Tail-Tied Ligands: An Immobilized Analogue of (*R*)-2-Piperidino-1,1,2-triphenylethanol with Intact High Catalytic Activity and Enantioselectivity

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Abstract: A functional analogue of (*R*)-2-piperidino-1,1,2-triphenylethanol was synthesized and anchored to different polymeric supports by a position remote from the active region. This strategy, leading to what we call a tail-tied ligand, allows for the achievement of the optimal transition state geometry in the catalytic process. The catalytic activity of the resulting heterogenized ligands was investigated by online FTIR analysis. The optimum polymer was assayed in the addition reaction of diethylzinc to a large family of aldehydes rendering essentially intact high catalytic activity and enantioselectivity compared to its homogeneous counterpart.

Keywords: amino alcohol ligands; asymmetric synthesis; diethylzinc additions; FTIR online analysis; heterogeneous catalysis; ligand immobilization

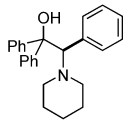
Introduction

The use of polymer-bound ligands has significant advantages compared to the use of the corresponding ligands in the homogeneous phase, thus representing a very attractive approach in asymmetric catalysis. Besides the advantages of simple separation, recovery and reuse of the catalysts, and the possibility of performing the chemical reactions where they act in a continuous mode in a flow reactor, immobilized ligands have an additional interest in connection with the now widely expanding field of combinatorial catalysis.[1]

Since the pioneering work by Fréchet[2] and Soai,[3a] the idea of controlling the enantioselectivity of the addition of dialkylzinc reagents to aldehydes by means of ligands anchored to insoluble organic polymers has received considerable attention. As already mentioned, many different types of advantages could, in principle, be awaited from this type of ligands, but they are often counterpoised by some apparently inherent limitations derived from the heterogeneous nature (i.e., diminished catalytic activity and reduced enantioselectivity). To overcome these difficulties, the target ligands have become progressively more complex and this can represent, in the limit, a complete absence of practical interest.

We have recently described amino alcohol **1**, derived from easily accessible enantiopure triphenylethylene oxide,[4] which stands out as one of the best ligands for the enantioselective addition of diethylzinc to aldehydes.[5] Ligand **1** combines easy access, through a simple preparation procedure, with excellent results in terms of catalytic activity and enantiomeric purity of the resulting alcohols.

We report now on the preparation of an immobilized analogue of **1** and its use as a ligand in the addition of diethylzinc to aldehydes. This novel polymer-bound ligand possesses the advantages of heterogenized catalysts while keeping, in practice, the same catalytic activity and enantioselectivity as its homogeneous template **1**.



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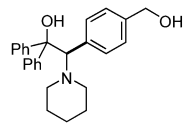

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Results and Discussion

Since ligand **1** cannot be directly immobilized to a resin, a new amino alcohol had to be designed with structural characteristics closely related to **1** and with an additional

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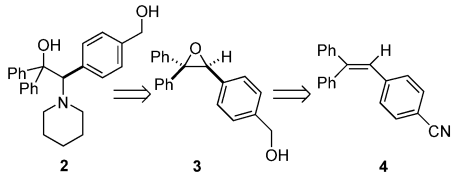
position suitable for anchoring. In order to mimic as much as possible the catalytic properties of ligand **1** in solution, we developed compound **2**, which possesses an additional hydroxymethyl substituent at the *para* position in the phenyl group adjacent to the piperidino moiety. This functionality, while providing a connection point for the anchoring process, is placed in the molecular periphery, far away from the region where the catalysis event takes place.

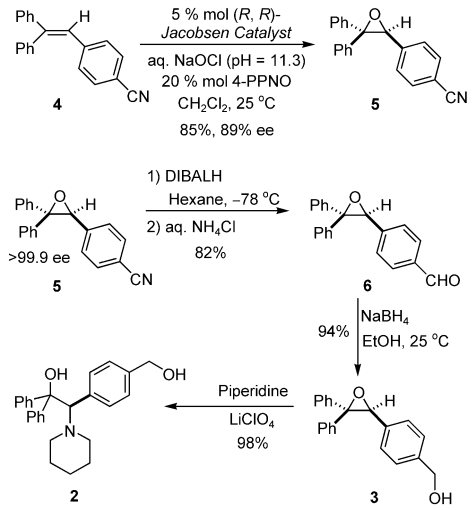
Ligand **2** has, in our opinion, three valuable structural properties that, once anchored to a polymeric support, should rebound in very similar catalytic behavior compared to its homogeneous analogue **1**. First, the substituents around the amino alcohol catalytic site are exactly the same; next, anchoring to the resin takes place through the remotest extremity of the phenyl substituent; finally, the hydroxymethyl substituent allows for enough flexibility and further separates the ligand from the polymer backbone.

Ligand **2** was prepared by regioselective and stereospecific ring opening of epoxy alcohol **3**, which, in turn, was obtained from olefin **4** *via* Jacobsen epoxidation followed by a two-stage reduction of the nitrile to a hydroxymethyl group (Scheme 1).



Scheme 1. Retrosynthetic strategy for the preparation of ligand **2**.

