Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 12111–12120

Polystyrene-supported amino alcohol ligands for the heterogeneous asymmetric addition of phenyl zinc reagents to aldehydes

David Castellnou,[b] Montserrat Fontes,[b] Ciril Jimeno,[a] Daniel Font,[a] Lluís Solà,[a] Xavier Verdaguer[b] and Miquel A. Pericàs[a,b,*]

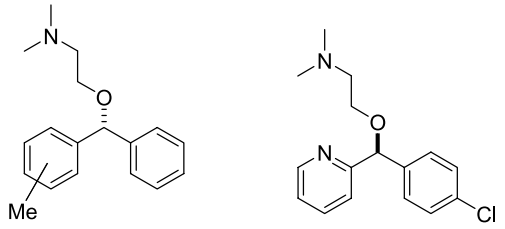
[a]*Institute of Chemical Research of Catalonia (ICIQ), Av.Països Catalans 16, 43007 Tarragona, Spain*
[b]*Departament de Química Orgànica, Universitat de Barcelona, 08028 Barcelona, Spain*

Received 30 June 2005; revised 15 July 2005; accepted 15 July 2005

Abstract—A family of polystyrene-supported amino alcohols, characterized by a high catalytic activity in alkyl transfer from zinc to formyl groups has been successfully tested in the enantioselective addition of phenyl zinc reagents to aldehydes to afford chiral diarylmethanols. Enantioselectivities higher than 90% (mean ee 90.5%; eight examples) are recorded with aromatic aldehydes in what represents the first successful use of heterogeneous, polymeric reagents for enantiocontrol in the phenylation of aldehydes.

1. Introduction

Enantiomerically pure diarylmethanols are important building blocks for biologically active compounds.[1] For example, (*R*)-neobenodine, (*R*)-orphenadrine, or (*S*)-carbinoxamine (Fig. 1) have been used for a long time as muscle relaxants or antihistaminics.[2] However, their preparation by asymmetric synthesis is challenging, because the asymmetric reduction of the appropriate diaryl ketone is usually hampered by low ee's due to the steric and electronic similitudes between both aryl groups.[3] Then, the enantioselective addition of an aryl fragment to an aldehyde (where all groups are easily distinguishable by the catalyst) appears as the most convenient way to gain access to these structural motifs.[4]



p-Me: (*R*)-neobenodine
o-Me: (*R*)-orphenadrine

(*S*)-carbinoxamine

Figure 1. Some pharmaceutically active diarylmethanols.

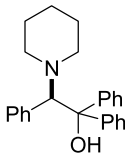
Diphenylzinc could be in principle a suitable reagent for this task, but it has the problem that the uncatalyzed background addition to aldehydes is a significant competing reaction with deletereous effects on the enantiomeric purity of the resulting diarylmethanols. In any case, since the pioneering work by Fu in 1997,[5] several efficient homogeneous catalytic systems for the enantioselective addition of diphenylzinc to aldehydes have been successfully developed relying in two basic strategies: the use of diluted reaction conditions to increase the rate difference between the catalyzed and the uncatalyzed processes,[6] or the in situ formation of a less reactive, mixed EtPhZn species extensively studied by Bolm.[7]

Over the last years, our research group has been involved in a project devoted to the synthesis of highly modular, synthetic yet enantiopure β-amino alcohol ligands using the Sharpless epoxidation of allyl alcohols or the Jacobsen epoxidation of arylethylenes as the ultimate source of chirality.[8] The modular nature of these species has allowed the simultaneous optimization of their catalytic activity and enantioselectivity in different processes such as alkyl transfer to carbonyls[8,9] and imines,[10] oxazaborolidine-mediated reduction of ketones,[11] transfer hydrogenation of ketones,[12] and allylic alkylation.[13] Among these ligands, readily available 2-piperidino-1,1,2-triphenylethanol (**1**)[8b] depicts an excellent enantioselectivity/activity profile for

Keywords: Heterogenous reaction; Ligand immobilization; Enantioselective synthesis; Aldehyde arylation.
* Corresponding author. Tel.: +34 977 920 211; fax: +34 977 920 222; e-mail: mapericas@iciq.es

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.07.112

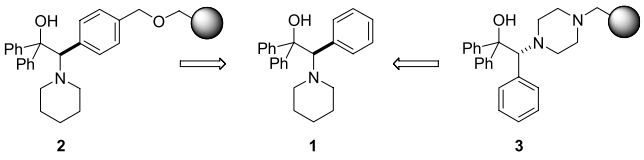
alkyl transfer to aldehydes[8b,14] and has also been found to be a most efficient mediator for the enantioselective phenyl transfer to these substrates,[15] enantioselectivities of 91–99% being achieved with only 1.5 mol% of **1** in reactions that typically require less than 1 h for completion.



1

From a general perspective, homogeneous catalysis has notably contributed to the clean and efficient production of chiral compounds as single enantiomers. Homogeneous catalytic processes, however, are usually performed in a batch manner, and work-up 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.[16] 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, attention has been paid to the enantioselective arylation of aldehydes, but only partial success has been achieved. In 1999, Pu and co-workers used a soluble, rigid BINOL polymer to perform the catalytic asymmetric addition of $ZnPh_2$ to aldehydes under much diluted conditions, achieving ee's up to 92% (Fig. 2). However, a high catalyst loading (40 mol%) was needed to drive the reaction to completion, and some of the main advantages associated to the use of polymer-supported ligands (easy recovery and reuse) were absent from this approach.[6b] Later on, Bolm immobilized a ferrocenyloxazoline ligand onto polymeric supports and studied the enantioselective phenyl transfer to *p*-chlorobenzaldehyde. When the ligand was bound to an insoluble trityl chloride resin, the polymer proved to be unsuitable for the catalysis of the asymmetric process, and only racemic product was obtained. On the other hand, when the ligand was bound to a soluble MeO–PEG resin, the resulting catalyst led to the addition product with high enantioselectivity.[17] It is clear from these results that low activity, insoluble resins fail to induce the enantioselective reaction at a sufficient rate to compete with the rather fast,[15] uncatalyzed background reaction, and that very active ligands should be designed to achieve high enantiocontrol levels in this class of heterogeneous reaction.

Using the highly active ligand (*R*)-2-piperidino-1,1,2-triphenylethanol (**1**),[8b] as the basis of our design,[18] we have developed polystyrene supported amino alcohols **2**[19] and **3**,[20] and have introduced for their designation the term tail-tied ligands. Gratifyingly enough, both the catalytic activity and the enantioselectivity exhibited by **2** and **3** are among the highest ever recorded for supported ligands, and this fact converts them into qualified candidates for the achievement of enantiocontrol in the phenylation of aldehydes.



