A Polymer-Supported Proline-Based Diamine Catalyst for the Kinetic Resolution of Racemic Secondary Alcohols

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The preparation of polymer-supported proline-based diamine catalyst **12** for the kinetic resolution of racemic mixtures of secondary alcohols is described. Not only is the catalyst effective for the resolution of a host of different alcohols, it can also be recovered and reused several times without loss of either activity or selectivity. The catalyst has been used in conjunction with a polymer-supported sequestration strategy, giving rise to an essentially pure mixture of resolved products that can be separated using flash chromatography.

Introduction

The preparation of organic compounds in high enantiomeric purity is a goal that has seen an intense amount of research over the last few decades. Significant progress has been made by utilizing chiral reagents, catalysts, or auxiliaries in pursuit of this objective.[1] An alternative procedure involves the resolution of a racemic mixture into its isomeric components, enabling access to both enantiomers in just one operation. Traditionally, kinetic resolutions have been performed using enzyme catalysts that react selectively with only one of the enantiomers, enabling physical separation after the reaction.[2] More recently, several groups have achieved nonenzymatic kinetic resolutions by using chiral acylation catalysts that facilitate the stereoselective esterification of one enantiomer from a racemic mixture of alcohols.[3] Although such catalysts have been or could be recovered after reaction using chromatography, it is envisaged that this process for recycling is uneconomical and would be difficult to automate.

Solid-phase chemistry is now the preferred method for the preparation of large numbers of potential drug candidates.[4] The development of combinatorial solid-phase technologies has also been applied toward the discovery of new catalysts.[5] In addition, there has been a renewed interest in the development of polymer-supported versions of existing solution-phase catalysts.[6] These advances are of great importance from both economical and environmental viewpoints: The discovery of new catalysts will ensure more efficient processes for preparing specific compounds. Indeed, reactions performed using polymer-supported catalysts can be purified by filtration of the reaction mixture, enabling recovery and reuse of potentially valuable species.

One of the main themes of our group's research is the development of polymer-supported methodologies, including new polymer-supported reagents[7] and catalysts. We have introduced poly(ethylene glycol) (PEG)-supported triarylphosphine reagents[8] and also PEG-supported triflating reagents.[9] In addition, we have reported the synthesis and application of PEG-supported Sharpless dihydroxylation catalysts[10] and, more recently, both PEG and resin-supported Jacobsen epoxidation catalysts.[11] To our knowledge, there are no reported examples of the kinetic resolution of alcohols using polymer-supported catalysts.[12] We report herein the preparation of a polymer-supported proline-based diamine catalyst that is effective for the kinetic resolution of secondary alcohols. The catalyst can be recovered after the reaction and reused without loss of activity or selectivity. Additionally, we have shown that it can be used in conjunction with a solid-phase sequestration procedure.[13] In this way, the byproducts from the reaction can be removed from the reaction in a high-throughput manner, precluding the requirement for aqueous workup procedures.

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(1) (a) Ager, D. J.; East, M. B. *Asymmetric Synthetic Methodology*; CRC Press: London, 1996. (b) *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Chapman and Hall: London, 1996. (c) Ho, T.-L. *Stereoselectivity in Synthesis*; John Wiley & Sons: New York, 1999.

(2) Davies H. G.; Green, R. H.; Kelly, D. R.; Roberts, S. M. *Biotransformations in Preparative Organic Chemistry*; Academic Press Ltd.: London, 1989.

(3) (a) Somfai, P. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 2731. (b) Long, Y. O.; Paquette, L. A. *Chemtracts* **2000**, *13*, 1. (c) Yamada, T. *Chemtracts* **2000**, *13*, 9.

(4) (a) Bunin, B. A. *The Combinatorial Index*; Academic Press Ltd.: London, 1998. (b) *Combinatorial Chemistry, Synthesis and Application*; Wilson, R. W., Czarnik, A. W., Eds.; John Wiley & Sons: New York, 1997. (c) Obrecht, D.; Villalgordo, J.-M. *Solid-Supported Combinatorial and Parallel Synthesis of Small Molecular Weight Compound Libraries;* Tetrahedron Organic Chemistry Series, Vol. 17; Pergamon: New York, 1998.