The starting olefin was readily prepared *via* a Wittig reaction from commercial 4-cyanobenzaldehyde and benzhydryltriphenylphosphonium bromide in 75% yield. Epoxidation of olefin **4** was performed through the Jacobsen protocol[6] described for trisubstituted olefins,[7] using 5% of the standard (*R*,*R*)-salen catalyst and 20% of 4-phenylpyridine *N*-oxide (4-PPNO) in dichloromethane, with buffered bleach as stoichiometric oxidant (Scheme 2). The reaction was carried out at room temperature, since slightly better performance in yield and ee of epoxide **5** was observed in comparison to the standard reaction conditions (0–5 °C). Epoxide **5**, obtained in 85% yield and 89% ee, can be easily enriched to >99% after two recrystallizations from hexane. The nitrile group present in **5** was reduced to a hydroxymethyl substituent in two steps, first treatment with DIBALH at −78 °C produced the intermediate aldehyde, and subsequently reaction with sodium borohydride in ethanol at room temperature gave epoxy alcohol **3** (Scheme 2). Ring opening of **3** proceeded smoothly in quantitative yield using a modified procedure of the method described by Crotti,[8] and already used for the preparation of **1** from triphenylethylene oxide. Following this reaction sequence, aminodiol **2** ready for anchoring, can be obtained from enantiopure epoxide **5** in three steps with 76% overall yield.



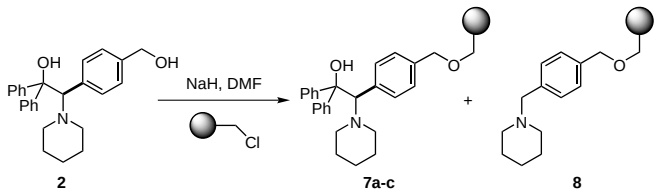
Scheme 2. Synthesis of ligand **2**.

Taking into account our previous experience,[9] anchoring of aminodiol **2** was assayed onto two polystyrene-based polymers; the commercially available Merrifield[10] and Barlos[11] resins. Resins with different degrees of cross-linking and levels of functionalization were used with the aim to evaluate the effect of these parameters on the catalytic performance of the polymer-supported ligands.

Immobilization of **2** to a Merrifield resin was planned through the formation of an ether linkage arising from the nucleophilic coupling of the deprotonated primary alcohol and the chloromethyl substituent of the resin. The reaction was first performed on a resin with low levels of substitution and cross-linkage (Merrifield Resin **a**), under conditions previously optimized for a similar process[9] (Table 1, entry 1). Surprisingly, the ^{13}C gel-phase NMR spectrum[12] of the functionalized resin did not correspond to what would be expected if ligand **2** had been successfully anchored. What was actually immobilized to the resin was the (4-piperidin-1-ylmethylphenyl)methanol (**8**) moiety, likely arising from the decomposition of ligand **2** through the cleavage of the carbon-carbon bond connecting the amino and alcohol functional groups.

The rather unusual fragmentation observed[13] was confirmed when ligand **2** was treated under the same reaction conditions with benzyl bromide as a simplified model of the resin. Benzophenone and 1-(4-benzyloxymethylbenzyl)piperidine (**9**) were isolated as the main products (68% yield each), together with the *o*-benzyl derivative of **2** (11% yield) as shown in Scheme 4.

In an attempt to suppress this unwanted fragmentation, several reaction conditions were studied for the anchoring of **2** to the Merrifield resin **a** (Table 1, entries

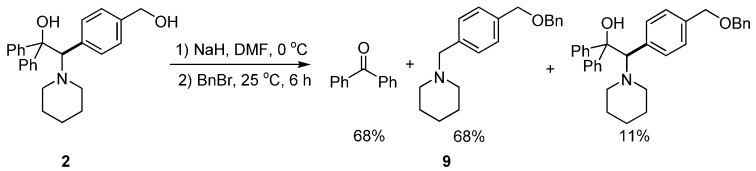


Scheme 3.

Table 1. Anchoring of ligand **2** to Merrifield Resins

Entry	Starting Merrifield Resin (% DVB; f_0[a])	Equivs. of base[b]	Equivs. of **2**[b]	T (^{0}C)	Time (h)	**7:8**	f[c]/f_{max}[d]	ee of **11a**
1	**a** (1%; 0.63)	5	2.5	0	60	0:1	–	6
2	**a** (1%; 0.63)	3.3	2	25	5	2:3	–	47
3	**a** (1%; 0.63)	1.1	1.1	25	5	7:3	–	84
4	**a** (1%; 0.63)	1.1	1.1	0	15	1:0	0.375/0.515	95
5	**b** (1%; 1.49)	1.0 + 0.7	1.0 + 0.7	0 + 25	15 + 0.45	1:0	0.850/0.977	93
6	**c** (2%; 0.84)	1.1	1.1	25	2	1:0	0.389/0.648	95

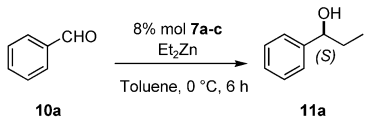
[a] f_0 = mmol Cl/g resin (initial substitution level).
[b] Referred to equivalents of chloro substitution level in the starting Merrifield resin.
[c] f = mmol/g resin (calculated by elemental analysis of nitrogen with the following formula: $f = 0.714\%$ N).
[d] f_{max} = maximum ligand substitution level (mmol ligand/g resin), calculated as described in ref.[7]).



Scheme 4. Fragmentation of ligand **2** under basic conditions.

2 and 3). It is clear from the results of these reactions that higher temperatures, long reaction times and use of excess base, all favor the amino alcohol cleavage. Finally, reaction conditions exclusively leading to the desired anchorage could be developed by careful adjustment of these parameters (Table 1, entry 4).

