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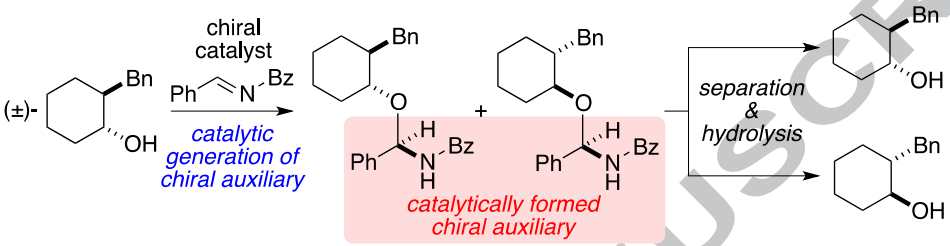

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Optical Resolution via Catalytic Generation of Chiral Auxiliary.

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ABSTRACT

A new catalytic method for separating enantiomers of racemic compounds is proposed. Catalytic asymmetric addition of chiral *trans*-2-substituted cyclohexanols to imines provided diastereomeric mixtures of aminals, and the subsequent separation of the enantiomers by silica-gel column chromatography and the hydrolysis of the aminals produced the alcohols in an optically active form.

Optical resolution is one of the oldest and most reliable methodologies used to obtain optically pure chiral compounds.[1] For instance, a racemic secondary alcohol is covalently connected to an optically pure acyl group (R*CO) producing a mixture of diastereomeric esters, which are then separated, taking advantage of their different physical properties (Figure 1a). Conventional optical resolution has two important drawbacks: (1) the maximum yield of a desired enantiomer is 50%, and (2) a stoichiometric amount of optically pure compounds, or resolving agents is required. The first drawback, however, becomes an advantage when divergence is oriented and when both enantiomers are required, such as for biological tests. With respect to the second drawback, catalytic kinetic resolution (Figure 1b) is one method of addressing the issue, whereby enantiomers are resolved by a catalytic asymmetric reaction in which the enantiomers have different reaction rates; thus, only a catalytic amount of a chiral source is required.[2] Here we propose another concept to resolve enantiomers using a catalytic asymmetric reaction.[3]

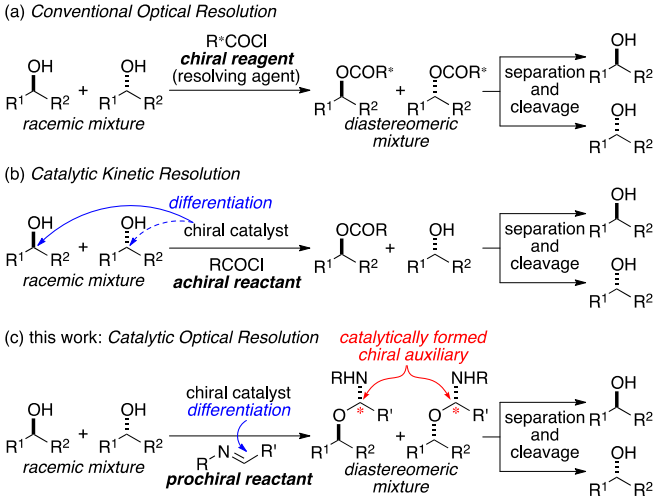

Figure 1. Separating Enantiomers of Racemic Secondary Alcohols.

Our basic proposed concept is presented in Figure 1c. When a racemic mixture of alcohol is subjected to a catalytic asymmetric reaction with a prochiral reactant, such as aldimine RCH=NR', the newly created chirality makes the products diastereomeric.[4] Both alcohol enantiomers can be isolated after the separation of the diastereomers followed by the corresponding retro-reaction. Thus, the chirality created by the catalytic asymmetric reaction is used as a substitute for chirality provided by a resolving agent in conventional optical resolution. For successful resolution, the catalytic asymmetric reaction should be highly enantioselective and catalyst-controlled, and the product must be returnable to the substrate by a retro-reaction under certain conditions. In contrast to catalytic kinetic resolution, which relies on recognition of the chirality of "the substrate" by the chiral catalyst that causes an energy difference between the transition states of the both substrate enantiomers, the chiral catalyst discriminate the prochirality of "the reactant". Thus, in principle, the selectivity of the reactions could be less dependent on the substrate structures. Accordingly, this method was expected to provide another effective way to obtain enantiomeric purity in addition to optical resolution and kinetic resolution. Chiral alcohols are fundamental and important chiral building blocks for pharmaceutical, agrochemical, and fragrance compounds. To demonstrate the method, the reported asymmetric addition of alcohols to imines