(5) (a) Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Curr. Opin. Chem. Biol.* **1999**, *3*, 313. (b) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H.; *Chem. Eur. J.* **1998**, *4*, 1855.

(6) (a) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035. (b) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, *11*, 1217.

(7) Brümmer, O.; Clapham, B.; Janda, K. D. *Curr. Opin. Drug Discovery Dev.* **2000**, *3*, 462.

(8) (a) Sieber, F.; Wentworth Jr., P.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. *J. Org. Chem.* **1999**, *64*, 5188. (b) Wentworth Jr., P.; Vandersteen, A. M.; Janda, K. D. *Chem. Commun.* **1997**, *8*, 759. (c) Janda, K. D.; Reed, N. N. *Org. Lett.* **2000**, *2*, 1311.

(9) Wentworth, A. D.; Wentworth Jr., P.; Mansoor, U. F.; Janda, K. D. *Org. Lett.* **2000**, *2*, 477.

(10) (a) Han, H.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 1527. (b) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632.

(11) Reger, T. S.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 6929.

(12) For the kinetic resolution of *meso*-epoxides using polymer-supported catalysts, see: (a) Peukert, S.; Jacobsen, E. N. *Org. Lett.* **1999**, *1*, 1245. (b) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147.

(13) Parlow, J. J.; Devraj, R. V.; South, M. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320.

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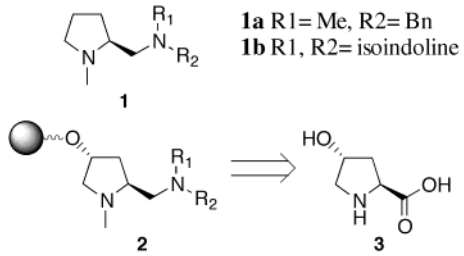
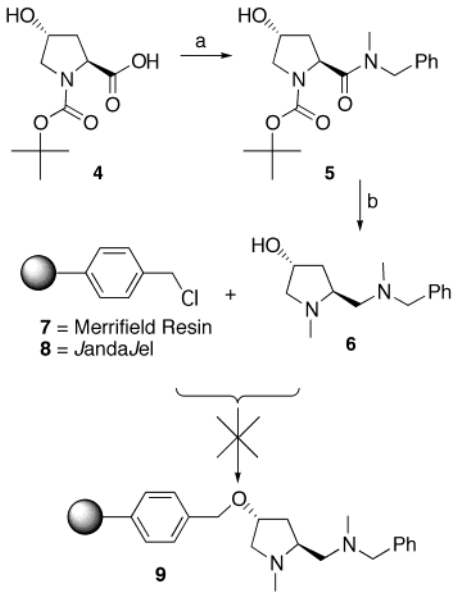


Figure 1. Polymer-supported proline ligand strategy.

Scheme 1[a]



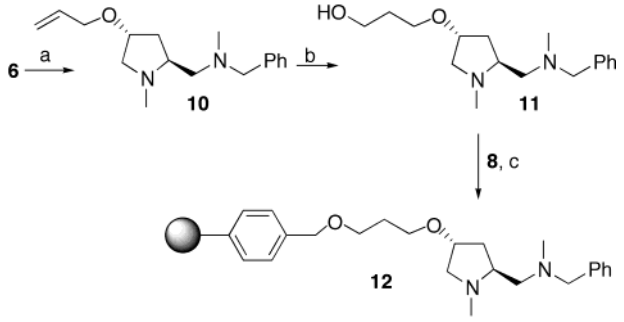
[a] Conditions: (a) DCC, HOBT, benzylmethylamine, CH_2Cl_2, 98%. (b) (i) $LiAlH_4$, THF. (ii) $Na_2SO_4 \cdot 10H_2O$, 98%.

Results and Discussion

Oriyama and co-workers have recently reported the utility of proline-based ligands **1** as catalysts for kinetic resolution (Figure 1).[14] These ligands are particularly attractive for further development because they have been utilized in other applications such as the asymmetric acylation of *meso*-diols,[15] asymmetric Mukiyama aldol reaction,[16] and the asymmetric rearrangement of allylic imidates to allylic amides.[17] *trans*-4-Hydroxyproline **3** was chosen as a starting point for the preparation of the polymer-supported ligand **2**, since the secondary alcohol would serve as a convenient site for attachment of the catalyst to the resin[18] (Figure 1).