To test the influence of **8** on the performance of the anchored ligands, the resins prepared in entries 1–4 (Table 1) were used in the addition reaction of diethylzinc to benzaldehyde (Scheme 5). As can be seen, the smaller the proportion of **8** in the functionalized resin, the higher is the ee of the resulting addition alcohol (Table 1, entries 1–3). Very gratifyingly, when using resin **7a**, where **8** is not detected in the ^{13}C gel-phase NMR spectrum (Table 1, entry 4), the addition alcohol (*S*)-1-phenylpropanol was obtained in an excellent enantiomeric excess of 95%. Based on the reaction conditions optimized for the preparation of **7a**, ligand **2** was successfully anchored to Merrifield resins **b** and **c**. Very interestingly, no fragmentation at all was detected by ^{13}C gel-phase NMR spectroscopy during the anchoring step leading to resins **7b, c**. Moreover, polymer **7c** acted as an excellent ligand when assayed in the addition reaction of diethylzinc to benzaldehyde, producing (*S*)-1-phenylpropanol with the same ee as **7a**. On the other hand, **7b** performed the reaction with a slightly smaller ee of 93%.

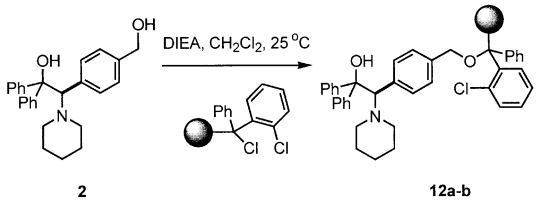


Scheme 5. Addition reaction of diethylzinc to benzaldehyde catalyzed by **7a–c**.

Immobilization of ligand **2** to Barlos resins with two levels of substitution ($f_o = 1.6$ and 1.24) proceeded smoothly in dichloromethane at room temperature in the presence of diisopropylethylamine (DIEA),[11] to afford modified resins **12a, b** (Scheme 6). Interestingly, the fragmentation product was never observed under these milder reaction conditions.

When resins **12a, b** were used as catalytic ligands in the addition reaction to benzaldehyde, the corresponding alcohol was obtained again in very good enantiomeric excesses: 93% for **12a** and 92% for **12b** (Table 2).

The catalytic behavior of the five resins prepared (**7a–c** and **12a, b**) with respect to the enantioselectivity in the addition reaction of diethylzinc to benzaldehyde was excellent and very similar for all of them, rendering (*S*)-1-phenylpropanol with ees between 92 and 95%. At this point, and in order to discriminate between the



Scheme 6

Table 2. Anchoring of ligand **2** to Barlos Resins

Entry	Starting Barlos Resin(f_0)	Functionalized Resin (f/f_{max})	ee of **11a**
1	**a** (1.6)	**12a** (0.925/1.023)	93
2	**b** (1.24)	**12b** (0.689/0.863)	92

functionalized polymers, their catalytic activity was monitored using online FTIR analysis.[14] The addition of diethylzinc to benzaldehyde could be easily monitored following the absorbance values due to the characteristic stretching vibration of the benzaldehyde carbonyl at 1710 cm^{-1}, or the absorbance values of a band at 990 cm^{-1}, associated to the zinc alkoxide product (Figure 1). Absorbance values can be easily related to benzaldehyde conversion. A graphical representation of benzaldehyde conversion for the addition reactions in the presence of resins **7a – c** and **12a, b** (Figure 2) allows for a direct comparison of the catalytic activity of the different functionalized polymers.[15] In this respect, all Merrifield resins have a similar activity, which is consistently higher than the activity of the Barlos resins. Very surprisingly, resin **12b**, which had been prepared some weeks before its use in this experiment, gave very low conversion after 8 hours at 0 °C, and the resulting alcohol was obtained in only 85% ee, a considerably lower value compared to when this same resin was used freshly prepared. This result warns on the use of the Barlos resin supported ligands **12a, b** as stock reagents, since the rather labile chlorotrityl ether linkage can slowly decompose on standing at room temperature. It can be concluded that anchoring of **2** to Merrifield resins leads to much more robust and efficient immobilized ligands for catalytic purposes in comparison to the corresponding anchoring to Barlos resins.

While all functionalized Merrifield resins follow a very similar profile of catalytic activity, slightly better enantiomeric excess is recorded when polymers with low levels of substitution are employed (**7a, 7c**). Cross-linking seems not to be a key variable for this reaction since little difference is observed between **7a** and **7c**. On the other hand, **7c** is significantly easier to prepare compared to **7a**, since the fragmentation reaction takes place in much lower extent when ligand **2** is anchored to a Merrifield resin with a high level of cross-linking (**7c**). Taking into account the ease of preparation, catalytic

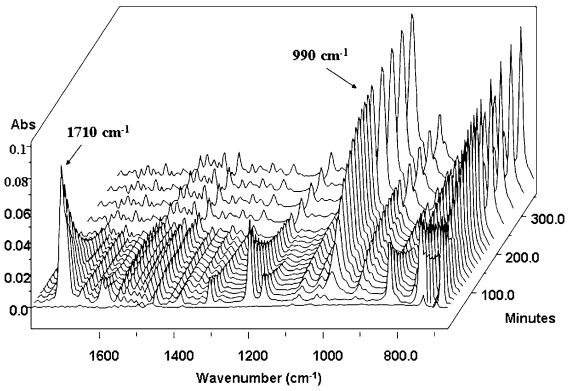


Figure 1. FTIR absorbance spectra during the addition of diethylzinc to benzaldehyde mediated by resin **7a**.