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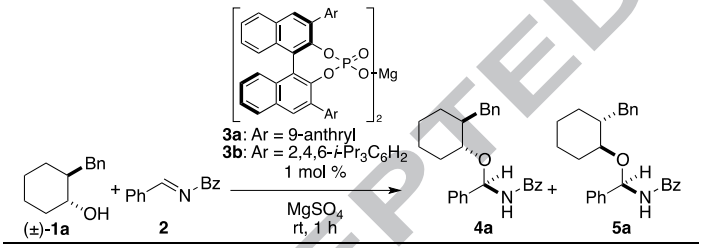
catalyzed by chiral magnesium phosphate [5] was applied to racemic secondary alcohols.

First, we compared two chiral magnesium phosphates **3a**[6] and **3b**[7] in the reaction with racemic secondary alcohol (±)-**1a**[8] (Table 1, entries 1 and 2) because these were reported as good catalysts for the asymmetric addition of ω-halo alkanols to imines.[5a] The phosphate salts were prepared according to the literature.[5] A 2:1 mixture of the corresponding phosphoric acids and magnesium *tert*-butoxide was stirred in CH_2Cl_2–MeOH under an argon atmosphere at rt for 1 h, and volatile materials were removed *in vacuo*. The addition of dry CH_2Cl_2 and *in vacuo* concentration were repeated three times to remove the residual alcohol. In the presence of prepared **3a** and $MgSO_4$, the reaction of (±)-**1a** and imine **2**[9] was conducted in EtOAc at rt (Table 1, entry 1). After 1 h, diastereomeric adducts **4a** and **5a** were quantitatively produced and separated by silica gel column chromatography. Chiral HPLC analysis revealed the enantiomeric excesses (ee) of **4a** and **5a** were 88% and 74%, respectively. The absolute configurations of **4a** and **5a** were assigned on the basis of the stereochemistry of recovered **1a** (*vide infra*) and the enantioselectivity reported for the addition to imine.[5] The use of **3b** resulted in better selectivity, producing **4a** and **5a** with 92% ee and 91% ee, respectively (entry 2). Changing the solvent to toluene or $CHCl_3$ failed to improve the selectivity, and the obtained products had slightly lower ee of 89% and 90%, and 79% and 87%, respectively (entries 3 and 4). The reaction rate significantly decreased when the reaction was conducted in THF, where **4a** and **5a** were produced in 46% and 47% yield, respectively, in 9 h (entry 5); however, almost complete conversion was observed in 1 h when the other solvents were used (entries 1–4).

Table 1. Optimization of the Reaction Conditions.[a]

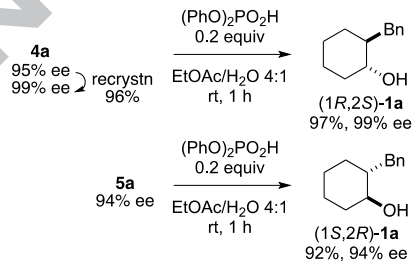


entry	catalyst	solvent	4a		5a	
			% yield	% ee	% yield	% ee
1	**3a**	EtOAc	50	88	50	74
2	**3b**	EtOAc	45	92	45	91
3	**3b**	toluene	48	89	48	90
4	**3b**	$CHCl_3$	50	79	50	87
5[b]	**3b**	THF	46	85	47	85
6	**3a**[c]	EtOAc	49	94	49	90
7	**3b**[c]	EtOAc	50	97	50	96
8[d]	**3b**[c]	EtOAc	39	95	44	94

[a] The reaction was conducted with **2** (0.4 mmol), **1a** (0.2 mmol), **3** (2 μmol), and $MgSO_4$ (50 mg) in solvent (1 mL) under Ar atmosphere. The ee's were determined by chiral HPLC analysis. [b] For 9 h. [c] Freshly prepared and dried at 100 °C in vacuo prior to use. [d] The reaction was conducted with **2** (8.75 mmol), **1a** (832 mg, 4.37 mmol), **3** (0.04 mmol), and $MgSO_4$ (550 mg) in EtOAc (22 mL) under Ar atmosphere for 3 h.