Accordingly, *N*-BOC hydroxyproline **4** was reacted with benzylmethylamine in the presence of DCC and HOBt to provide amide **5** in 98% yield (Scheme 1). The corresponding hydroxy-functionalized diamine **6** was then prepared by reduction of amide **5** using excess $LiAlH_4$.

Scheme 2[a]

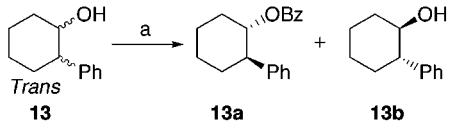


[a] Conditions: (a) (i) KH, THF. (ii) allyl bromide, 91%. (b) (i) 9-BBNH, THF. (ii) H_2O_2, NaOH, EtOH, 74%. (c) (i) KH, THF. (ii) **8**, KI (cat.), 18-crown-6 (cat.), THF.

After the reaction was quenched with $Na_2SO_4 \cdot 10H_2O$, it was critical to extract the resulting salts in a Soxhlet apparatus using dioxane to ensure a good recovery of product. While the preparation of the polymer-supported catalyst from hydroxy diamine **6** using a Williamson ether formation reaction appeared to be straightforward, our initial attempts to attach the ligand to Merrifield (**7**) and chloromethyl *J*anda*J*el[19] (**8**) resins were unsuccessful. Numerous bases (NaH, $NaN(SiCH_3)_2$, and $KN(SiCH_3)_2$) in the presence of various catalysts (18-crown-6 and KI) using different solvents (THF and DMF) failed to produce the desired product **9**.

An alternative procedure was developed whereby a short spacer unit was attached to the diamine ligand **6** before reaction with the resin (Scheme 2). It was also anticipated that having additional distance between the catalyst cleft and the polymer backbone would reduce the detrimental effect caused by the bulky polymer and possibly enhance catalyst performance. Here, hydroxy diamine **6** was treated with excess potassium hydride, and the resulting alkoxide was reacted with allyl bromide at reflux temperature for several hours to give allyl ether **10**. Next, the corresponding hydroxypropyl ether **11** was prepared by hydroboration of allyl ether **10** using 9-borabicyclononane hydride (9-BBNH). The hydroxypropyl ether functionalized diamine **11** could now be attached to chloromethyl *J*anda*J*el **8** using a Williamson ether formation reaction to provide polymer-supported catalyst **12**. The increase in mass of the polymer after reaction indicated quantitative attachment of the ligand onto the resin. Using the original chloride resin loading of 0.70 mmol g^{-1} and this mass increase of the polymer, a resin loading of 0.59 mmol g^{-1} was calculated.

To evaluate the amount of catalyst **12** required and the length of reaction time needed for kinetic resolution, a standard set of parameters, based on Oriyma's report,[14b] were used (eq 1, conditions (a) **12**, BzCl (0.75 equiv), Et_3N (0.5 equiv), molecular sieves (4 Å), CH_2Cl_2, −78 °C). These



(1)

conditions included the addition of molecular sieves to

(14) (a) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543. (b) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, 265.

(15) (a) Oriyama, T.; Imai, K.; Hosoya, T.; Sano, T. *Tetrahedron Lett.* **1998**, *39*, 397. (b) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529.

(16) (a) Kobayashi, S.; Horibe, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2565. (b) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805.

(17) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449.

(18) For an alternative method for preparing polymer-supported proline-derived ligands, see: Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712.

(19) *J*anda*J*el resins are now commercially available from Aldrich Chemical Co. See also: Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40*, 6329.