2 **1** **3**

We wish to report here the preparation of a new tail-tied ligand (**5**), a regioisomer of **2** and **3**, conceptually derived from the highly active and enantioselective amino alcohol

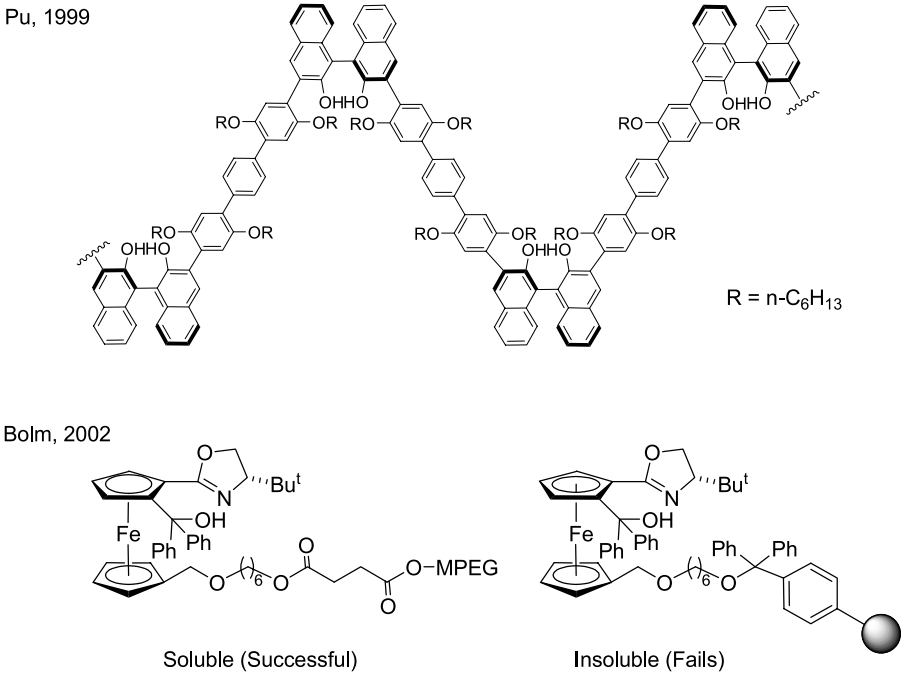
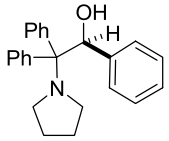
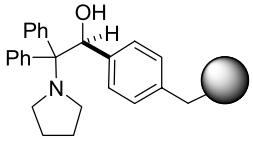


Figure 2. Soluble and insoluble polymer-supported ligands employed in the enantioselective phenylation of aldehydes.

4,[8c] and its evaluation in the enantioselective ethylation of aldehydes. In addition, the evaluation of **2**, **3**, and **5** in the enantioselective phenylation reaction leading to the identification of the first insoluble, polymeric ligands successful in the considered reaction is also reported.



4



5

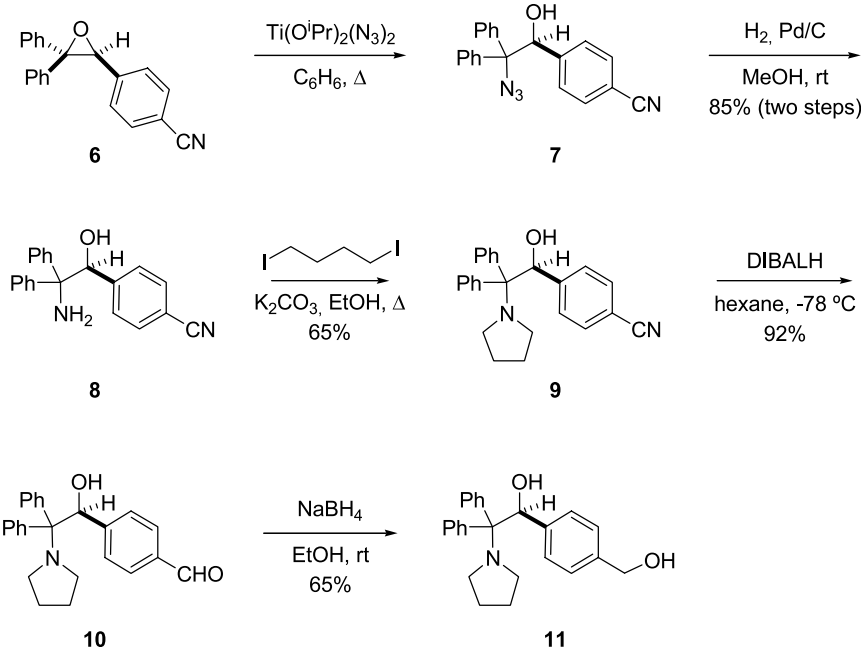
2. Results and discussion

2.1. Synthesis and anchoring to Barlos' resins of (*S*)-1-(4-(hydroxymethyl)phenyl)-2,2-diphenyl-2-(pyrrolidin-1-yl)-ethanol

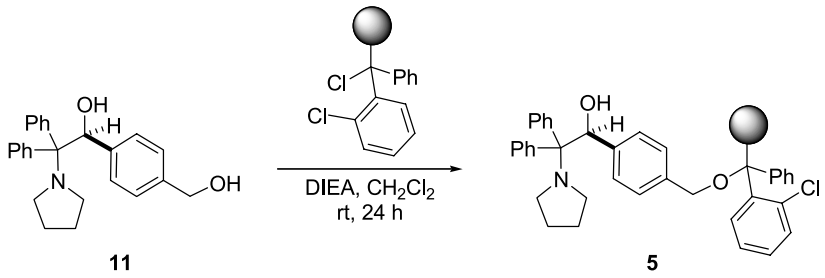
As we have already mentioned, a primary goal in the present research was the synthesis of resins **5** which, on one side, possess the characteristic of the ligand being anchored to the polymeric support through a position remote from the active center and, on the other side, exhibit a functional group arrangement opposite to the one present in **2** and **3**. We have previously shown[8c–d] that the regiochemistry of the ring-opening of triarylethylene oxides with nitrogen nucleophiles can be exclusively directed to the more substituted carbon by the use of diisopropoxytitanium diazide,[21] although some additional functional group manipulation can be required. According to this strategy (Scheme 1), the known epoxide **6**, that is readily available in enantiomerically pure form (>99.9% ee) by Jacobsen epoxidation[22] and recrystallization from hexane, would be the starting material for the synthesis. It is interesting to note that **6** is also the starting material for the preparation of the supported ligand **2**.

When enantiomerically pure (*S*)-**6** was treated with diisopropoxytitanium diazide in benzene at reflux, a totally regioselective ring-opening took place leading to azido-alcohol (*S*)-**7**, arising from attack to the more heavily substituted carbon of the epoxide. The crude azidoalcohol was directly submitted to hydrogenolysis in methanol (1 atm H_2; Pd/C) to afford amino alcohol **8** in 85% overall yield.