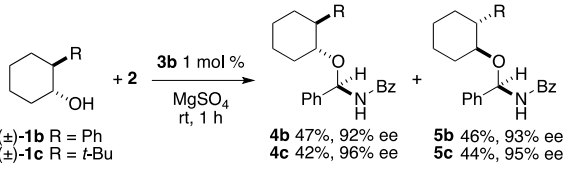
In this reaction, modification on the catalyst preparation procedure effectively improved the results. After mixing the corresponding phosphoric acids and magnesium *tert*-butoxide in CH_2Cl_2–MeOH under argon atmosphere at rt for 1 h, volatile materials were removed *in vacuo*, and the resulting solid material was further dried at 100 °C *in vacuo*, instead of through azeotropic distillation, and freshly used as a catalyst. When **3a** prepared by the modified procedure was used, **4a** and **5a** were obtained with improved ee values (from 88% and 74% to 94% and 90%, respectively; entries 1 and 6). The improvement was also observed with **3b**, producing **4a** and **5a** with 97% ee and 96% ee, respectively (entry 7 vs entry 2).

The catalytic optical resolution protocol was conducted at a preparative scale (Table 1, entry 8). The catalytic asymmetric addition of (±)-**1a** (832 mg) to **2** furnished **4a** (674 mg) and **5a** (784 mg) with 95% ee and 94% ee in 39% and 44% isolated yields, respectively. The optical purity of **4a** was enriched by recrystallization from EtOAc–hexane to give **4a** with 99% ee in 96% yield (Scheme 1). The subsequent hydrolysis produced optically pure (1*R*,2*S*)-**1a** with $[\alpha]_D^{30}$ –41.6 (*c* 1.00, $CHCl_3$) in 97% yield. The other isomer **5a** was also hydrolyzed to give (1*S*,2*R*)-**1a** with $[\alpha]_D^{30}$ +36.0 (*c* 1.13, $CHCl_3$)[10] in 92% yield. Thus, the three-step sequence (the catalytic asymmetric addition, the enantiomer separation, and the retro-reaction) illustrates the proposed catalytic optical resolution.



Scheme 1. Recovery of Enantiomerically Enriched Alcohol **1a**.

The catalytic optical resolution was applied to cyclohexanols bearing other substituents (Scheme 2). The catalytic asymmetric addition of 2-phenylcyclohexanol **1b** to imine **2** produced diastereomeric **4b** and **5b** with 92% and 93% ee in 47% and 46% yield, respectively. *tert*-Butyl substituted cyclohexanol **1c**[11] was also determined to be a good substrate for this reaction, producing **4c** and **5c** with 96% and 95% ee in 42% and 44% yield, respectively. The both diastereomeric adducts were separable by silica gel column chromatography; thus, these results exemplified the present catalytic optical resolution. Notably, the pairs of the diastereomers (i.e., **4a**–**5a**, **4b**–**5b**, and **4c**–**5c**) were produced with almost the same yield and ee. This clearly shows that the **3b**-catalyzed reaction was highly catalyst-controlled. In contrast, the reactions of **1b** and **1c** using achiral catalyst, magnesium bis(diphenyl phosphate), were substrate-controlled and produced (1*RS*,2*SR*)-isomers **4b** and **4c** with slight preference over (1*RS*,2*RS*)-isomers **5b** and **5c** (ca. 2:1), respectively.



Scheme 2. Catalytic Asymmetric Addition of Other Cyclohexanols **1** to Imine **2**.

In summary, we have proposed a new method of separating racemic chiral compounds using a catalytic amount of a chiral source, namely, the catalytic optical resolution. The catalytic

asymmetric addition of *trans*-2-substituted cyclohexanol to imine produced separable mixtures of diastereomeric adducts, the hydrolysis of which provided enantiomerically enriched alcohols. This result clearly demonstrated that the proposed concept is functional, and it is possible that the scope of the concept could be extended to substrates bearing functionality other than alcohol.

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Supplementary Material

Experimental detail and characterization data for new compounds are available as a Supplementary Material.

References and notes

1 (a) Siedlecka, R.; *Tetrahedron* **2013**, *69*, 6331. (b) Faigl, F.; Fogassy, E.; Nógrádi, M.; Pálovics, E.; Schindler, J. *Tetrahedron: Asymmetry* **2008**, *19*, 519. (c) Sakai, K.; Hirayama, N.; Takamura, R. *Top. Curr. Chem.* **2007**, *269*, 233. (d) Fogassy, E.; Nógrádi, M.; Kozma, D.; Egri, G.; Pálovics, E.; Kiss, V. *Org. Biomol. Chem.* **2006**, *4*, 3011. (e) Eliel, E. L.; Wilen, S. H.; Mander, L. N. in *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; pp 297–264.