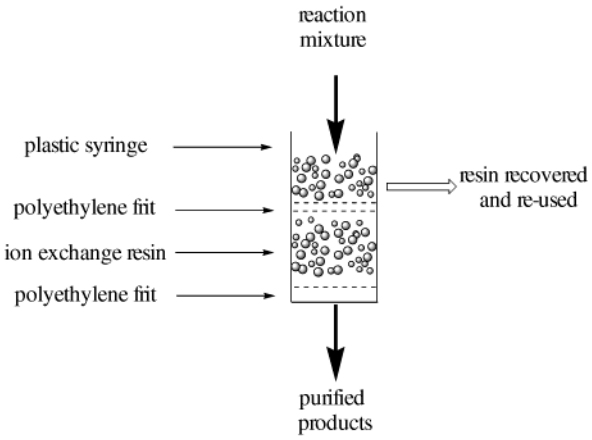


Figure 2. Schematic representation of the polymer-supported purification/workup strategy.

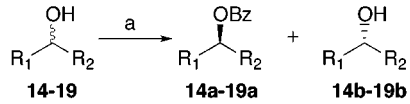
Table 1. Optimization of Reaction Conditions for Kinetic Resolution Using catalyst 12

run	amt of **12** (mol %)	time (h)	yield[a] of **13a** (%)	ee of **13a** (%)	yield of **13b** (%)	ee of **13b** (%)	S
1	5	3	21	92	72	NR	NR
2	10	6	32 (33)	96	58	47	78
3	12.5	9	43 (44)	95	43	74	88
4	15	11	44 (47)	96	45	85	134
5	18	12	45 (45)	96	45	78	118

[a] Percent conversion given in parentheses.

the reaction, thus removing traces of water which retard reaction rates. During the optimization of reaction conditions, a simple filtration workup procedure was also developed that enabled isolation of the reaction products free from any byproducts produced during the course of the reaction. In Oriyama's report,[14b] the reaction was quenched using an aqueous buffer and then purified using conventional organic/aqueous separation and extraction techniques. To circumvent the requirement for this workup, the reaction mixture was filtered through a small cartridge of mixed-bed ion-exchange resin. This cartridge was prepared by placing the ion-exchange resin in a plastic syringe fitted with a polyethylene frit,[20] and an additional frit was then placed on top of the resin. Thus, after completion of the reaction, the polymer was separated from the molecular sieves by removing resin from the reaction flask with a pipet and then transferring it to the ion-exchange cartridge. In this manner, after filtration and washing, the polymer-supported catalyst **12** could then also be recovered separately from the ion-exchange resin (Figure 2). The filtrate was then concentrated under reduced pressure to provide a mixture of resolved products that were free of any of the reagents used in the reaction. After separation of the products by flash chromatography, they were analyzed for enantiomeric excess using chiral HPLC. The results for the kinetic resolution of *trans*-2-phenyl-1-cyclohexanol (**13**) (eq 1) and the corresponding catalyst selectivity factor[21] (*S*) are presented in Table 1.

After 3 h in the presence of 5 mol % catalyst, the yield of resolved ester **13a** was only 21% (Table 1, run 1); however, the enantiomeric purity (92%) of this product was encouraging. A further increase of catalyst loadings and extended reaction times gave rise to superior conversions and enantiomeric purity of the products, with the optimal being run 4, where the ester **13b** (44%, 96% ee) and alcohol **13a** (45%, 85% ee) were recovered. However, at 18 mol % catalyst loading, the reaction was apparently slowed by the use of too large a quantity of resin for the given amount of solvent, and we have attributed this to inefficient agitation of the reaction mixture because of its viscous nature (run 5). Interestingly, during the course of reaction condition optimization, different selectivity factors (*S*) were observed. The *S* factors should remain constant with reaction concentration and with catalyst loading; however, this has been observed elsewhere,[14b] and we have attributed our observations to experimental error. Using the optimum reaction conditions (run 4, $S = 134$), a series of racemic secondary alcohols **13**−**19** were resolved using the polymer-supported catalyst **12** (eq 2, conditions (a) **12** (15 mol %), BzCl (0.75 equiv), Et_3N (0.5 equiv), molecular sieves (4 Å), CH_2Cl_2, −78 °C, 11 h). In all cases optical purity was determined using chiral



(2)

HPLC analysis. Unreacted alcohols **13b**−**19b** were analyzed directly, and esters **13a**−**19a** were converted back to the parent alcohol using $LiAlH_4$ prior to analysis. Absolute configurations were determined by either comparison of retention times of the resolved products with commercially available material or by comparison of their optical rotations with previously reported materials. Finally, some of these experiments were also performed under solution-phase conditions using ligand **1a**, enabling a comparison between the performance of the homogeneous and heterogeneous catalysts to be made. These results are presented in Table 2.