It is interesting to note that the amino group of **8** offers a good possibility for structural diversity, since many different groups could be installed on it by alkylation, cyclialkylation, and reductive amination processes.[8c] In the present case, the planned pirrolidine ring was constructed by cyclialkylation with 1,4-diiodobutane in ethanol at reflux in the presence of potassium carbonate. To achieve a good yield in this reaction, it was necessary to maintain in the reaction medium an excess of 1,4-diiodobutane during the whole reaction time. In this way, a 65% yield of **9** was obtained after 72 h, with periodical addition of alkylating agent (up to 7 equiv). Finally, the cyano group in **9** was reduced to hydroxymethyl through a two-stage process: First, the aldehyde **10** was obtained in 92% yield by treatment of **9** with DIBALH at −78 °C in hexane/ether solution; then, the primary alcohol **11** was formed (65% yield) by reduction of **10** with sodium borohydride in ethanol at room temperature. For the anchoring of **11** to polymeric supports, a chlorotritylated polystyrene resin (Barlos' resin)[23] was selected as the most convenient alternative[24] (Scheme 2). Starting from a Barlos' resin with f_o: 1.60, and using the standard anchoring conditions (Scheme 2), a functionalized resin 5, with *f*: 0.90 (calculated by nitrogen elemental analysis with the formula; *f*: 0.714[%N]) was obtained. Since f_{max} for this particular resin is 1.06[19] the yield of the anchoring process turns out to be 85%.



Scheme 1. Enantioselective synthesis of amino alcohol **11**, the precursor of resin **5**.



11 5

Scheme 2. Anchoring of amino alcohol **11** to a Barlos' resin.

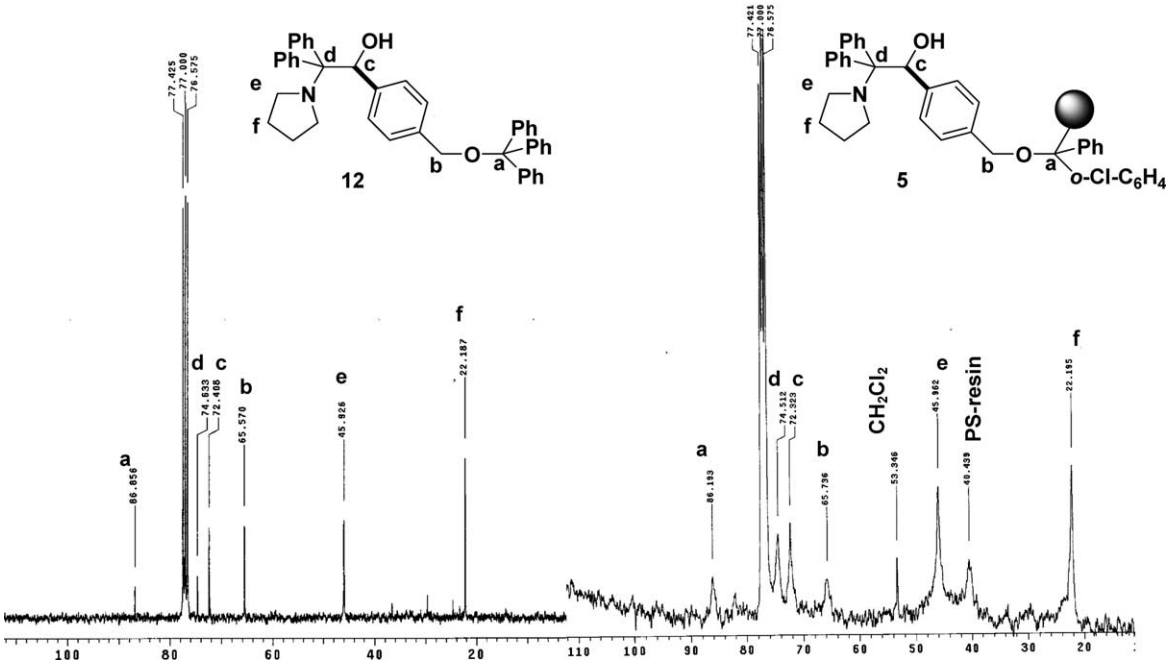


Figure 3. Monitoring of the anchoring of amino alcohol **11** to a Barlos' resin by gel phase ^{13}C NMR. The NMR spectrum of the model compound **12** is included for comparison.

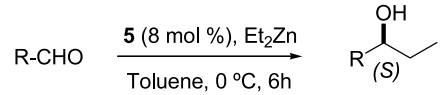
The progress of the anchoring process can be easily monitored by gel-phase ^{13}C NMR.[25] For comparison purposes, the trityl-protected amino alcohol **12** was easily prepared by treatment of **11** with *N*-tritylpyridinium tetrafluoroborate in acetonitrile. The diagnostic region of the ^{13}C NMR spectra of both compounds (**12** in solution; **5** in gel) is represented in Figure 3.

2.2. Evaluation of resin 5 as a ligand for enantioselective ethylation and phenylation of aldehydes

Resin **5** was initially tested in the enantioselective addition of diethylzinc to aldehydes (**13**). A representative set of aldehydes **13a–h**, mostly containing difficult substrates (aliphatic, α,β-unsaturated), was selected, and the ethylation reaction leading to 1-propanols **14a–h** was performed in toluene at 0 °C, in the presence of a 8 mol% of **5**. The results of these additions have been summarized in Table 1.

As it can be seen, resin **5** provides high conversion numbers for the ethylation of aromatic aldehydes (**13a–c**) and for aliphatic and α,β-unsaturated aldehydes not fully substituted at the α position (**13e–f** and **13d**, respectively). With

Table 1. Enantioselective ethylation of aldehydes **13a–h** mediated by resin **5** (8 mol%)

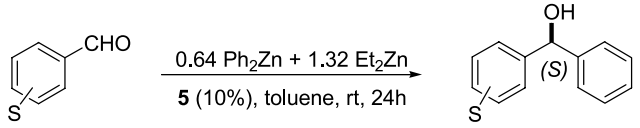


13 14

Starting aldehyde	Conv (%)	ee (%)
o-Methoxybenzaldehyde (**13a**)	95	86
m-Tolualdehyde (**13b**)	90	90
p-Fluorobenzaldehyde (**13c**)	94	84
Cinnamaldehyde (**13d**)	89	71
Heptanal (**13e**)	93	90
3-Phenylpropanal (**13f**)	94	89
2-Ethylbutanal (**13g**)	50	91
α-Methylcinnamaldehyde (**13h**)	55	89

respect to enantioselectivity, good results are obtained for aromatic aldehydes. However, the most noteworthy enantioselectivities are those obtained with aliphatic and α,β-unsaturated aldehydes, where many homogeneous and heterogeneous ligands fail. Encouraged by these results, we decided to test the use of resin **5** for the enantioselective phenylation reaction leading to diarylmethanols **15**. The phenyl transferring system developed by Bolm and co-workers,[7] that involves the use of a Ph_2Zn/Et_2Zn mixture and has provided excellent results in the enantioselective phenylation mediated by the monomeric ligand **1** was also used in this case.[15] The reactions were initially tested on a limited set of aromatic aldehydes (**13i–13l**) by using a 10% molar amount of catalyst. Since our primary interest was on enantioselectivity, no attention was paid to optimization of reaction time. The results of this study have been summarized in Table 2.