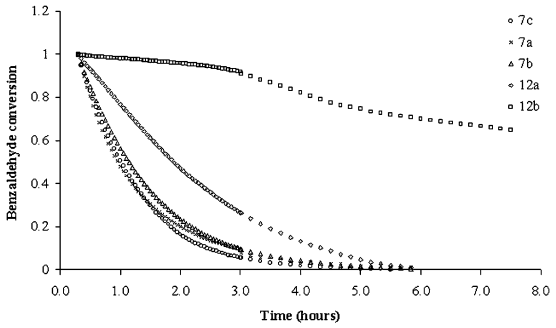


Figure 2. Profiles of benzaldehyde conversion for the addition of diethylzinc to benzaldehyde mediated by resin **7a – c** and **12a, b**.

activity and enantiomeric excess results, ligand **2** anchored to a Merrifield resin with a low level of substitution and a high level of cross-linking (**7c**) stands out as the optimal immobilized polymer among all prepared in the present study.

In order to test the stability and performance of **7c** after reuse, the addition reaction of diethylzinc to benzaldehyde was repeatedly run using the same recovered resin. Very gratifyingly, after six recycling cycles, the conversion, selectivity and enantiomeric excess were strictly maintained. In this respect, polymer **7c** can effectively be reused without loss, either in enantiomeric excess of the resulting alcohol or in activity of the resin.

Most gratifying is the similar catalytic behavior of the fuctionalized resin **7c** compared to its homogeneous counterpart **1**. When the addition of diethylzinc to benzaldehyde was performed using a 6% molar amount of **1**, under optimized reaction conditions,[16] total disappearance of the starting material was extremely fast, and the reaction took place to completion in less than one hour (Figure 3). On the other hand, when the heterogenized analogue was used in the same conditions, reaction proceeded again very fast, total consumption of benzaldehyde being detected in less than three hours. For both cases the same enantiomer of 1-

Table 3. Catalytic enantioselective addition of Et_2Zn to aldehydes **10a – o** leading to alcohols **11a – o** mediated by ligand **7c**.

Starting Aldehyde	Resulting Alcohol[a]	Conversion (%)[b]	Selectivity (%)[c]	Enant. Excess with **7c** (%)[d]	Enant. Excess with **1** (%)[d]
Benzaldehyde (**10a**)	**(*S*)-11a**	> 99	99	95	98
o-Fluorobenzaldehyde (**10b**)	**(*S*)-11b**	97	> 99	95	96
o-Tolualdehyde (**10c**)	**(*S*)-11c**	98	97	95	97
o-Methoxybenzaldehyde (**10d**)	**(*S*)-11d**	97	98	96	96
m-Fluorobenzaldehyde (**10e**)	**(*S*)-11e**	99	98	93	97
m-Tolualdehyde (**10f**)	**(*S*)-11f**	> 99	98	96	97
m-Methoxybenzaldehyde (**10g**)	**(*S*)-11g**	99	98	95	97
p-Fluorobenzaldehyde (**10h**)	**(*S*)-11h**	97	99	95	98
p-Tolualdehyde (**10i**)	**(*S*)-11i**	98	99	95	98
p-Methoxybenzaldehyde (**10j**)	**(*S*)-11j**	97	> 99	95	98
2-Naphthaldehyde (**10k**)	**(*S*)-11k**	97	99	95	98
Heptanal (**10l**)	**(*S*)-11l**	> 99	> 99	90	92
3-Phenylpropanal (**10m**)	**(*S*)-11m**	95	97	90	93
2-Ethylbutyraldehyde (**10n**)	**(*S*)-11n**	98	99	94	97
(*E*)-α-Methylcinnamaldehyde (**10o**)	**(*S*)-11o**	60	> 99	92	95

[a] Reaction conditions: 6% molar ligand **7c** and 2.2 equivs. of Et_2Zn, in toluene at 0 °C for 4 hours.
[b] Determined by integration of residual **10** in front of all new products in the gas chromatogram of the reaction crude.
[c] Determined by integration of **11** (both enantiomers) in front of all new compounds in the gas chromatogram of the reaction crude.
[d] Determined by GC on a β-DEX™ 120 column.

phenylpropanol was obtained in a completely selective manner and with very high enantiomeric excess. Only a 3% decrease in ee with respect to the monomer ligand **1** is observed when **7c** is used (95% ee). The same trend was observed when **7c** was used as a ligand for the addition of diethylzinc to a broad family of structurally diverse aldehydes (Table 3). Almost insignificant decreases in ee, in the order of 1 – 3%, were recorded in comparison to the use of the homogeneous ligand **1**. Moreover, the addition process was very fast for all aldehydes assayed: after 4 hours reaction, the corresponding alcohols were obtained in > 97% conversion and > 98% selectivity.