When the conversion rates of the polymer-supported catalyst **12** are compared with those of the solution-phase catalyst **1a**, it can be seen that the polymer-supported catalyst **12** gives slightly slower conversion rates. However, the most important feature of catalysts for kinetic resolution is high selectivity factors (*S*). Table 2 shows clearly that the polymer-supported catalyst **12** gives *S* values to comparable to those of the solution-phase analogue **1a**, as can be seen when entries 1 and 2, 6 and 7, and 8 and 9 are compared. The phenyl-substituted cycloalkanols **14** and **15** were all resolved with reasonable ee's (entries 1, 3, and 4), while the fused ring cycloalkanols **16** and **17** gave slightly poorer resolution (entries 5 and 6). Finally, the open chain alcohols **18** and **19** gave little or no resolution (entries 8 and 10). Although the polymer-supported catalyst is slightly less active than the solution-phase analogue, the comparable selectivities suggest that further development of these resin-bound proline-based ligands will yield catalysts with superior performance in the kinetic resolution of alcohols.

One of the most important features of a polymer-supported catalyst is that it can be conveniently recovered and reused. This was examined by performing repeated resolutions of *trans*-2-phenyl-1-cyclohexanol (**13**) using 15 mol % catalyst for 6 h. These results are presented in Table 3. The reaction was performed five

(20) The material used was Fritware, a 70 μm polyethylene sheet available from Scienceware. Small disks were prepared using conventional cork boring tools and placed within standard plastic syringes.

(21) Chen, C.-S. Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.

Table 2. Kinetic Resolution of Various Alcohols Using Catalyst 12

Entry	Catalyst	Alcohol	Yield (%)[a] ester **a**	ee (%) ester **a**	Yield (%) alcohol **b**	ee (%) alcohol **b**	Selectivity factor (S)
1	**12**	**13** 	44 (47)	96 (1*S*, 2*R*)	45	85	134
2	**1a**[b]	**13** 	48	97 (1*S*, 2*R*)	49	97	200
3	**12**	**14** 	47 (46)	85 (1*S*, 2*R*)[c]	49	72	27
4	**12**	**15** 	15 (15)	78[d]	58	14	9
5	**12**	**16** 	44 (46)	58 (*R*)	47	50	6
6	**12**	**17** 	44 (44)	38 (*R*)	47	30	3
7	**1a**	**17** 	53 (59)	37 (*R*)	47	53	4
8	**12**	**18** 	46 (50)	16 (*S*)	49	16	2
9	**1a**	**18** 	54 (59)	23 (*S*)	34	33	2
10	**12**	**19** 	53	0	24	0	0

[a] Percent conversions are given in parentheses. [b] Reference 14b. [c] Mandal, A. K.; Jadhav, P. K.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 3543. [d] *trans* isomer prepared according to Hiroaki, T.; Brener, L.; Brown, H. C. *J. Am Chem. Soc.*, **1976**, *98*, 7107. The absolute stereochemistry of this compound was not determined.

Table 3. Recycling of Catalyst 12

run	yield of **13a** (%)	ee of **13a** (%)	yield of **13b** (%)	ee of **13b** (%)
1	36	96	57	62
2	35	96	62	58
3	34	95	63	58
4	36	94	59	56
5	35	95	58	58

times using the same sample of recovered catalyst, and as the table shows, there is no loss of either catalyst activity or selectivity.

Conclusion

In conclusion, we have developed an effective polymer-supported catalyst that effects the kinetic resolution of a series of racemic secondary alcohols. The reaction is fully automatable and does not require an aqueous workup; however, the separation of the resolved products using chromatography remains the limiting factor for the process. We are currently investigating methods to resolve this problem. In addition, we have shown that the polymer-supported catalyst can be recovered and reused multiple times without loss of either activity or selectivity. Although the polymer-supported catalyst is slightly less active than the corresponding solution-phase analogue, it gives comparable selectivity factors (*S*). A high catalyst loading (15 mol %) was required to achieve resolution in an acceptable period of time. As a consequence, a larger mass of polymer-supported ligand than substrate is used in the reaction; however, this was not a practical problem, since both the catalyst and the substrates were recovered in nearly quantitative yield upon completion of the reaction. Additional developments using polymer-supported proline ligands are ongoing in our laboratory and will be reported in due course.

