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Polystyrene-Supported (*R*)-2-Piperazino-1,1,2-triphenylethanol: A Readily Available Supported Ligand with Unparalleled Catalytic Activity and Enantioselectivity

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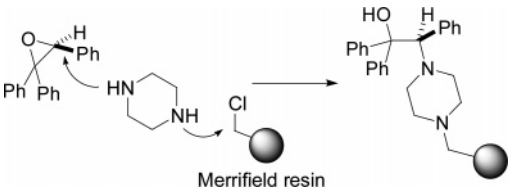

A very active and highly enantioselective catalytic resin, designed for minimal perturbation of the catalytic center by the polymer matrix, has been assembled in two steps from (*S*)-triphenylethylene oxide, piperazine, and Merrifield resin and tested in the enantioselective ethylation of aldehydes. 1-Arylpropanols of 94−95% ee are obtained in high yield by the use of only 2 mol % of catalytic resin at 0 °C for 4 h.

Introduction

Long before the term green chemistry[1] was coined, substantial research effort had already been devoted to the development of processes involving a rational use of raw materials, the minimization of energy consumption, and the avoidance of residue generation.

The venue of catalytic synthetic processes represented a giant step toward these goals, and the introduction of homogeneous catalysis paved the way for the clean and efficient production of chiral compounds as single enantiomers. Homogeneous catalytic processes, however, are usually performed in a batch manner, and workup stages required for product isolation and catalyst recovery are detrimental to their overall sustainable characteristics.

To solve this problem, covalent anchoring of properly functionalized ligands to polymeric supports has been widely applied.[2] While this method can ultimately allow performing catalytic enantioselective reactions in a continuous mode, it is usually accompanied by a decrease in catalytic activity and enantioselectivity with respect to structurally referable, homogeneous ligands.

Within this approach, the achievement of enantiocontrol in the alkylation or the arylation of aldehydes has received considerable attention. The forementioned drawbacks are not absent from this chemistry, and its solution has been addressed by means of the introduction of increasingly sophisticated ligands.[3] Since synthetic complexity in catalytic ligands severely hinders its practical use, further work in this field is clearly warranted.

Since the early work by Fréchet and Soai,[4] different polymer-supported amino alcohols such as **1**−**4** (Figure 1) have been introduced for the ethylation of benzaldehydes.[5] When their structures are analyzed, it becomes

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(1) Oldest hit in SciFinder for *green chemistry*: Pavel, D. *Chem. Listy* **1991**, *85*, 1144−1149.

(2) (a) Bräse, S.; Lauterwasser, F.; Ziegert, R. E. *Adv. Synth. Catal.* **2003**, *345*, 862−929. (b) Special Issue on Recoverable Catalysts and Reagents; Gladisz, J. A., Ed. *Chem. Rev.* **2002**, *102*, 3215−3892. (c) *Chiral Catalyst Immobilization and Recycling*; de Vos, D. E., Vankelekom, I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: Weinheim, Germany, 2000.

(3) For a successful, polymer-supported yet soluble ligand for enantioselective phenylation of aldehydes, see: Bolm, C.; Hermanns, N.; Classen, A.; Muñiz, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1795−1798.

(4) (a) Itsuno, S.; Fréchet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4140−4142. (b) Soai, K.; Niwa, S.; Watanabe, M. *J. Org. Chem.* **1988**, *53*, 927−928.

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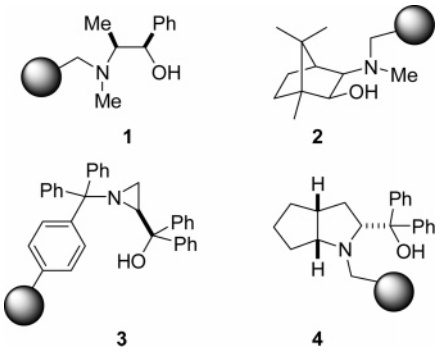


FIGURE 1. Some amino alcohol ligands anchored to polymeric matrixes through the nucleophilic nitrogen atom.

evident that taking advantage of the nucleophilic properties of the amino group has been the favorite anchoring strategy.