Among the heterogeneous ligands described so far for the catalytic enantioselective alkylation of aldehydes, those formed by anchoring enantiopure amino alcohols to polystyrene type resins,[2,3,9,17] (**13 – 16**) or those

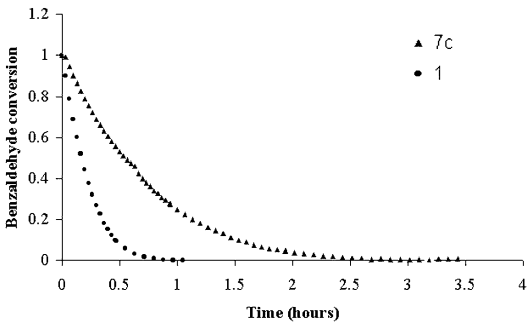
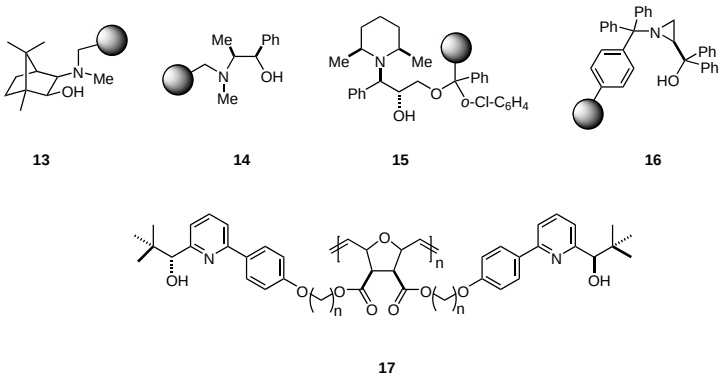


Figure 3. Profiles of benzaldehyde conversion for the addition of diethylzinc to benzaldehyde mediated by resin **7c** and the homogeneous phase ligand **1**.



formed by ROM polymerization of amino alcohol derivatives (**17**) represent the most readily available alternatives. However, their catalytic activity is usually low, and the enantioselectivity recorded in their reactions only moderate.[2,3,18] Even those ligands of this type exhibiting a good enantioselectivity profile[9,17] require high catalyst loading as well as long reaction times for complete conversion.

When the structures of these ligands are analyzed, and the nature of the catalytically active species in the amino alcohol-mediated enantioselective addition of dialkylzinc to aldehydes (Figure 4) is considered, it becomes evident that the easiest anchoring strategy (i.e., using the nucleophilic properties of the amino group as in **13**, **14**, and **16**) should not necessarily lead to the most catalytically active species. In effect, it is highly probable that the presence of the polymeric matrix near the active site poses an additional difficulty to the achievement of

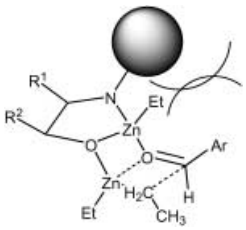


Figure 4. Perturbation of the active site by the polymeric matrix in amino alcohol ligands anchored through the nitrogen atom.

transition state geometry, thus reducing the catalytic efficiency of the system.

As already mentioned, it is this simple consideration that led us to the design principle applied to ligands like **7a – c** and **12a, b**: To start from a homogeneous ligand like **1**, known to be very active and highly enantioselective, and attaching it to the polymer by a point remote from the active region (tail-tie).

Conclusions

It is evident from the results reported in this paper that the application of this principle has been fully successful, since the prepared ligands, and especially **7c**, combine a profile of very high enantioselectivity in the addition of diethylzinc to aldehydes of essentially all structural types with a very high level of catalytic activity. When these characteristics are considered together with the simplicity and modularity associated to the synthesis of these species, polymer **7c** stands as the most efficient covalently immobilized ligand for the enantioselective alkylation of aldehydes not only among those of the amino alcohol type, but also among the normally more synthetically complex of BINOL[19] or TADDOL[20] types.

Work directed to the preparation of new tail-tied ligands is in progress in our laboratories and will be reported on due course.

Experimental Section

General Remarks

Optical rotations were measured at 23 °C (concentration in g/100 mL). Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded as film between NaCl plates or by KBr pellet techniques. ^{1}H NMR and ^{13}C NMR spectra in solution were recorded in $CDCl_3$. Carbon multiplicities have been assigned by distortionless enhancement by polarization transfer (DEPT) experiments. The NMR gel samples were prepared as follows: the appropriate mass of resin was placed in a 5 mm NMR tube, and the mass volume of solvent was added. When the solvent had been absorbed, small additional fractions of solvent were added to obtain a homogeneous gel. The so-prepared samples were allowed to stand for 8 – 12 h before recording the spectra. ^{13}C NMR gel phase NMR spectra were recorded at 75.4 MHz in $CDCl_3$. Elemental analyses were carried out by the Servei d'Anàlisis Elementals del C.S.I.C. de Barcelona. Tungsten(IV) oxide was used in the resin analyses to ensure total combustion of the samples. DMF, piperidine and CH_2Cl_2 were distilled from CaH_2 and stored under N_2. Hexane, THF and toluene were distilled from Na and stored under N_2. Merrifield and Barlos resins were obtained from commercial sources. Online FTIR analysis were performed in a React IR-1000 fitted with an immersible diamond (DiComp) ATR probe from Mettler Toledo.

Preparation of the Amino Alcohol Precursor in the Anchoring Step

4-(2,2-Diphenylvinyl)-benzonitrile (4): A suspension of potassium *tert*-butoxide (6.25 g, 56 mmol) in THF (80 mL) was added to a suspension of benzhydryltriphenylphosphonium bromide (25.0 g, 49 mmol) in THF (100 mL) at room temperature under vigorous stirring. After 23 hours, the resulting phosphorus ylide, which has a strong red color, was added to a solution of 4-formylbenzonitrile (4.3 g, 33 mmol) in benzene (60 mL). The mixture was kept 44 hours at reflux, it was cooled to room temperature and solvents were eliminated under vacuum. The residual solid was purified by chromatography to afford olefin **4** as a white solid; yield: 6.9 g (75%); mp 110 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.94$ (s, 1H), 7.06 – 7.42 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 109.7$ (C), 119,0 (C), 126.1 (CH), 127.7 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.8 (CH), 129.9 (CH), 130.1 (CH), 131.6 (CH), 139.3 (C), 142.0 (C), 142.4 (C), 146.1 (C); IR (KBr): $\nu = 3085, 3045, 3025, 2220, 1597$ cm^{-1}; MS (CI, NH_3): $m/e = 299$ [$(M + NH_4)^+$, 100]; anal. calcd. for $C_{21}H_{15}N$: C 89.65, H 5.37, N 4.98; found: C 89.87, H 5.45, N 4.97.