Table 2. Enantioselective phenylation of aldehydes **13i–l** mediated by resin **5** (10 mol%)



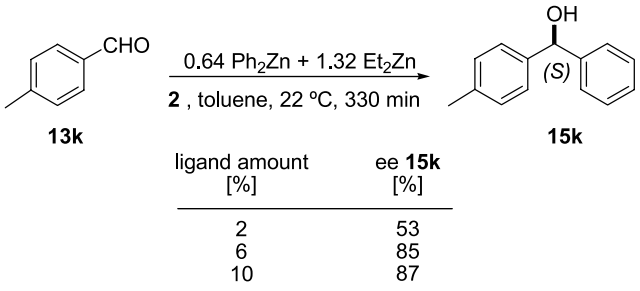
13i-l **15**

Starting aldehyde	Conv (%)	ee (%)
o-Fluorobenzaldehyde (**13i**)	90	43
o-Tolualdehyde (**13j**)	99	38
p-Tolualdehyde (**13k**)	99	48
m-Methoxybenzaldehyde (**13l**)	99	42

A first aspect of these results to be highlighted is that the heterogeneous ligand **5** is able to induce enantioselectivity in the phenylation reaction, albeit to a moderate level. It thus appears that the strategy of structural modification of ligands known to be very active and enantioselective to allow anchoring to a polymeric matrix without perturbing the catalytic center (tail-tied ligands) can provide a solution for the problem of the enantioselective phenylation of aldehydes with heterogeneous ligands. In any case, when the behavior of the polymer-supported ligand **5** is compared with that of its homogeneous counterpart **4**,[8c] it becomes evident that in this case the anchoring process provokes some decrease in the enantioselectivity characteristics of the homogeneous ligand. As we have previously shown,[19–20] this is not the case for polymer-supported ligands **2** and **3**, conceptually derived from amino alcohol **1**. In view of the results obtained in the preliminary evaluation of resin **5**, its use as a catalytic ligand for the catalytic enantioselective phenylation of aldehydes was abandoned. Alternatively, the evaluation of resins **2** and **3** with the same purpose was undertaken.

2.3. Evaluation of resin 2 as a ligand for enantioselective phenylation of aldehydes

According to precedents in the enantioselective ethylation of aldehydes with this family of polymer-supported ligands, a resin with a rather high cross-linking level (2% DVB) and a functionalization level (f) of 0.35 mmol ligand/g was used in this study. The optimal molar amount of resin was determined first, working on *p*-tolualdehyde (**13k**) and performing the reactions in toluene (for optimal resin swelling) at room temperature (Scheme 3).



Scheme 3. Optimization of ligand amount in the phenylation of *p*-tolualdehyde mediated by resin **2**.

It was already clear from these experiments that **2** was a much better ligand than **5** for the asymmetric phenyl transfer reaction. With respect to the optimal amount of ligand, it was decided to perform the reaction with a 10% molar amount of **2** in order to secure the highest possible enantioselectivity in the shortest reaction time. It is important to recall here that this level of ligand loading is the usual one in phenyl transfer reactions with homogeneous, monomeric ligands.

Next, the phenyl transfer reaction was performed on a representative family of aldehydes under the optimized conditions. To test the preparative merits of the procedure, the diarylmethanol products **15** were isolated and quantified after each reaction. Results arising from this study have been summarized in Table 3, where the enantioselectivities recorded with the homogeneous ligand **1** under identical experimental conditions have also been included for comparison.

Table 3. Enantioselective phenylation of aldehydes mediated by resin **2** (10 mol%)

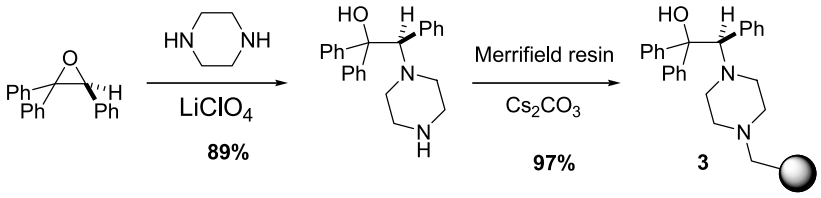
Starting aldehyde	Yield (%)	ee (%)	ee with **1** (%)
α-Methylcinnamaldehyde (**13h**)	75	87	94[a]
o-Fluorobenzaldehyde (**13i**)	99	85	98
o-Tolualdehyde (**13j**)	98	91	99
p-Tolualdehyde (**13k**)	96	87	98
m-Methoxybenzaldehyde (**13l**)	74	90	—
Pivalaldehyde (**13m**)	78	80	92
Biphenyl-4-carbaldehyde (**13n**)	86	91	97
2-Naphthaldehyde (**13o**)	81	90	96

[a] Reaction in toluene at 0 °C.

As it can be readily seen, high yields of diarylmethanols **15** are obtained in the phenyl transfer reaction mediated by resin **2**. Even more importantly, a uniformly high enantioselectivity is recorded in the reactions, the mean ee of the resulting products **15** being 87.6%.

2.4. Evaluation of resin 3 as a ligand for enantioselective phenylation of aldehydes

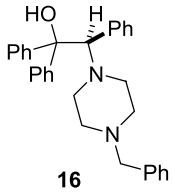
While it is clear that resin **2** depicts a very interesting profile as a ligand for the catalytic enantioselective phenyl transfer to aldehydes, it is also true that its synthesis (as in the case of



Scheme 4. Two-step assembly of ligand **3** from its precursors.[22]

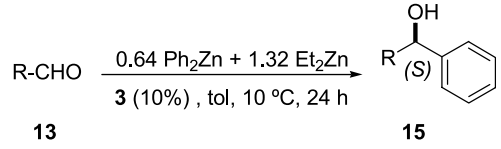
resin **5**) from commercial precursors is rather lengthy. This observation, that could be of practical interest if the application of these resins at a larger scale was considered, boosted the development of resin **3**, that can be straightforwardly assembled from its fragments: enantiomerically pure triphenylethylene oxide, piperazine, and a Merrifield resin, as shown in Scheme 4.[20]

In addition to the ease of its preparation, resin **3** was shown to be a most efficient ligand for the enantioselective ethyl transfer to aldehydes, with catalytic activity and enantioselectivity that did not show any decrease with respect to the referable, homogeneous ligand **16**.[20,26]



According to these precedents, resin **3** was an ideal candidate for a successful ligand in enantioselective phenyl transfer to aldehydes. As in the case of **2**, a preliminary screening confirmed these expectations (Table 4).