Since the amino group critically participates in the transition states (TS) leading to product formation in the considered reaction, we reasoned that the close vicinity of the polymeric backbone could perturb the geometry of the TS's and, hence, could be responsible for the decreases in catalytic activity and enantioselectivity generally observed with these ligands in comparison with their homogeneous counterparts.[6]

In an attempt to solve these problems, we reasoned that structural modification of homogeneous ligands aimed at its conversion into supported ones should preferably by done at positions remote from the atoms involved in the catalytic event, so that a minimal perturbation was introduced on the corresponding transition states. As an application of this idea, and basing our design on (*R*)-2-piperidino-1,1,2-triphenylethanol (**5**),[7] we have developed polystyrene-supported amino alcohols **6**, and have introduced for their designation the term *tail-tied ligands*.[8] Gratifyingly enough, both the catalytic activity and the enantioselectivity exhibited by **6** are among the highest ever recorded for supported ligands. However, the price paid for efficiency was still high, since the preparation of the ready-to-anchor ligand involved up to five steps from commercial precursors (Figure 2).

We wish to report here the preparation of a second-generation tail-tied ligand (**7**), available in enantiopure form in only two steps from (*S*)-triphenylethylene oxide, and exhibiting an optimal activity/enantioselectivity profile.

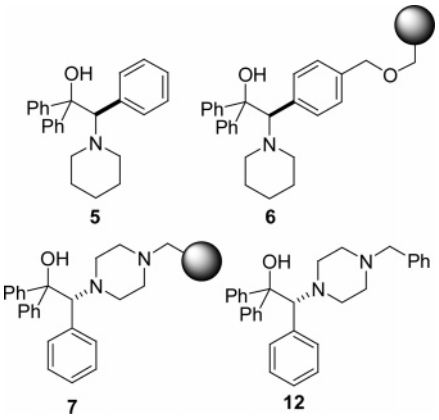
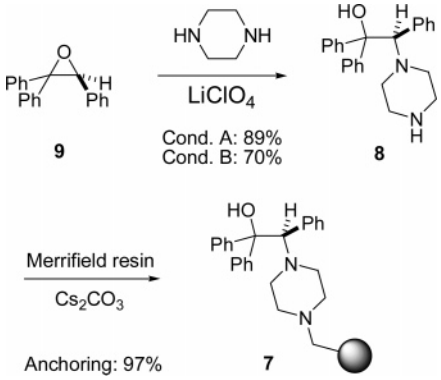


FIGURE 2. Tail-tied ligands **6** and **7**, conceptually derived from amino alcohol **5** by functionalization of the para positions of the phenyl and piperidino rings, and model compound **12**.

SCHEME 1. Assembly of the Supported Ligand 7 by Sequential Nucleophilic Ring-Opening Plus Alkylation with Piperazine[a]



[a] Conditions A: $LiClO_4$ (2 equiv), piperazine (32 equiv), 160 °C, 4 h. Conditions B: $LiClO_4$ (2 equiv), piperazine (5 equiv), *N*,*N*-dimethylacetamide, 160 °C, 3 h.

Results and Discussion

Our strategy for the immediate availability of **7** from commercial precursors involves the sequential participation of the two nitrogen atoms of piperazine in nucleophilic displacements. In the first place, and according to our general strategy for the synthesis of modular amino alcohols, (*R*)-2-piperazino-1,1,2-triphenylethanol (**8**) was simply prepared by lithium perchlorate-induced ring-opening[9] of readily available enantiomerically pure (*S*)-triphenylethylene oxide (**9**)[10] with piperazine (Scheme 1).

Thanks to the sensitivity of these ring-opening processes to the steric characteristics of the nucleophile, no partial protection in piperazine was required, and product arising from double ring-opening was never detected in the reaction crudes. While the highest yielding reaction conditions (Conditions A: 89% yield) involved the use of excess piperazine as a solvent, workup was highly simplified under Conditions B (70% yield), which re-

(5) For **3**, see: ten Holte, P.; Wijgergangs, J.-P.; Thijs, L.; Zwanenburg, B. *Org. Lett.* **1999**, *1*, 1095−1097. For **4**, see: Burguete, M. I.; Garcia-Verdugo, E.; Vicent, M. J.; Luis, S. V.; Pennemann, H.; Graf von Keyserling, N.; Martens, J. *Org. Lett.* **2002**, *4*, 3947−3950.