(*S*)-4-(3,3-Diphenyloxiranyl)-benzonitrile (5): Buffered bleach (165 mL, 0.11 mol, pH 11.3) was added dropwise to a solution of **4** (15.6 g, 55 mmol), [(*R*,*R*)-Jacobsen catalyst [(*R*,*R*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese (III) chloride] (1.70 g, 2.67 mmol) and 4-phenylpyridine *N*-oxide (2.00 g, 11.7 mmol) in CH_2Cl_2 (46 mL) at room temperature. After 3 h, the mixture was filtered through Celite, phases were separated, the organic phase was washed with water (2×200 mL), brine (1×200 mL), dried and concentrated under vacuum. The residual oil was purified by chromatography to afford epoxide **(*S*)-5** as a white solid; yield: 14.0 g (85%); 89% ee, which was enriched to >99% ee after recrystallizing twice in hexane. Conditions of HPLC analysis: Chiralcel OD column, 25 cm, 30 °C; eluent: hexane/propan-2-ol (95 : 5); flow rate, 0.5 mL/min; *R* isomer, t_R: 8.7 min and *S* isomer t_R: 11.3 min: mp 96 °C; $[\alpha]_D^{23}$: + 52.2 (*c* 1.03 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 4.37$ (s, 1H), 7.14 – 7.46 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 67.1$ (CH), 69.2 (C), 111.3 (C), 118.6 (C), 126.2 (CH), 127.2 (CH), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.4 (CH), 128.9 (CH), 131.5 (CH), 134.7 (C), 139.9 (C), 140.8 (C); IR (KBr): $\nu = 3060, 2230, 1586, 1497, 1451$ cm^{-1}; MS (CI, NH_3): $m/e = 298$ [$(M + H)^+$, 15], 315 [$(M + NH_4)^+$, 100]; anal. calcd. for $C_{21}H_{15}NO$: C 84.82, H 5.08, N 4.71; found: C 84.79, H 5.10, N 4.68.

(*S*)-4-(3,3-Diphenyloxiranyl)-benzaldehyde (6): A solution of DIBALH (61 mL, 61 mmol) in hexane was added dropwise to a solution of **(*S*)-5** (4.50 g, 15.1 mmol) in hexane at $-78\,^{\circ}C$. After 2.25 h, ethyl acetate (20 mL) was slowly added, and the reaction mass was allowed to warm to room temperature, when a saturated solution of NH_4Cl was added. The resulting mixture was kept at 25 °C for 2 h, the crude was filtered through Celite, the two phases were separated, the aqueous phase was extracted with ethyl acetate, and the combined organic phases were dried and concentrated under vacuum. The residual solid was purified by chromatography to afford the aldehyde **(*S*)-6** as a white solid; yield: 3.73 g (82%); $[\alpha]_D^{23}$: +60.9 (*c* 1.01 in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.39$ (s, 1H), 7.19–7.37 (m, 12H), 7.65 (d, $J = 8.4$ Hz, 2H), 9.87 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 67.3$ (CH), 68.7 (C), 126.2 (CH), 127.1 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.8 (CH), 129.1 (CH), 135.0 (C), 135.6 (C), 140.2 (C), 142.2 (C), 191.7 (CH); IR (NaCl, film): $\nu = 3060, 2851, 2747, 1699\ cm^{-1}$; MS (CI, NH_3): *m/e* = 318 [$(M + NH_4)^+$, 100].

(*S*)-[4-(3,3-Diphenyloxiranyl)-phenyl]-methanol (3): Portions of $NaBH_4$ (3.69 g, 12.3 mmol) were slowly added to a solution of **(*S*)-6** in ethanol (95 mL). After 1 h at room temperature, saturated aqueous NH_4Cl solution was added dropwise, and the resulting aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were washed with water (3×50 mL), dried and concentrated under vacuum. The residual solid was purified by chromatography to afford **(*S*)-3** as a white solid; yield: 3.47 g (94%); $[\alpha]_D^{23}$: +55.4 (*c* 1.02 in $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.62$ (bs, 1H), 4.32 (s, 1H), 4.59 (s, 2H), 7.04–7.35 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 64.9$ (CH_2), 67.9 (CH), 68.7 (C), 126.2 (CH), 126.3 (CH), 126.9 (CH), 127.5 (CH), 127.7 (CH), 127.8 (CH), 128.3 (CH), 129.1 (CH), 134.7 (C), 135.6 (C), 140.2 (C), 140.8 (C). IR (NaCl, film): $\nu = 3363, 3060, 3031, 2927\ cm^{-1}$; MS (CI, NH_3): *m/e* = 320 [$(M + NH_4)^+$, 100]; anal. calcd. for $C_{21}H_{18}O_2$: C 83.42, H 6.00; found: C 83.35, H 5.94.