Experimental Section

General Methods. All reagents were purchased from commercial sources and used as received with the following exceptions: Benzoyl chloride was distilled from aluminum chloride under reduced pressure and stored over molecular sieves under an argon atmosphere. Triethylamine (Et_3N) was distilled from calcium hydride and stored over molecular sieves under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketal, and CH_2Cl_2 was

distilled from calcium hydride. The ion-exchange resins, Dowex 50WX2-200 and Dowex 1X2-400, were washed with distilled water, acetone, methanol, and CH_2Cl_2 prior to use. A batch of mixed-bed resin was prepared by mixing equal quantities of these acidic and basic resins. The filtration/workup cartridges were prepared by placing 1.0 g of the mixed-bed resin in a 5 mL plastic syringe, equipped with a polyethylene frit; an additional frit was then placed over the top of the resin. The enantiomeric excess of resolved compounds was determined using a Hitachi 655A liquid chromatograph equipped with a Chiracel OD-H chiral column. Premixed isocratic mixtures of 2-propanol/hexanes were used throughout. Compounds were injected at 10 mM in a solution of hexanes, and products were detected at 254 nm. Optical rotations were determined at 598 nm in a conventional 10 cm cell using a Perkin-Elmer 241 MC polarimeter.

BOC Hydroxyproline Methylbenzylamide 5. A solution of BOC hydroxyproline **4** (10.0 g, 43.3 mmol), HOBt (5.85 g, 43.3 mmol), benzylmethyamine (5.60 mL, 43.4 mmol), and CH_2Cl_2 (300 mL) was cooled in a salt/ice bath. To this solution was added DCC (8.92 g, 43.3 mmol) in CH_2Cl_2 (150 mL) in a dropwise fashion over a period of 30 min. The resulting mixture was allowed to warm to room temperature over 6 h, during which time the urea precipitate was formed. The mixture was filtered and the precipitate washed with CH_2Cl_2. The organic liquors were evaporated to dryness under reduced pressure and dissolved in ethyl acetate (300 mL). The ethyl acetate solution was washed with saturated sodium carbonate, 10% citric acid, and brine, dried ($MgSO_4$), and concentrated to give amide **5** as an oil which solidified on standing (14.2 g, 98%): mixture of rotamers; $[\alpha]^D_{22}$ −14.1 (*c* = 1, MeOH); IR 3411, 1681, and 1648 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 and 1.46 (s, 9H), 1.86−1.92 (m, 1H), 2.09−2.28 (m, 2H), 2.99 and 3.04 (s, 3H), 3.44−3.62 (m, 1H), 3.69−3.79 (m, 1H), 4.42−4.60 (m, 2H), 4.68−4.89 (m, 1H) and 7.19−7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 28.4, 34.5, 34.8, 38.2, 38.8, 51.5, 54.9, 55.1, 55.2, 69.5, 70.4, 79.9, 126.5, 126.6, 127.2, 127.7, 128.4, 128.5, 128.6, 128.9, 136.9, 154.0, 154.6, 172.8, and 173.0; HRMS calcd for $C_{18}H_{26}N_2O_4$ 334.1893, found 334.1893.