Table 4. Preliminary screening of resin **3** (10 mol%) in the enantioselective phenylation of aldehydes



Starting aldehyde	ee (%)
α-Methylcinnamaldehyde (**13h**)	90
o-Fluorobenzaldehyde (**13i**)	84
o-Tolualdehyde (**13j**)	91
m-Methoxybenzaldehyde (**13l**)	89
Pivalaldehyde (**13m**)	89
2-Naphthaldehyde (**13o**)	90

Next, some key parameters related to the use of **3** in the reaction were optimized. On the first place, since it is known that phenyl transfer from zinc to carbonyl groups usually presents an isoinversion temperature,[27] and the temperature for optimal enantioselectivity had been previously established as 10 °C working with ligand **1** in the addition to *p*-tolualdehyde (**13k**),[15] the optimization was repeated for ligand **3** working on the same substrate. By using a 5% molar amount of **3** in reactions at 0, 10, and 23 °C, the corresponding diarylcarbynol **15k** was obtained with enantiomeric purities of 92, 94, and 91%, respectively. It is thus confirmed that, at least for **13k**, 10 °C represents the optimal temperature for reaction. To simultaneously gain information on the kinetics of the process at different temperatures, the forementioned experiments were performed with continuous monitoring of the reaction progress by in situ FTIR spectroscopy. This was done with an immersible DiComp ATR diamond probe, and the disappearance of the band corresponding to the carbonyl group of **13k** was analyzed. We have represented in Figure 4 the evolution of this band in the experiments at 0, 10, and 23 °C in the presence of 5 mol% of **3**.

Two aspects of this graph deserve a comment: On one hand, the important acceleration experienced by the reaction when the temperature increases from 0 to 10 °C, that has necessarily to obey to a combination of physical (mass transport) and chemical (kinetic) factors. On the other hand, the high catalytic activity exhibited by **3** at 10 °C or above, that leads to complete conversion in only 50 min. Keeping in mind the possibility of a future use of **3** in a continuous flow system, we also wanted to test if reaction time could be further reduced if catalyst loading was increased. To this end, the reaction at 23 °C was repeated with a 10 mol% catalyst loading. The progress of this reaction has been represented in Figure 5 along with that of the experiment with 5% catalyst loading at the same temperature.

It is interesting to observe that the time required for complete conversion is essentially divided by a factor of **2** when catalyst loading is increased from 5 to 10%. This is clearly indicative that even much shorter contact times could be sufficient for complete conversion at higher catalyst loadings, and tells in favor of **3** as a suitable candidate ligand for enantioselective phenylation in continuous flow systems. As an additional point, it is to be mentioned that the ee of the resulting arylcarbynol **15k** increases in only 1% (from 91 to 92%) while increasing from 5 to 10% catalyst loading. As a result of these observations, a set of optimized practical conditions for the use of **3** in enantioselective phenylation reactions was developed (5 mol% **3**, toluene, 10 °C, 2 h) and tested on a diverse set of aldehydes. The results of this study have been summarized in Table 5.

As inspection of Table 5 reveals, excellent results are obtained for *p*-substituted substrates under this set of experimental conditions. On the other hand, since the studied reaction is in general highly responsive to small variations in experimental conditions (temperature, solvent, catalyst amount), the possibility that higher enantiomeric

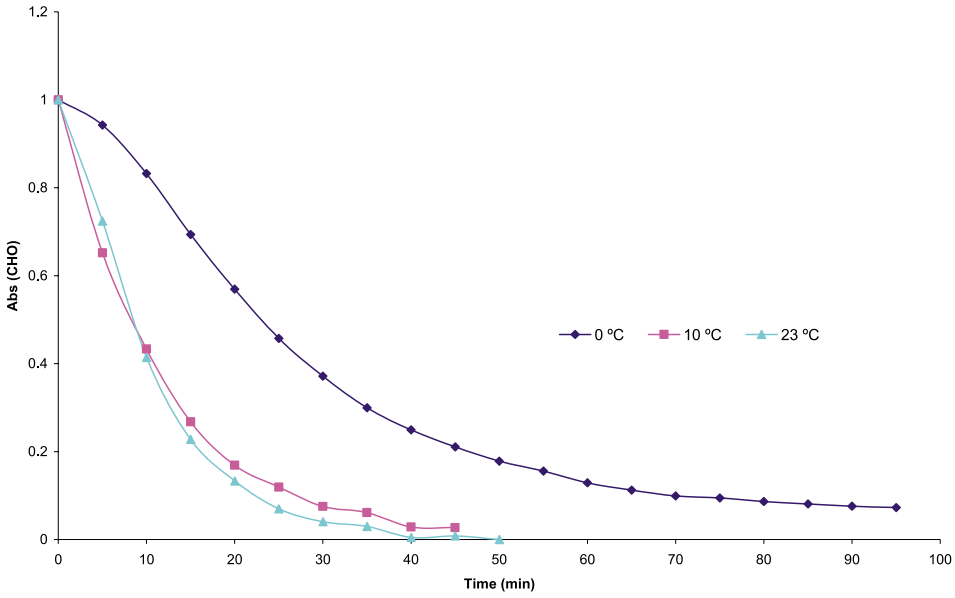


Figure 4. Progress of the phenylation of **13k** mediated by **3** (5 mol%) at different temperatures.

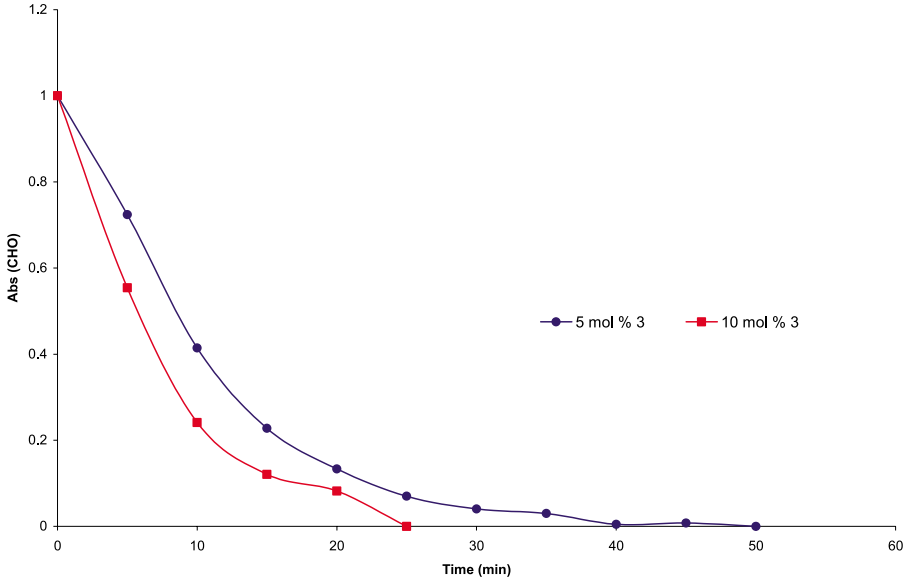


Figure 5. Progress of the phenylation of **13k** mediated by **3** at 23 °C with different catalyst loadings.

excesses can be achieved for some of the substrates under different experimental conditions can not be excluded. In this respect, it is illustrative to compare the results obtained for **13h**, **13m**, and **13o** using either 10 mol% (Table 4) or 5 mol% (Table 5) of resin **3**.