(*R*)-2-(4-Hydroxymethylphenyl)-1,1-diphenyl-2-piperidin-1-ylethanol (2): A mixture of **(*S*)-3** (3.40 g, 11.2 mmol), $LiClO_4$ (14.4 g, 0.13 mol) and piperidine (55 mL, 0.56 mol) was heated at 80 °C under N_2. After 48 h, the reaction mixture was cooled to room temperature, CH_2Cl_2 (30 mL) was added, the organic phase was washed with water (3×200 mL), dried and concentrated under vacuum. The residual solid was purified by chromatography to afford **(*R*)-2** as a white solid; yield: 4.25 g (98%); mp 125–127 °C; $[\alpha]_D^{23}$: −127.6 (*c* 0.98 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.2–1.3$ (m, 2H), 1.3–1.5 (m, 4H), 1.8–2.1 (m, 2H), 2.25–2.5 (m, 2H), 4.5 (s, 1H), 4.6 (s, 2H), 6.8–7.4 (m, 12H), 7.5–7.7 (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 24.1$ (CH_2), 26.8 (CH_2), 54.4 (CH_2), 65.0 (CH_2), 77.3 (CH), 78.6 (C), 125.6 (CH), 125.7 (CH), 126.0 (CH), 126.2 (CH), 126.8 (CH), 127.2 (CH), 127.9 (CH), 131.4 (CH), 136.7 (C), 139.3 (C), 145.6 (C), 149.1 (C); IR (NaCl, film): $\nu = 3262$, 2934, 2805, 1449, 746, 702 cm^{-1}; MS (CI, NH_3): *m/e* = 387 [$(M + H)^+$, 100]; anal. calcd. for $C_{26}H_{29}NO_2$: C 80.59, H 7.54, N 3.61; found: C 80.75, H 7.51, N 3.51.

Anchoring (*R*)-2-(4-Hydroxymethylphenyl)-1,1-diphenyl-2-piperidin-1-ylethanol (2) to Merrifield Resins

Resin 7a (1% DVB, f_{max}: 0.52) from Chloromethylated Polystyrene (1% DVB, f_0: 0.63): A solution of **2** (0.11 g, 0.28 mmol) in DMF (1 mL) was added to a suspension of sodium hydride (7 mg, 0.29 mmol) in DMF (1 mL) at 0 °C under N_2. The mixture was stirred for 20 min and quickly poured into a smoothly stirred suspension of the Merrifield resin (0.40 g, 0.25 mmol of active Cl) in DMF (2 mL) at 0 °C. After 15 h, the suspension was filtered, washed with DMF (4×10 mL) and CH_2Cl_2 (4×10 mL) and concentrated under vacuum to constant weight to afford the functionalized resin **7a** (1% DVB, $f = 0.37$); yield: 0.43 g (93%); ^{13}C gel-phase NMR (75.4 MHz, $CDCl_3$): $\delta = 24.1$ (CH_2), 26.8 (CH_2), 40.3 (CH), 43.8 (CH_2), 54.4 (CH_2), 71.4 (2 CH_2), 77.4 (CH), 78.6 (C); anal. calcd. for f_{max}: N 0.72; found: N 0.52.

Resin 7b (1% DVB, f_{max}: 0.98) from Chloromethylated Polystyrene (1% DVB, f_0: 1.49): Compound **2** (0.24 g, 0.62 mmol) in DMF (2 mL), sodium hydride (15 mg, 0.6 mmol) in DMF (2 mL) and the Merrifield resin (0.40 g, 0.56 mmol of active Cl) in DMF (2 mL) were treated as described for **7a** to afford a poorly functionalized resin; yield: 0.42 g (82%). The anchoring step was repeated for 45 min at 25 °C, starting from the partially functionalized resin (0.42 g, $f = 0.51$) in DMF (1.3 mL), compound **2** (0.17 g, 0.43 mmol) in DMF (1.3 mmol) and sodium hydride (10 mg, 0.4 mmol) in DMF (1.3 mL). After both anchoring steps resin **7b** (1% DVB, $f = 0.85$) was obtained; yield: 0.43 g (72%); ^{13}C gel-phase NMR: the set of data was fully coincident with the one described above; anal. calcd. for f_{max}: N 1.36; found: N, 1.19.

Resin 7c (2% DVB, f_{max}: 0.65) from Chloromethylated Polystyrene (2% DVB, f_0: 0.84): A solution of **2** (1.00 g, 2.6 mmol) in DMF (8 mL) was added to a suspension of sodium hydride (62 mg, 2.6 mmol) in DMF (7 mL) at 0 °C under N_2. The mixture was stirred for 20 min and quickly poured into a smoothly stirred suspension of the Merrifield resin (2.80 g, 2.35 mmol of active Cl) in DMF (9 mL) at room temperature. After 2 h, the suspension was filtered, and treated as described for **7a** to afford the functionalized resin **7c** (1% DVB, $f = 0.39$); yield: 2.80 g (85%); ^{13}C gel-phase NMR: the set of data was fully coincident with the one described above; anal. calcd. for f_{max}: N 0.90, found: N 0.54.