(6) (a) For insoluble, polymer-supported amino alcohol ligands whose anchoring does not involve the amino moiety, see: Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309−6318. (b) For soluble, polymer-supported ligands with positive support effects, see: Fan, Q.-H.; Wang, R.; Chan, A. S. C. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1867−1871 and references therein.

(7) (a) Solà, L.; Reddy, K. S.; Vidal-ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7078−7082. (b) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532−2543. (c) García-Delgado, N.; Fontes, M.; Pericàs, M. A.; Riera, A.; Verdaguer, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2085−2090.

(8) Pericàs, M. A.; Castellnou, D.; Rodríguez, I.; Riera, A.; Solà, L. *Adv. Synth. Catal.* **2003**, *345*, 1305−1313.

(9) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1993**, *58*, 1221−1227.

(10) This epoxide can be routinely prepared at the molar scale in >99.9% ee by Jacobsen epoxidation of triphenylethylene (Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378−4380) and recrystallization from hexane.

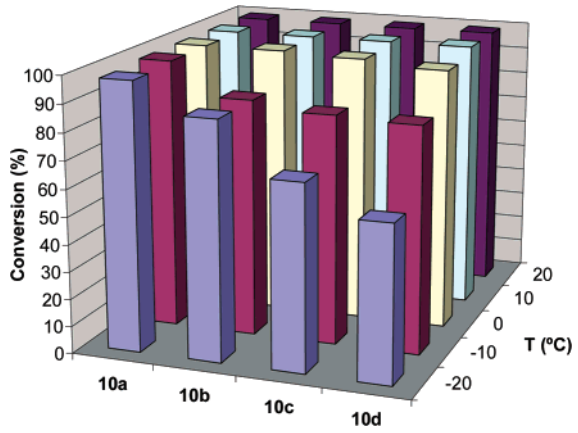
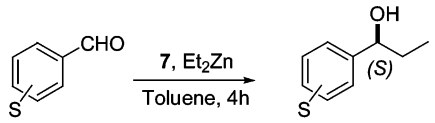


FIGURE 3. Bar chart showing the efficiency of ligand **7** in the ethylation of aldehydes **10a**−**d** at different temperatures, after 4 h.

SCHEME 2. Catalytic Enantioselective Ethylation of Aldehydes Mediated by the Supported Ligand 7



10 **11**

quired the use of only 3 equiv of piperazine in *N*,*N*-dimethylacetamide as a solvent.

Anchoring of **8** to a Merrifield resin (2% DVB, $f_0 = 0.84$) was performed in a straightforward manner by shaking under nitrogen a 1.2:1:2.4 mixture of **8**, Merrifield resin, and cesium carbonate in DMF for 72 h at room temperature. A 97% yield could be calculated for the anchoring stage by nitrogen elemental analysis of the functionalized resin **7**.[11]

With ligand **7** in hand,[12] optimal conditions for its use in the selected benchmark (i.e., the catalytic enantioselective ethylation of aldehydes, Scheme 2) were studied.

The optimization was performed in parallel on a set of four aromatic aldehydes [*o*-fluorobenzaldehyde (**10a**), *m*-anisaldehyde (**10b**), *p*-tolualdehyde (**10c**), *o*-tolualdehyde (**10d**)] comprising substitution in ortho, meta, and para positions, with both electron-donating and electron-withdrawing groups on the critical ortho position.