Table 5. Enantioselective phenylation of a selected set of aldehydes mediated by resin **3** (5 mol%) under optimized reaction conditions

Starting aldehyde	Yield (%)	ee (%)
2-Ethylbutanal (**13g**)	83	75
α-Methylcinnamaldehyde (**13h**)	82	79
p-Tolualdehyde (**13k**)	100	94
Pivalaldehyde (**13m**)	97	68
Biphenyl-4-carbaldehyde (**13n**)	69	92
2-Naphthaldehyde (**13o**)	100	85
p-Methoxybenzaldehyde (**13p**)	75	>99
p-Chlorobenzaldehyde (**13q**)	80	82

3. Summary and outlook

In summary, the first polymeric heterogeneous ligands (**2** and **3**) for the highly enantioselective phenyl transfer to aldehydes have been developed. The high catalytic activity depicted by these ligands, probably arising from a design where the handle used for the anchoring of the monomers to the polymer backbone introduces a minimal perturbation on the catalytic center, appears to be key to this behavior. With respect to enantioselectivity, **2** and **3** appear to be complementary in many aspects, and experimental conditions have been found for efficiently controlling the enantioselectivity of the phenylation of aromatic aldehydes (90.5% mean ee, eight examples) by a proper ligand choice. Although fewer examples have been studied, only marginally inferior results are recorded with α-substituted aliphatic

and α,β-unsaturated aldehydes. With respect to catalytic activity, reaction times of only 25 min have been determined by on-line FTIR analysis through the use of 10 mol% amounts of ligand **3**. As an application of this property, the development of flow systems for the continuous enantioselective phenylation of aromatic aldehydes is being actively pursued in our laboratories and will be reported in due course.

4. Experimental

4.1. General

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 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. Barlos resins were obtained from commercial sources. Online FTIR analysis were performed with a React IR-4000 instrument fitted with an immersible diamond (DiComp) ATR probe from Mettler Toledo.

4.1.1. (*S*)-4-(2-Azido-1-hydroxy-2,2-diphenylethyl)-benzonitrile (7). Enantiomerically pure (>99.9% ee) (*S*)-**6** (4.8 g; 16.1 mmol), prepared according to a reported procedure, were dissolved in 40 mL anhydrous benzene, and added to a freshly prepared suspension of diisopropoxytitanium diazide (5 g; 19.9 mmol) in anhydrous benzene (40 mL) under reflux. After 320 min, the mixture was cooled down, benzene was removed under vacuum, and the residue was dissolved in diethyl ether (50 mL). Aqueous 5% H_2SO_4 (50 mL) and the mixture was vigorously stirred for 60 min. Phases were then separated, and the aqueous one extracted with diethyl ether (4×50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to afford 6.21 g of crude (*S*)-**7**, that was submitted to azide reduction without further purification. $[\alpha]_D^{23}$ −35.8 (*c* 1.01, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.78 (br s, 1H), 5.73 (s, 1H), 7.01–7.44 (m, 14H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 75.8 (C), 78.4 (CH), 111.4 (C), 118.7 (C), 127.3 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 130.9 (CH), 139.3 (C), 140.0 (C), 144.3 (C) ppm. IR (film, NaCl) υ_{max}: 3457, 2228, 2109 cm^{-1}. MS (CI, NH_3) *m/e*: 359 ($[M+19]^+$, 26%), 358 ($[M+18]^+$, 100%).

4.1.2. (*S*)-4-(2-Amino-1-hydroxy-2,2-diphenylethyl)-benzonitrile (8). The crude azide **7** (6.21 g; 18.4 mmol) was dissolved in MeOH (100 mL) and added via canula to a suspension of 10% Pd/C (0.76 g) in MeOH (100 mL) under hydrogen (1 atm). After 15 h stirring at room temperature, the reaction mixture was filtered through a pad of Celite to remove the catalyst, and MeOH was evaporated under vacuum. The residue was purified by column chromatography on Et_3N pre-treated SiO_2 (2.5% v/v) eluting with hexane/ethyl acetate mixtures of increasing polarity to afford (*S*)-**8** (4.40 g) in 85% yield [from (*S*)-**6**] as a white solid. Mp: 166 °C. $[\alpha]_D^{23}$ −249.5 (*c* 1.02, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.2–2.8 (br s, 2H), 5.6 (s, 1H), 6.8–7.7 (m, 14H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 65.9 (C), 76.9 (CH), 111.0 (C), 118.8 (C), 126.6 (CH), 127.0 (CH), 127.2 (CH), 127.5 (CH), 128.0 (CH), 128.5 (CH), 130.9 (CH), 144.4 (C), 145.3 (C), 145.4 (C) ppm. IR (film, NaCl) υ_{max}: 3478, 3350, 3290, 3090, 3060, 2228 cm^{-1}. MS (CI, NH_3) *m/e*: 315 ($[M+1]^+$, 100%), 316 ($[M+2]^+$, 23%). Elemental analysis: calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.21; H, 5.75; N, 8.92.

4.1.3. (*S*)-4-(1-Hydroxy-2,2-diphenyl-2-(pyrrolidin-1-yl)-ethyl)benzonitrile (9). Amino alcohol (*S*)-**8** (3.49 g, 11.1 mmol) was dissolved in absolute ethanol (21 mL). Anhydrous potassium carbonate (3.10 g; 22.4 mmol) and 1,4-diiodobutane (2.92 mL, 22.2 mmol) were added to the solution, and the resulting mixture was heated under reflux. Over 3 days, additional 1,4-diiodobutane (7.6 mL; 57.4 mmol) was added in portions to the refluxing reaction mixture. Afterwards, the reaction mixture was cooled down and filtered, and ethanol was removed at reduced pressure. The residue was purified by column chomatography on Et_3N pre-treated SiO_2 (2.5% v/v) eluting with hexane/ethyl acetate mixtures of increasing polarity to afford (*S*)-**9** (2.60 g) in 64% yield as a white solid. Mp: 71 °C. $[\alpha]_D^{23}$ +39.6 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.4–1.8 (br s, 4H), 2.2–2.6 (br s, 4H), 5.9 (s, 1H), 6.9–7.5 (m, 14H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 22.1 (CH_2), 45.9 (CH_2), 71.8 (CH), 110.3 (C), 119.0 (C), 126.3 (CH), 126.9 (CH), 127.0 (CH), 127.5 (CH), 128.4 (CH), 130.5 (CH), 130.7 (CH), 146.2 (C) ppm. IR (film, NaCl) υ_{max}: 3400, 2228 cm^{-1}. MS (CI, NH_3) *m/e*: 368 (M^+, 100%), 369 ($[M+1]^+$, 28%). Elemental analysis: calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60. Found: C, 81.50; H, 6.57; N, 7.62.