Anchoring (*R*)-2-(4-Hydroxymethylphenyl)-1,1-diphenyl-2-piperidin-1-ylethanol (2) to Barlos Resins

Resin 12a (f_{max}: 1.02) from Barlos Resin with Initial Substitution Level 1.60 mmol Cl/g: DIEA (0.17 mL, 1.0 mmol) was added to a mixture of alcohol **2** (260 mg, 0.67 mmol) and the resin (300 mg, 0.48 mmol of active Cl) in CH_2Cl_2 (3 mL), under nitrogen, at room temperature. After smoothly stirring for 24 h, the resulting mixture was filtered, washed with DMF (2×10 mL), DMF:water 1:1 (4×10 mL), water (4×10 mL), pH 9 bicarbonate buffer (4×10 mL), water (8×10 mL), MeOH (4×10 mL), toluene (4×10 mL) and CH_2Cl_2 (4×10 mL), and concentrated under vacuum to constant weight to afford **12a** ($f = 0.93$); yield: 0.36 g (80%); ^{13}C gel-phase NMR (75.4 MHz, $CDCl_3$): $\delta = 24.0$ (CH_2), 26.6 (CH_2), 40.4 (CH), 54.3 (CH_2), 65.7

(CH_2), 76.5 (CH), 78.5 (C), 86.2 (C); anal. calcd. for f_{max}: N 1.43; found: N 1.30.

Resin 12b (f_{max}: 0.86) from Barlos Resin with Initial Substitution Level 1.24 mmol Cl/g: DIEA (0.13 mL, 0.77 mmol) was added to a mixture of alcohol **2** (200 mg, 0.52 mmol) and the resin (300 mg, 0.37 mmol of active Cl) in CH_2Cl_2 (3 mL), under nitrogen, at room temperature. After smoothly stirring for 24 h, the resulting mixture was treated as described for **12a** to afford **12b** ($f = 0.69$); yield: 0.32 g (80%); ^{13}C gel-phase NMR (75.4 MHz, $CDCl_3$): $\delta = 24.0$ (CH_2), 26.6 (CH_2), 40.4 (CH), 54.3 (CH_2), 65.7 (CH_2), 76.5 (CH), 78.5 (C), 86.2 (C); anal. calcd. for f_{max}: N 1.20; found: N 0.96.

1-(4-Phenoxymethylbenzyl)-piperidine (9)

A solution of **2** (100 mg, 0.26 mmol) in DMF (0.9 mL) was added *via* cannula to a suspension of sodium hydride (22 mg, 0.92 mmol) in DMF (0.9 mL), at 0 °C, under nitrogen. After 20 min, benzyl chloride (0.03 mL, 0.26 mmol) was added, the mixture was allowed to warm to room temperature, and kept under vigorous stirring for 6 h. The resulting suspension was quenched with methanol (3 mL) and water (3 mL), the aqueous phase was extracted with CH_2Cl_2 (3×5 mL) and the combined organic phases were dried and concentrated under vacuum. The crude was purified by chromatography to afford **9** as an oil; yield: 52 mg (68%), and benzophenone; yield: 32 mg (68%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.30-1.45$ (m, 2H), 1.45–1.62 (m, 4H), 2.25–2.45 (m, 4H), 3.5 (s, 2H), 4.5 (s, 2H), 4.6 (s, 2H), 7.2–7.4 (m, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta =$ 24.4 (CH_2), 26.0 (CH_2), 54.4 (CH_2), 63.6 (CH_2), 72.0 (CH_2), 72.1 (CH_2), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 129.3 (CH), 136.8 (C), 138.1 (C), 138.3 (C); IR (NaCl, film): $\nu = 2934$, 2853, 1454, 1097, 1074, 696 cm^{-1}; MS (CI, NH_3) :*m/e* = 296 [$(M+H)^+$, 100].

Enantioselective Amino Alcohol-Catalyzed Addition of Diethyzinc to Aldehydes; General Procedure

A suspension of the polymer bound catalyst **7a–c, 12a, b** (6% molar) in toluene (0.5 mL) was smoothly stirred under N_2 at room temperature to swell the polymer: 30 minutes for a modified Merrifield resin and 24 h for a modified Barlos resin. The corresponding swelled resin was cooled to 0 °C and a solution of diethylzinc (1.1 mL, 1.1 mmol) was added. After 20 minutes, the aldehyde (**10a–o**) (0.5 mmol) was dropwise added and the resulting mixture was kept under smooth stirring for 4 hours, after which the reaction was quenched by the addition of saturated NH_4Cl solution (5 mL). The resin was removed by filtration, the aqueous solution was extracted with CH_2Cl_2 (3×5 mL) and the combined organic phases were dried and concentrated under vacuum. Conversion, selectivity and enantiomeric excesses were determined from the crude mixture by GC. For **11a–o** conditions of analyses and retention times of the *R*- and *S*- isomers have been reported elsewhere.[4]

Ligand Recycling

A suspension of the functionalized resin **7c** (6% molar) in toluene (1 mL) was allowed to stir smoothly under N_2 at room temperature for 30 minutes in order to swell the polymer. The resin was then cooled to 0 °C and a solution of diethylzinc (2.2 mL, 2.2 mmol) was added. After 20 minutes, benzaldehyde (102 μL, 1 mmol) was dropwise added. After smooth stirring for 4 hours the resulting crude mixture was filtered *via* a cannula which had been previously packed with glass wool in one of its endings. The resin was then washed with toluene ($2 \times$ 5 mL) which was also removed by filtration under the same anhydrous conditions. After every filtration procedure the liquid obtained was removed from the flask *via* syringe and put into a third flask where the crude material could be finally quenched by the addition of saturated NH_4Cl solution (10 mL). The two phases were separated and the aqueous solution was extracted with CH_2Cl_2 (3×5 mL) and the combined organic phases were dried and concentrated under vacuum. The washed resin was reused six times in the addition of diethylzinc to benzaldehyde following the described protocol. Conversion, selectivity and enantiomeric excess were determined from the crude mixture by GC.

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