For reaction temperature optimization, the reactions were performed in toluene with 6 mol % of **7** at five temperatures between −20 and +20 °C. Very interestingly, all four alcohols **11a**−**d** were obtained with excellent enantioselectivity (96−95% ee) at −20 °C, 95−94% ee at 0 °C, and 93−92% ee at +20 °C. With respect to conversion (Figure 3), all substrates were completely converted (>99%) after 4 h at 10 °C, and only traces of the starting aldehydes remained after 4 h at 0 °C. By further lowering the reaction temperature, conversion of **10a** remained complete over the whole range, while the

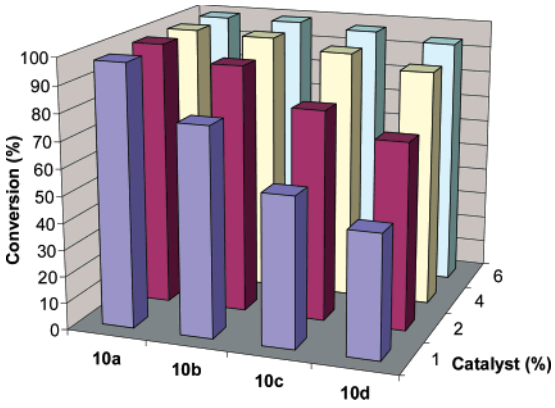


FIGURE 4. Bar chart showing the efficiency of ligand **7** in the ethylation of aldehydes **10a**−**d** at different loadings in toluene at 0 °C, after 4 h.

less reactive, electron-rich substrates **10b**−**d** required extra reaction time with the considered catalyst loading.[13]

For practical purposes the activity/enantioselectivity profile exhibited by **7** at 0 °C was optimal. Next in the optimization, we explored the possibility of reducing the amount of catalyst at this temperature. In a series of experiments with **10a**−**d**, the amount of **7** was reduced from 6 to 1 mol %. We were pleased to observe that, for all substrates, enantioselectivities decreased by only 1% with this change in catalyst amount. With respect to conversion (Figure 4), the amount of catalyst exerted a deeper influence, and only the highly reactive aldehyde **10a** was completely consumed in the presence of 1 mol % of **7** (0 °C, 4 h).

Since we were interested in determining *practical conditions*[14] for the use of **7** in enantioselective ethylation reactions, two sets of reaction conditions (2 mol % of **7**, 0 °C, 8 h and 4 mol % of **7**, 0 °C, 6h) were tested with a diverse and representative family of 15 aldehydes **10a**−**o** (Table 1). While for most aromatic aldehydes the first conditions set would be sufficient, the second one ensures complete conversion for all types of aromatic aldehydes (95% ee) and α-unsubstituted aliphatic (85−88% ee) or α,β-unsaturated aldehydes (82% ee). For α-substituted aldehydes (**10n**−**o**), higher enantioselectivities are recorded, but at an unaffordable low-activity price.

Although it is already clear from the results in Table 1 that the activity and enantioselectivity of **7** approach or even surpass those of many homogeneous ligands, a direct comparison with a referable, soluble species would be preferable. To this end, amino alcohol **12** (Figure 2) was prepared either by simple benzylation of **8** (BnCl, Cs_2CO_3, DMF, rt, 77%) or by ring opening of **9** with *N*-benzylpiperazine in the presence of lithium perchlorate (84%), and subsequently used for enantiocontrol in the ethylation of benzaldehyde.

With respect to enantioselectivity, when 6 mol % of **12** was used in the alkylation reaction, a complete conversion was recorded after 4 h at 0 °C in toluene, and alcohol

(11) Yield calculated as $100f/f_{max}$, where f [mmol ligand/g resin] is calculated from the nitrogen elemental analysis with the formula $f = 0.375(\%N)$, and f_{max} [mmol ligand/g resin], the maximum ligand substitution level, is calculated as described in ref 6.

(12) For the immobilization of **8** on silica by sol−gel synthesis and grafting, see: Fraile, J. M.; Mayoral, J. A.; Serrano, J.; Pericàs, M. A.; Solà, L.; Castellnou, D. *Org. Lett.* **2003**, *5*, 4333−4335.

(13) At −10 °C, all substrates reacted completely in 24 h. At −20 °C, over 90% conversion was recorded for all substrates in 24 h.

(14) In the context of this research, most practical conditions are those involving the minimal catalyst amount leading to complete conversion at the nearest to ambient temperature in the shortest reaction time with an affordable decrease in enantioselectivity with respect to its optimal value.