4.1.4. (*S*)-4-(1-Hydroxy-2,2-diphenyl-2-(pyrrolidin-1-yl)-ethyl)benzaldehyde (10). A solution of DIBALH (2.7 mL, 2.7 mmol) in hexane was added dropwise to a solution of (*S*)-**9** (0.252 g, 0.70 mmol) in hexane (6.5 mL) and diethyl ether (2 mL) at −78 °C. After 1 h, ethyl acetate (1 mL) was slowly added, and the reaction mass was allowed to heat to room temperature. After 20 min, a saturated solution of NH_4Cl (3 mL) was added, and the resulting mixture was stirred at room temperature for 2 h. The crude was then filtered through a pad of Celite, the two phases were separated, the aqueous phase was extracted with ethyl acetate (3×10 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column

chomatography on Et_3N pre-treated SiO_2 (2.5% v/v) eluting with hexane/ethyl acetate mixtures of increasing polarity to afford (*S*)-**10** (0.231 g) in 92% yield as a white solid. Mp: 67 °C. $[\alpha]_D^{23}$ +51.1 (*c* 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.5–1.8 (br s, 4H), 2.2–2.8 (br s, 4H), 5.9 (s, 1H), 6.8–7.6 (m, 14H), 9.8 (s, 1H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 22.1 (CH_2), 45.9 (CH_2), 72.1 (CH), 74.6 (C), 126.2 (CH), 126.8 (CH), 126.9 (CH), 127.4 (CH), 128.2 (CH), 128.5 (CH), 130.6 (CH), 130.8 (CH), 134.9 (C), 147.8 (C), 192.2 (CH) ppm. IR (film, NaCl) υ_{max}: 3380, 2834, 1697 cm^{-1}. MS (CI, NH_3) *m/e*: 371 (M^+, 100%), 372 ($[M+1]^+$, 27%).

4.1.5. (*S*)-1-(4-(Hydroxymethyl)phenyl)-2,2-diphenyl-2-(pyrrolidin-1-yl)ethanol (11). $NaBH_4$ (71.4 mg, 1.88 mmol) was added to a solution of (*S*)-**10** (176 mg; 0.5 mmol) in absolute ethanol (3.5 mL). After 0.5 h at room temperature, saturated aqueous NH_4Cl solution was added dropwise, and the resulting aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were washed with water (3×5 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by column chomatography on Et_3N pre-treated SiO_2 (2.5% v/v) eluting with hexane/ethyl acetate mixtures of increasing polarity to afford (*S*)-**11** (113 mg) in 65% yield as a white solid. Mp: 79 °C. $[\alpha]_D^{23}$ +18.0 (*c* 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.5–1.8 (br s, 4H), 2.2–2.7 (br s, 4H), 4.5 (s, 2H), 5.9 (s, 1H), 6.6–6.8 (m, 2H), 6.8–7.5 (m, 12H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 22.2 (CH_2), 45.9 (CH_2), 65.0 (CH_2), 72.3 (CH), 74.5 (C), 125.3 (CH), 126.0 (CH), 126.6 (CH), 126.7 (CH), 127.1 (CH), 128.4 (CH), 130.9 (CH), 131.0 (CH), 137.3 (C), 139.4 (C), 139.5 (C) ppm. IR (film, NaCl) υ_{max}: 3397 cm^{-1}. MS (CI, NH_3) *m/e*: 373 (M^+, 100%), 374 ($[M+1]^+$, 29%).

4.1.6. Anchoring of amino alcohol 11 to a Barlos resin: resin 5 (f_{max}: 1.06) from Barlos' resin with an initial substitution level of 1.60 mmol Cl/g. Diisopropyletylamine (0.15 mL, 0.88 mmol) was added to a mixture of aminodiol **11** (171 mg, 0.46 mmol) and the resin (232 mg, 0.38 mmol of active Cl) in CH_2Cl_2 (2.5 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 $Na_2CO_3/NaHCO_3$ buffer (4×10 mL), water (8×10 mL), MeOH (4×10 mL), toluene (4×10 mL) and CH_2Cl_2 (4×10 mL), and dried under vacuum to constant weight to afford 0.301 g (100%) of resin **12** (*f*: 0.896). ^{13}C gel-phase NMR (75.4 MHz, $CDCl_3$) δ: 22.2 (CH_2), 40.4 (CH), 45.9 (CH_2), 65.7 (CH_2), 72.3 (CH), 74.5 (C), 86.2 (C). Anal. Calcd for f_{max}: N, 1.43. Found: N, 1.30. Anchoring yield: 85%.

4.1.7. (*S*)-2,2-Diphenyl-2-(pyrrolidin-1-yl)-1-(4-(trityloxymethyl)phenyl)ethanol (12). A solution of (*S*)-**11** (50 mg, 0.13 mmol) and *N*-tritylpyridinium tetrafluoroborate (66 mg, 0.16 mmol) in acetonitrile (0.6 mL) was kept under nitrogen at room temperature for 24 h. Diethyl ether (5 mL) was then added, and the resulting solid material was separated by filtration. Solvents were removed at reduced pressure, and the residue was purified by column chomatography on Et_3N pre-treated SiO_2 (2.5% v/v) eluting with hexane/ethyl acetate mixtures of increasing polarity to afford (*S*)-**12** (68 mg) in 83% yield as a white solid. Mp: 79 °C. $[\alpha]_D^{23}$ +34.0 (*c* 0.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.5–1.8 (br s, 4H), 2.3–2.6 (br s, 4H), 3.9 (s, 2H), 5.9 (s, 1H), 6.6–6.7 (m, 2H), 6.8–7.6 (m, 27H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 22.2 (CH_2), 45.9 (CH_2), 65.6 (CH_2), 72.4 (CH), 74.6 (C), 86.8 (C), 125.4 (CH), 126.0 (CH), 126.6 (CH), 126.9 (CH), 127.1 (CH), 127.7(CH), 128.1 (CH), 128.7 (CH), 130.9 (CH), 137.5 (C), 138.9 (C), 144.2 (C) ppm. IR (film, NaCl) υ_{max}: 3385 cm^{-1}. MS (CI, NH_3) *m/e*: 243 (Ph_3C^+, 100%), 615 (M^+, 9%), 616 ($[M+1]^+$, 4%).