Hydroxy Diamine 6. A solution of amide **5** (14.0 g, 41.9 mmol) in THF (200 mL) was cooled to 0 °C, and a solution of $LiAlH_4$ (1 M in THF, 90.0 mL, 90.0 mmol) was added over 30 min. *Caution: Hydrogen gas evolved!* After being stirred for 1 h, the mixture was heated to reflux for 5 h and was then cooled in a salt/ice bath. The flask was opened to the atmosphere, and a stream of argon was passed over the reaction. Next, $NaSO_4 \cdot 10H_2O$ was added in small portions until no further hydrogen gas was evolved. The solid material was isolated by filtration and extracted in a Soxhlet apparatus using dioxane overnight. The organic extracts were combined and concentrated under reduced pressure to give a yellow oil. Purification by bulb to bulb distillation (175−180 °C, 2.5 mmHg) gave the desired hydroxy diamine **6** as a colorless oil (8.71 g, 89%): $[\alpha]^D_{22}$ −80.9 (*c* = 1, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.75−1.87 (m, 2H) 2.12 (dd, 1H, *J* = 9.9, 5.9), 2.13 (s, 3H), 2.20 (dd 1H *J* = 12.1, 7.3), 2.31 (s, 3H), 2.45 (dd, 1H, *J* = 12.1, 4.8), 2.57−2.61 (m, 1H), 3.31 (dd, 1H, *J* = 9.9, 6.3), 3.35 (d, 1 H, *J* = 13.2), 3.45 (d, 1H, *J* = 13.2), 4.25−4.29 (m, 1H), 7.22−7.25 (m, 1H), and 7.29−7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.2, 41.5, 43.1, 61.7, 62.2, 63.1, 65.9, 69.5, 126.9, 128.1, 129.0, and 139.1; HRMS calcd for $C_{14}H_{22}N_2O$ 234.1732, found 234.1732.

Diamine Allyl Ether 10. A suspension of potassium hydride (35 wt % in mineral oil, 5.00 g, 43.7 mmol) in THF (100 mL) was cooled to 0 °C, and a solution of hydroxy diamine **6** (8.53 g, 36.4 mmol) in THF (50 mL) was slowly added. The mixture was warmed to room temperature and stirred for an additional 2 h. Next, allyl bromide (3.15 mL, 36.4 mmol) was added, and the resulting mixture was heated at reflux for 3 h. After cooling, excess potassium hydride was destroyed by the slow addition of water (20 mL) followed by HCl_{aq} (1 M, 50 mL). The phases were separated, and the organic layer was extracted with HCl_{aq} (1 M, 2 × 50 mL). The acidic aqueous extracts were combined, washed with ether (2 × 50 mL), and made alkaline by the addition of $NaOH_{aq}$ (4 M, 50 mL). The alkaline solution was extracted with ether (3 × 50 mL), and the combined ether extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil. Purification using bulb to bulb distillation (130−135 °C, 0.85 mmHg) gave the desired allyl ether **10** as a colorless oil (9.11 g, 91%): $[\alpha]^D_{22}$ −76.0 (*c* = 1, MeOH); IR 993 and 922 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.75−1.81 (m, 1H), 2.01−2.05 (m, 1H), 2.20 (s, 3H), 2.23−2.30 (m, 1H), 2.38 (s, 3H), 2.53 (dd, 1H, *J* = 12.1, 4.3), 2.59−2.62 (m, 1H), 3.38 (dd, 1H, *J* = 9.9, 6.3), 3.43 (d, 1H, *J* = 13.2), 3.55 (d, 1H, *J* = 13.2), 3.91−3.93 (m, 1H), 3.94−3.98 (m, 1H), 4.02−4.04 (m, 1H), 5.13 (ddd, 1H, *J* = 10.7, 3.0, 1.5), 5.27 (ddd, 1H, *J* = 17.3, 3.3, 1.5), and 7.22−7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.2, 41.1, 43.0, 61.8, 62.2, 63.1, 63.6, 70.2, 76.4, 116.9, 126.8, 128.1, 128.9, 134.8, and 139.1; HRMS calcd for $C_{17}H_{26}N_2O$ 274.2045, found 274.2045.