TABLE 1. Enantioselective Ethylation of Aldehydes Mediated by 7

starting aldehyde	2 % of 7[a] conv (%)	2 % of 7[a] ee (%)	4% of 7[b] conv (%)	4% of 7[b] ee (%)
o-fluorobenzaldehyde (**10a**)	>99	94	>99	95
m-methoxybenzaldehyde (**10b**)	98	95	99	95
p-tolualdehyde (**10c**)	94	94	98	95
o-tolualdehyde (**10d**)	83	94	95	95
benzaldehyde (**10e**)	98	95	99	95
o-methoxybenzaldehyde (**10f**)	99	94	>99	95
m-fluorobenzaldehyde (**10g**)	98	94	>99	94
m-tolualdehyde (**10h**)	98	95	>99	95
p-fluorobenzaldehyde (**10i**)	>99	94	>99	95
p-methoxybenzaldehyde (**10j**)	75	94	98	95
cinnamaldehyde (**10k**)	97	80	98	82
heptanal (**10*l***)	96	85	97	85
3-phenylpropanal (**10m**)	98	88	99	88
2-ethylbutanal (**10n**)	27	86	35	89
α-methylcinnamaldehyde (**10o**)	52	91	63	91

[a] Reaction in toluene at 0 °C for 8 h. [b] Reaction in toluene at 0 °C for 4 h

11e was formed with >99% selectivity and 96% ee. As can be seen in Table 1, performing the reaction with 4 mol % of **7** under the same experimental conditions leads to **11e** of 95% ee. Thus, the enantioselectivity of the homogeneous ligand **12** is not affected when this ligand was incorporated to a polymer through a position remote from the catalytic site.

To evaluate the effect of heterogenization on catalytic activity, two parallel kinetic measurements on the diethylzinc addition to benzaldehyde mediated by **7** and **12** were carried out in an Omnical reaction calorimeter. The reactions were performed in toluene at 20 °C with a 4 mol % catalytic ligand. According to usual practice the raw heat flow data, acquired every 3 s, were corrected for the response time of the instrument (τ correction, see Supporting Information) and, after confirming that the ethylation of **10e** takes place to completion in a strictly selective manner under the employed reaction conditions, transformed to conversion data.[15] The corresponding conversion vs time curves have been represented in Figure 5.

It is clear from this plot that *the homogeneous ligand **12** and the polymer-supported ligand **7** are practically identical in terms of reaction rate and activity.* At short reaction times, **7** is even slightly more active than **12** (83% conversion for the polymer-supported ligand and 80% for the homogeneous ligand after 30 min), but these differences vanish as the reaction proceeds. Thus, after 60 min conversion was 96% (with **7**) and 95% (with **12**) and after 80 min both reactions had reached 98% conversion.

In addition to that, it is interesting to compare these results with those reported for other supported ligands. The poly(styrene) bonded analogue of DAIB,[4a] for instance, requires 73 h in toluene at 0 °C for a 91% yield in the same reaction (3.3 mol % of ligand), while a poly(styrene) supported version of ephedrine[4a,b] requires 48 h in toluene at room temperature (the same conditions studied here) for a 95% yield in the considered process (10 mol % of ligand).

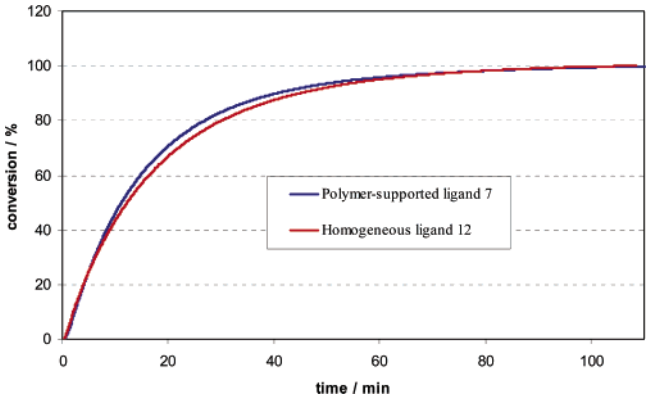


FIGURE 5. Profiles of benzaldehyde conversion in the addition of diethylzinc to benzaldehyde mediated by resin **7** and homogeneous ligand **12** (4 mol %) in toluene at 20 °C.