4.2. General procedure for the enantioselective addition of $ZnEt_2$ to aldehydes catalyzed by resin 5

Twenty three milligram of resin **5** (8 mol%, *f*: 0.90) were suspended under a nitrogen atmosphere in 125 μL of anhydrous toluene. After swelling for 24 h under slow stirring, 0.5 mL (0.5 mmol) of diethylzinc 1 M in hexanes were added. The mixture was cooled to 0 °C, and 125 μL of a 2 M solution of four aldehydes (0.062 mmol of each one) in hexanes were added dropwise. After 6 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl, extracted with dichloromethane (3×15 mL), and the aqueous extracts dried over Na_2SO_4. The resulting solution was analyzed by GC using a chiral β-DEX capillary column and a FID detector. The analysis method was developed using a racemic sample. For the particular analytical conditions for each alcohol, see Ref. 8a.

4.3. Typical procedure for the enantioselective phenyl transfer to aldehydes catalyzed by resins 2, 3, and 5

In first place, a mixture of 293 mg (1.33 mmol) of $ZnPh_2$ and 333 mg (2.7 mmol) of pure $ZnEt_2$ was dissolved in 25 mL of anhydrous toluene. Then, the corresponding weight of resin, according to f and to the desired molar amount, was suspended in 6.4 mL of the $ZnPh_2/ZnEt_2$ solution under argon, and allowed to swell for 1 h. After cooling to 10 °C, 59 μL (0.50 mmol) of *p*-tolualdehyde were added. After 2 h, the reaction was quenched with saturated aqueous NH_4Cl, filtered under vacuum to remove the catalyst, extracted with CH_2Cl_2 (3×15 mL), dried (Na_2SO_4), and solvents removed under vacuum. The diarylcarbynol was obtained in quantitative yield. Enantiomeric excess was determined by HPLC with a Chiralcel OD chiral column. For the particular analytical conditions for each alcohol, see Ref. 15.

Acknowledgements

We thank DGI-MCYT (Grant BQU2002-02459), DURSI (Grant 2001SGR50), Fundación Ramon Areces and ICIQ Foundation for financial support. D.C. and D.F. thank MEC for fellowships, and C.J. and L.S. thank MEC for Torres Quevedo contracts.

References and notes

1. (a) Bolshan, Y.; Chen, C.-Y.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111–114. (b) El Ahmad, Y.; Maillet, P.; Laurent, E.; Talab, A.; Teste, J. F.; Cédat, M. J.; Fiez-Vandal, P. Y.; Dokhan, R.; Ollivier, R. *Eur. J. Med. Chem.* **1997**, *32*, 205–218. (c) Botta, M.; Summa, V.; Corelli, F.; Di Pietro, G.; Lombardi, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1263–1266. (d) Stanchev, S.; Rakovska, R.; Berova, N.; Snatze, G. *Tetrahedron: Asymmetry* **1995**, *6*, 183–189. (e) Toda, F.; Tanaka, K.; Koshiro, K. *Tetrahedron: Asymmetry* **1991**, *2*, 873–874. (f) Meguro, K.; Aizawa, M.; Sohda, T.; Kawamatsu, Y.; Nagaoka, A. *Chem. Pharm. Bull.* **1985**, *33*, 3787–3797.
2. (a) Harms, A. F.; Nauta, W. T. *J. Med. Pharm. Chem.* **1960**, *2*, 57–77. (b) Sperber, N.; Papa, D.; Schwenk, E.; Sherlock, M. *J. Am. Chem. Soc.* **1949**, *71*, 887–890.
3. Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659–662. And references therein.
4. For a review, see: Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284–3308.
5. Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444–445.
6. (a) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222–4223. (b) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940–7956.
7. (a) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465–3467. (b) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P.; Raabe, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 1488–1490. (c) Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295–1296. (d) Hermanns, N.; Dahmen, S.; Bolm, C.; Brase, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692–3694. (e) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851. (f) Rudolph, J.; Hermanns, N.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 3997–4000.
8. (a) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970–4982. (b) Solà, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1998**, *63*, 7078–7082. (c) Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 3969–3974. (d) Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synthesis* **2000**, 165–176. (e) Jimeno, C.; Pastó, M.; Riera, A.; Pericàs, M. A. *J. Org. Chem.* **2003**, *68*, 3130–3138.
9. (a) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773–8776. (b) Jimeno, C.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synlett* **2001**, 1155–1157. (c) Fontes, M.; Verdaguer, X.; Solà, L.; Vidal-Ferran, A.; Reddy, K. S.; Riera, A.; Pericàs, M. A. *Org. Lett.* **2002**, *4*, 2381–2383.
10. (a) Jimeno, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1999**, *40*, 777–780. (b) Jimeno, C.; Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 3157–3159.
11. Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902–7911.
12. (a) Pastó, M.; Riera, A.; Pericàs, M. A. *Eur. J. Org. Chem.* **2002**, 2337–2341. (b) Ferrer, M.; Pastó, M.; Rodríguez, B.; Riera, A.; Pericàs, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1747–1752.
13. Pericàs, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gómez, M.; Jiménez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 2164–2178.
14. García-Delgado, N.; Fontes, M.; Pericàs, M. A.; Riera, A.; Verdaguer, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2085–2090.
15. Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532–2543.
16. For recent reviews, see: (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, 2000. (d) *Polymeric Materials in Organic Synthesis and Catalysis*; Buchmeiser, M. R., Ed.; Wiley-VCH: Weinheim, 2003.
17. Bolm, C.; Hermanns, N.; Claβen, A.; Muñiz, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1795–1798.
18. For a precedent, see: Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309–6318.
19. Pericàs, M. A.; Castellnou, D.; Rodríguez, I.; Riera, A.; Solà, L. *Adv. Synth. Catal.* **2003**, *345*, 1305–1313.
20. Castellnou, D.; Solà, L.; Jimeno, C.; Fraile, J. M.; Mayoral, J. A.; Riera, A.; Pericàs, M. A. *J. Org. Chem.* **2005**, *70*, 433–438.
21. Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185–5187.
22. Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378–4380.
23. Barlos, K.; Gatos, D.; Kallitsis, J.; Papaphotiu, G.; Sotiriu, P.; Wenging, Y.; Schäfer, W. *Tetrahedron Lett.* **1989**, *30*, 3943–3946.
24. Fragmentation of the 1,2-amino alcohol moiety was observed under the basic conditions required for anchoring of **11** to Merrifield resins. For precedents, see Refs. 8d and 19.
25. (a) Giralt, E.; Rizo, J.; Pedroso, E. *Tetrahedron* **1984**, *40*, 4141–4152. (b) Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588–7590. (c) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029–7030. See also Refs. 18–20.
26. For highly active analogues of **3**, immobilized 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.
27. Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477–515.