Hydroxypropyl Ether Diamine 11. A solution of 9-BBNH (0.5 M, 11 mL, 5.5 mmol) was cooled to 0 °C, and a solution of allyl ether **10** (312 mg, 1.14 mmol) in THF (10 mL) was added. The resultant mixture was allowed to warm to room temperature and stirred overnight. An alkaline solution of hydrogen peroxide (10 mL, 4 M NaOH, 30% H_2O_2, 2:1) and EtOH (10 mL) were slowly added, and the resulting mixture was stirred for an additional 30 min. The organic layer was separated and the aqueous layer extracted with ether (2 × 30 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (90% CH_2Cl_2, 9.5% MeOH, 0.5% concd NH_4OH_{aq}) gave the desired hydroxy ether diamine **11** as a colorless oil (247 mg, 74%). Larger scale reactions gave similar yields of product which were purified by bulb to bulb distillation (145−150 °C, 0.75 mmHg): $[\alpha]^D_{22}$ −49.2 (*c* = 1, MeOH); IR 3382 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.74−1.81 (m, 3H), 1.94−2.01 (m, 1H), 2.20 (dd, 1H, *J* = 9.9, 6.2) 2.21 (s, 3H), 2.27 (dd, 1H, *J* = 12.1, 7.7), 2.36 (s, 3H), 2.52 (dd, 1H, *J* = 12.1, 4.8), 2.56−2.60 (m, 1H), 3.37 (dd, 1H, *J* = 9.6, 6.3), 3.42 (d, 1H, *J* = 13.2), 3.50−3.53 (m, 1H), 3.54 (d, 1H, *J* = 13.2), 3.56−3.60 (m, 1H), 3.56−3.60 (m, 1H), 3.73 (t, 2H, *J* = 5.5), 3.93−3.98 (m, 1H), 7.20−7.24 (m, 1H), and 7.28−7.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.9, 36.1, 38.0, 40.9, 42.8, 61.5, 62.0, 63.0, 63.3, 68.2, 76.4, 126.7, 127.9, 128.7, and 138.8; HRMS calcd for $C_{17}H_{28}N_2O_2$ 292.2151, found 292.2151.

Polymer-Supported Catalyst 12. A suspension of potassium hydride (35% in mineral oil, 1.00 g, 8.73 mmol) in THF (50 mL) was cooled to 0 °C, and a solution of hydroxypropyl ether **11** (1.54 g, 5.27 mmol) in THF (50 mL) was slowly added. The resultant mixture was stirred at room temperature for 1 h and then added to a suspension of chloromethyl *J*anda*J*el (5.00 g, 0.70 mmol g^{-1}, 3.5 mmol), 18-crown-6 (100 mg, cat.), and potassium iodide (100 mg, cat.) in THF (50 mL). The reaction was stirred at reflux for 48 h. After cooling, the resin was filtered and washed with THF, dioxane/water (3:1), THF, THF/Et_3N (9:1), CH_2Cl_2, THF, ether, and pentane. Drying under vacuum overnight gave the polymer-supported catalyst **12** as a free-flowing white powder (5.91 g, 100%). A loading of 0.59 mmol g^{-1} was calculated from the mass increase of the polymer. IR 1119 and 976 cm^{-1}.

General Procedure for Kinetic Resolution Using Polymer-Supported Catalyst 12. Catalyst **12** (250 mg, 0.15 mmol, 15 mol %), 4 Å molecular sieves (500 mg), and *trans*-2-phenyl-1-cyclohexanol (**13**) (176 mg, 1.00 mmol) were placed in a 10 mL Wheaton vial equipped with a small stir bar. A stream of argon was purged into the flask, and CH_2Cl_2 (5 mL) was added. An inlet septum cap was fitted, the flask was cooled to −78 °C, Et_3N (70 μL, 0.50 mmol) and benzoyl chloride (87 μL, 0.75 mmol) were added, and the mixture was stirred at −78 °C for 11 h. The mixture was filtered through the ion-exchange resin cartridge, washed with CH_2Cl_2 and ether, and concentrated under reduced pressure. The resolved products were separated on a silica gel column (10 cm × 2.5 cm) which was eluted with 10% ethyl acetate in hexanes (200 mL) and 50% ethyl acetate in hexanes (100 mL), giving ester **13a** (123 mg, 44%) and alcohol **13b** (79 mg, 45%).

General Procedure for the Analysis of Enantiomeric Excess for Esters 13−19. Ester **13a** (100 mg) was dissolved

in THF (5.00 mL), a solution of $LiAlH_4$ (1 M, 2 mL) was added, and the resultant mixture was stirred for 1 h. The reaction was quenched by the addition of $Na_2SO_4 \cdot 10H_2O$, filtered through Celite, concentrated, and analyzed directly.

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Supporting Information Available: ^1H NMR spectra for **6**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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