Even more remarkably, the heterogeneous ligand **7** compares favorably in catalytic activity with (−)-DAIB,[16] the usual reference homogeneous ligand for carbonyl additions. Thus, while for aromatic aldehydes such as **10e** and **10j** the use of 2 mol % of (−)-DAIB in toluene at 0 °C for 6 h leads to essentially complete conversion, as with 2 mol % of **7** in 8 h (see Table 1), for α,β-unsaturated aldehydes such as **10k** the use of (−)-DAIB under the above conditions leads to incomplete conversion (81% yield), and for aliphatic aldehydes such as **10m** and **10*l*** a similar conversion is only achieved after 12 and 24 h, respectively. As shown in Table 1, an essentially complete conversion is achieved for all three last examples with 2 mol % of **7** at 0 °C for 8 h.[17]

As a final test on the performance of **7**, the possibility of its recovery and reuse was evaluated. Gratifyingly, the supported ligand **7** could be recycled without any loss in catalytic activity or in enantioselectivity. Thus, in five consecutive batches of 1-phenylpropanol (**11e**) prepared under standard conditions (4 mol % of **7**, toluene, 0 °C, 6 h) with the same catalyst sample, conversion and selectivity were complete (>99%) in all cases, with the enantiomeric purity of the resulting alcohol keeping constant within the limits of experimental error (95.2%, 94.9%, 95.1%, 95.0%, 95.1%).

Conclusions

In summary, we have succeeded in developing an immediately available, polymer-supported ligand for the enantioselective alkylation of aldehydes which exhibits the catalytic activity and enantioselectivity typical for a homogeneous, low-molecular weight species, and the ease for recovery and reuse characteristic of heterogeneous catalysts. We are currently extending the use of **7** to other processes with the aim of contributing to the establishment of more sustainable practices in enantioselective synthesis.

(15) For a discussion on the conversion of heat flow data into kinetic data see, for instance: Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360−1362, and the Supporting Information.

(16) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072.

(17) For the five examples where direct comparison is possible (**10e**, **10j**, **10k**, **10*l***, **10m**) the mean enantiomeric excess recorded with (−)-DAIB (2 mol %) is 87.6%, and that recorded with **7** (2 mol %) is 88.4%.