2 (a) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz. B. M. *Chem. Rev.* **2017**, *117*, 4528. (b) *Separation of Enantiomers*; Tod, M., Ed; Wiley-VCH: Weinheim, 2016. (c) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974. (d) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (e) Kagan, H. B.; Fiaud, J. C. in *Kinetic Resolution*; Eliel, E. L.; Wilen, S. H., Eds; Topics in Stereochemistry, Vol. 18; Wiley & Sons: New York, 1988; p. 249.

3 Our recent contributions: (a) Kang, B.; Wang, Y.; Kuwano, S.; Yamaoka, Y.; Takasu, K.; Yamada, K. *Chem. Commun.* **2017**, *53*, 4469. (b) Wang, Y.; Raphaël, O.; Oh, S.; Miyakawa, Y.; Yamaoka, Y.; Takasu, K.; Yamada, K. *Heterocycles* **2017**, *95*, 413. (c) Kuroda, Y.; Harada, S.; Oonishi, A.; Kiyama, H.; Yamaoka, Y.; Yamada, K.; Takasu, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 13137. (d) Yamada, K.; Oonishi, A.; Kuroda, Y.; Harada, S.; Kiyama, H.; Yamaoka, Y.; Takasu, K. *Tetrahedron Lett.* **2016**, *57*, 4098. (e) Arichi, N.; Yamada, K.; Yamaoka, Y.; Takasu, K. *J. Am. Chem. Soc.* **2015**, *137*, 9579. (f) Kuroda, Y.; Harada, S.; Oonishi, A.; Yamaoka, Y.; Yamada, K.; Takasu, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 8263. (g) Kang, B.; Sutou, T.; Wang, Y.; Kuwano, S.; Yamaoka, Y.; Takasu, K.; Yamada, K. *Adv. Synth. Catal.* **2015**, *357*, 131. (h) Kuwano, S.; Harada, S.; Kang, B.; Oriez, R.; Yamaoka, Y.; Takasu, K.; Yamada, K. *J. Am. Chem. Soc.* **2013**, *135*, 11485. (i) Harada, S.; Kuwano, S.; Yamaoka, Y.; Yamada, K.; Takasu, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 10227.

4 This class of reactions can also be regarded as examples of stereodivergent parallel kinetic resolution: (a) Dehli, R.; Gotor, V. *Chem. Soc. Rev.* **2002**, *31*, 365. (b) Miller, L. C.; Sarpong, R. *Chem. Soc. Rev.* **2011**, *40*, 4550.

5 (a) Nimmagadda, S. K.; Zhang, Z.; Antilla, J. C. *Org. Lett.* **2014**, *16*, 4098. (b) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216.

6 Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*,9360.

7 (a) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424. (b) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141.

8 Hazmi, A. M. A.; Sheikh, N. S.; Bataille, C. J. R.; Al-Hadedi, A. A. M.; Watkin, S. V.; Luker, T. J.; Camp, N. P.; Brown, R. C. D. *Org. Lett.* **2014**, *16*, 5104.

9 (a) Cowen, B. J.; Saunders, L. B.; Miller, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 6105. (b) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001,** *123*, 9696.

10 lit. $[\alpha]_D^{20}$ +49.2 (*c* 1, $CHCl_3$): (a) Fronza, G.; Fogliato, G.; Fuganti, C.; Lanati, S.; Rallo, R.; Servi, S. *Tetrahedron Lett.* **1995**, *36*, 121. (b) Fogliato, G.; Fronza, G.; Fuganti, C.; Lanati, S.; Rallo, R.; Rigoni, R.; Servi, S. *Tetrahedron* **1995**, *51*, 10231.

11 Alexakis, A.; Jachiet, D.; Normant, J. F. *Tetrahedron* **1986**, *42*, 5607.

Highlights

- The addition gave the catalytically formed chiral auxiliary with high selectivity.
- The diastereomeric adducts were chromatographically separated.
- Recrystallization enriched the enantiomeric excess of the adduct.
- Hydrolysis of the adducts gave the enantiomers of the alcohols in high yields.
- The concept could be extended to substrates bearing other functionality.