] $[\alpha]_D^{20}$ −13 (*c* 0.20, enantiopure, AcOEt) for (3*S*,4*S*)-alcohol]. Note that the chiral Cl-AZADOs **23a** and **23b**, which were identified as the plausible active species, exhibited almost the same enaitioselectivity as **1**. Enantiopure (+)-**40** was treated with *p*-methoxybenzyl chloride, providing *N*-Boc-piperidinyl ether in 91% yield. The deprotection of the Boc group in aq HCl and MeOH afforded the renin inhibitor **30** in 77% yield.

CONCLUSION

We have developed a highly enantioselective organocatalytic OKR of racemic secondary alcohols using chiral alkoxyamine as the precatalyst, which represents the first successful example of resolving various unactivated aliphatic secondary alcohols. A systematic synthesis and evaluation of the homoadamantane-type chiral alkoxyamines as catalysts led us to confirm that 7-Bn-3-*n*-Bu-4-oxa-5-azahomoadamantane (**1**) is the most effective precatalyst for the OKR of racemic secondary alcohols. The chlorine-containing oxoammonium species generated from the alkoxyamine were identified as active species, and it was revealed that the chlorine atom plays a key role in the high catalytic activity and enantioselectivity. OKR using the **1**/TCCA system exhibits good to excellent enantioselectivity for various unactivated aliphatic secondary alcohols, including synthetically useful heterocyclic alcohols. This study demonstrates not only the novel use of an alkoxyamine precatalyst for asymmetric catalysis but also the unprecedented stereoelectronic effect of the chlorine atom on oxoammonium species. We consider that the present OKR is a powerful tool

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for providing novel types of chiral alcohols, which are useful for the synthesis of bioactive compounds and natural products. Further study to clarify the effect of the chlorine atom is under way.

EXPERIMENTAL SECTION

Typical Procedure for Oxidative Kinetic Resolution (Table 4, entry 3). A 30 mL round-bottomed flask equipped with a magnetic stirring bar was charged with the racemic secondary alcohol **17** (200 mg, 1.14 mmol), $NaHCO_3$ (192 mg, 2.28 mmol, 2 equiv), **1** (6.8 mg, 22.8 μmol, 0.02 equiv), and CH_2Cl_2 (5.7 mL, 0.2 M). After cooling the mixture at −40 °C, TCCA (54.6 mg, 0.228 mmol, 0.2 equiv) was added, and the mixture was stirred at a fixed temperature for 12 h. The mixture was diluted with *i*-PrOH (1 mL) followed by saturated aqueous $NaHCO_3$ (10 mL) .The mixture was then allowed to warm to room temperature. The aqueous layer was separated and extracted with $CHCl_3$. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (AcOEt/hexane = 1/9 to 1/6) to give the chiral ketone (−)-**18b** (103 mg, 0.591 mmol, 52%) and the chiral alcohol (+)-**17a** (96 mg, 0.545 mmol, 48%).

Enantiomeric excess of chiral alcohols was determined by analytical chiral HPLC or chiral GC. The absolute configurations of the alcohols were determined by comparison of the measured optical rotation values with literature data or proposed by considering their reaction mechanism (see the Supporting Information for details).

ASSOCIATED CONTENT

Supporting Information

Optimization of the reaction conditions, synthetic procedures for the catalysts, preparation of the substrates, conditions for chiral HPLC analysis, characterization data (including a cif file), and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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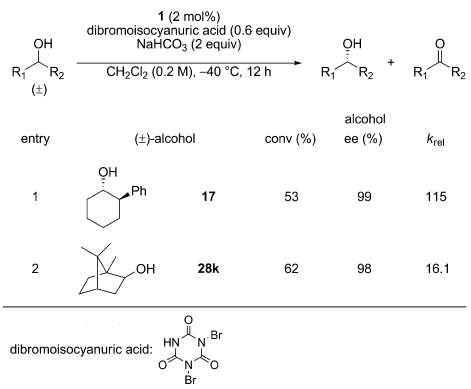

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