Experimental Section

(*R*)-1,1,2-Triphenyl-2-(piperazin-1-yl)ethanol (8). Conditions A (excess piperazine as the solvent): To a flame-dried 100-mL two-necked flask with reflux condenser and nitrogen inlet were added 1.0 g (3.67 mmol) of epoxide **9** (>99.9% ee), 1.0 g (9.4 mmol) of $LiClO_4$, and 10.0 g (0.116 mol) of piperazine. The mixture was heated to 160 °C under nitrogen for 4 h under stirring, cooled to room temperature, and treated with dichloromethane and water (equal volumes) until complete disolution of all precipitated matter. The aqueous phase, containing piperazine and $LiClO_4$, was discarded. To remove the remaining piperazine, the organic phase was repeatedly washed with water (8 × 20 mL), and the aqueous extracts were discarded. To remove impurities, the product amino alcohol was transferred to an aqueous phase by treating the organic extract with 100 mL of 1 N HCl, and the remaining organic phase was discarded. The acidic solution was then washed with dichloromethane (3 × 100 mL), and the organic phases were again discarded. Finally, the pH of the aqueous phase was adjusted to 10.5 by addition of aq 7.5 N NaOH, and amino alcohol **8** was extracted with dichloromethane (4 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness to afford pure **8** (1.16 g, 89% yield) as a white solid. **Conditions B (in *N*,*N*-dimethylacetamide):** To a thick-walled pressure tube, equipped with a Teflon screw-cap, and prepared for magnetic stirring, were added 6.0 g (22.0 mmol) of epoxide **9** (>99.9% ee), 4.7 g (44 mmol) of $LiClO_4$, 9.5 g (110 mmol) of piperazine and 11 mL of *N*,*N*-dimethylacetamide. The mixture was stirred at 160 °C for 3 h, cooled to room temperature, and treated with a 1:1 water:dichoromethane mixture (200 mL). Phases were separated with the aqueous phase being discarded and the organic phase being washed with H_2O (3 × 200 mL), the aqueous phases being discarded again. Hydrochloric acid (1 M, 200 mL) was next added, the organic phase was discarded, and the aqueous phase was washed with CH_2Cl_2 (3 × 200 mL), the organic extracts being discarded again. Finally, the pH of the aqueous phase was adjusted to 10.5 by addition of aq 7.5 M NaOH, and amino alcohol **8** was extracted with dichloromethane (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness to afford pure **8** (5.50 g, 70% yield) as a white solid. Mp 159−161 °C. $[\alpha]^{23}_D$ −126.3 (*c* 0.51, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50−1.80 (br, 1H), 1.90−2.10 (m, 2H), 2.30−2.50 (m, 2H), 2.60−2.80 (m, 4H), 4.54 (s, 1H), 5.40−5.70 (br, 1H), 6.80−7.40 (m, 13H), 7.60−7.80 (m, 2H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 46.6 (CH_2), 54.3 (CH_2), 77.3 (CH), 78.7 (C), 125.4 (CH), 125.5 (CH), 126.2 (CH), 126.4 (CH), 126.9 (CH), 127.2 (CH), 127.4 (CH), 127.9 (CH), 131.0 (CH), 137.1 (C), 145.6 (C), 149.0 (C) ppm. IR (film, NaCl) υ_{max} 3241, 2940, 2815, 1449, 1321, 702 cm^{-1}. MS (CI, NH_3) *m/e* 359 ($[M + 1]^+$, 100%), 360 ($[M + 2]^+$, 27%). Elemental Anal. Calcd for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.19; H, 7.30; N, 7.51.

Anchoring of Amino Alcohol 8 to a Merrifield Resin (0.84 mmol Cl/g; 2% DVB). Preparation of supported ligand 7: A solution of amino alcohol **8** (670 mg, 1.87 mmol) in DMF (6.7 mL) under N_2 was added via cannula to a suspension of Merrifield resin (1.72 g, 1.44 mmol of active Cl) and Cs_2CO_3 (1.22 g, 3.74 mmol) in DMF (12.6 mL), previously stirred at 25 °C for 45 min, and the resulting mixture was stirred at room temperature under nitrogen for 24 h. Solvent and excess reagents were separated by filtration, and the resulting resin was successively washed with DMF (2 × 10 mL), 1:1 DMF−water (4 × 10 mL), water (4 × 10 mL), pH 9 Na_2CO_3/$NaHCO_3$ buffer (4 × 10 mL), water (8 × 10 mL), MeOH (4 × 10 mL), toluene (4 × 10 mL), and CH_2Cl_2 (4 × 10 mL). After drying under vacuum until constant weight, 1.94 g of functionalized resin **7** (2% DVB, $f = 0.641$) was obtained. A 97% yield of functionalization is calculated on the basis of nitrogen elemental analysis [see below, $\%N_{found}/\%N_{calcd} = 1.79/1.85 = 0.97$]. ^{13}C NMR (gel, 75 MHz, $CDCl_3$) δ 40.3 (CH), 43.9 (CH_2), 53.0 (CH_2), 53.6 (CH_2), 62.4 (CH_2), 76.8 (CH), 78.6 (C) ppm. Elemental Anal. Calcd.: N, 1.85. Found: N, 1.79.

(*R*)-2-(4-Benzylpiperazin-1-yl)-1,1,2-triphenylethanol (12). (a) From 8: To a flame-dried 10-mL round-bottom flask prepared for magnetic stirring were added 50 mg (0.14 mmol) of **8** and 91 mg (0.28 mmol) of Cs_2CO_3 under nitrogen. DMF (0.5 mL) and benzyl chloride (16 μL, 0.14 mmol) were successively added, and the mixture was stirred under nitrogen for 24 h at room temperature. The solvent was removed under vacuum, CH_2Cl_2 (5 mL) and water (5 mL) were added to the residue, and the organic layer was washed with water (2 × 5 mL). The combined aqueous phase was then extracted with dichloromethane (CH_2Cl_2) (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness to afford crude **12** (55 mg). Final purification was achieved by column chromatography (2.5% v/v triethylamine: pretreated SiO_2), eluting with hexane ethyl acetate mixtures of increasing polarity. Pure **12** (48 mg, 77% yield) was obtained as a white solid. **(b) From 9:** To a flame-dried 50-mL two-necked flask with reflux condenser and nitrogen inlet were added 1.0 g (3.67 mmol) of epoxide **9** (>99.9% ee), 1.25 g (11.7 mmol) of $LiClO_4$, and 6.76 mL (6.88 g; 39.0 mmol) of *N*-benzylpiperazine. The mixture was heated to 100 °C under nitrogen for 22 h under stirring until the dissappearance of the starting epoxide (TLC), cooled to room temperature, and treated with 50 mL of dichloromethane and 50 mL of water. The aqueous phase was extracted with dichloromethane (2 × 50 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Final purification was achieved by column chromatography (2.5% v/v triethylamine:pretreated SiO_2), eluting with hexane ethyl acetate mixtures of increasing polarity. Pure **12** (1.38 g, 84% yield) was obtained as a white solid. Mp 162−163 °C. $[\alpha]^{23}_D$ −105.2 (*c* 0.65, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.0−2.2 (m, 2H), 2.31 (br, 4H), 2.41−2.47 (m, 2H), 3.38 (AB, $^2J_{HH} = 12.8$ Hz, 1H), 3.43 (AB, $^2J_{HH} = 12.8$ Hz, 1H), 4.59 (s, 1H), 5.65 (br, 1H), 6.91−7.33 (m, 18H), 7.70−7.72 (m, 2H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 53.8 (CH_2), 62.9 (CH_2), 76.8 (CH), 78.6 (C), 125.5 (CH), 125.6 (CH), 126.3 (CH), 126.5 (CH), 127.0 (CH), 127.2 (CH), 127.5 (CH), 128.0 (CH), 128.1 (CH), 129.1 (CH), 131.0 (CH), 137.4 (C), 138.0 (C), 145.8 (C), 149.2 (C) ppm. IR (film, NaCl) υ_{max} 3027, 2930, 2807, 1449, 740, 698 cm^{-1}. MS (CI, NH_3) *m/e* 450 ($[M + 1]^+$, 100%), 451 ($[M + 2]^+$, 40%). ES$^+$ HRM *m/z* found 449.2574 $(M + H)^+$, calcd for $C_{31}H_{33}N_2O$ 449.2593.

Kinetic Measurements. Reactions where carried out in a reaction microcalorimeter. In a typical experiment, 62 mg of resin **7** ($f = 0.641$, 4 mol % of ligand) was weighed in a calorimeter vessel and mixed with 0.25 mL of dry toluene for 30 min under argon atmosphere. After cooling at 0 °C, diethylzinc 1.1 M (1.1 mL, 1.1 equiv) was added dropwise, and the mixture was stirred for another 30 min. The vessel was then allowed to warm to room temperature and placed into the calorimeter. At the same time, a syringe containing 1 mmol of benzaldehyde (120 μL, 1 equiv) in 0.5 mL of dry toluene was placed in the addition port of the calorimeter. After 1 h of equilibration at 20 °C, the solution in the syringe was quickly added to the stirred reaction vessel, while monitoring the heat flow every 3 s. Simultaneously, a blank reaction was carried out in the twin vessel, which was identical to the previous reaction except that only toluene, and no benzaldehyde, was added in the final addition. $\Delta H_{reaction} = 153.4$ kJ/mol.

The calorimetric experiment with the homogeneous ligand was identical except that 18 mg (4 mol %) of amino alcohol **12** was used. $\Delta H_{reaction} = 144.4$ kJ/mol.

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Supporting Information Available: General experimental methods, conditions for GC analysis in the determination of enantiomeric composition, NMR spectra of new compounds, and details on the calorimetric−kinetic measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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