Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 1797–1804

TETRAHEDRON

Development of small focused libraries of supported amino alcohols as an efficient strategy for the optimization of enantioselective heterogeneous catalysts for the $ZnEt_2$ addition to benzaldehyde

M. Isabel Burguete,[a] Manuel Collado,[a] Eduardo García-Verdugo,[a] María J. Vicent,[a] Santiago V. Luis,[a,*] Nikolai Graf von Keyserling[b] and Jürgen Martens[b,*]

[a]*Departamento de Química Inorgánica y Orgánica, E.S.T.C.E., Universitat Jaume I, P.O. Box 224, E-12080 Castellón, Spain*
[b]*Fachbereich Chemie, Universität Oldenburg, Carl-von-Ossietzky-Str 9-11, 26129 Oldenburg, Germany*

Received 22 October 2002; revised 9 December 2002; accepted 9 January 2003

Abstract—A general methodology has been evaluated for the preparation and optimization and fine-tuning of polymer-supported chiral catalysts for the $ZnEt_2$ addition to benzaldehyde. This approach involves the use of parallel solid-phase chemistry and the use of cheap and easily available chiral starting materials, such as amino acids. In this way, small, focused polymer-supported libraries of α,α-substituted amino alcohols have been prepared and evaluated as chiral ligands for the above-mentioned catalytic reaction. This strategy allows for an easy and fast way to analyze the different factors affecting the efficiency of the supported species (including the polymeric network itself) and to improve the tuning of the chiral catalysts. For the cases studied, amino alcohols containing aliphatic α-substituents have been shown to give good results when in conjunction with both aliphatic side chains at the β position and a *N*-methyl substituent.

1. Introduction

The importance of enantiomerically pure organic compounds in pharmaceutical, agricultural, and food industries has stimulated for years the development of new methods in organic synthesis.[1] Although different strategies such as fermentation, chiral-pool synthesis or resolution have been used in order to obtain those high added value substances, asymmetric synthesis has been shown to be a very interesting approach to achieve this goal. Within this category, asymmetric catalysis is probably the most attractive strategy under an economical as well as an ecological point of view.[2] Ideally, the economic benefits of an efficient chiral catalyst are enormous: catalytic processes are less capital intensive, have lower operating costs and produce highly pure products. Those advantages are greatly increased when polymer-supported catalysts and ligands are considered, as their use has distinct advantages in terms of the simplification of the work-up, the reduction of the environmental impact and the facilitation of the recycling and use in flow systems and in automated syntheses.[3,4]

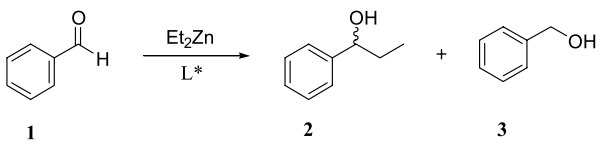
The design and optimization of a chiral catalyst being able to produce the expected enantiopure chiral compound requires a deep knowledge of all factors involved in the reaction. Unfortunately, in many cases, due to the lack of the appropriated theoretical background, catalyst design continues to be an arduous and rather unpredictable trial-and-error process. This is particularly true for the development of new and more efficient polymer-supported enantioselective catalysts for which both the structure of the ligand and the nature of the matrix need to be considered.[5] Accordingly, the development of new methodologies allowing an easier and faster way to find efficient enantioselective catalysts is highly desirable.

The most general approach for the preparation of polymer-supported enantioselective catalysts has been, up to now, the immobilization, via grafting or polymerization, of a chiral auxiliary whose structure has been optimized in the corresponding homogeneous process. Very often, however, the structural modifications required for the immobilization or the role played by the polymeric backbone are reflected in the observation of important changes in the behavior of the supported species.[5] An alternative approach is the use of combinatorial chemistry techniques with the preparation of large arrays of supported species.[4,6] The main limitation of this methodology continues being the screening of the

Keywords: optimization; $ZnEt_2$ addition; enantioselective heterogeneous catalysts.

* Corresponding authors. Fax: +34-964-728-214;
e-mail: luiss@qio.uji.es; juergen.martens@uni-oldenburg.de

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00071-1



Scheme 1.

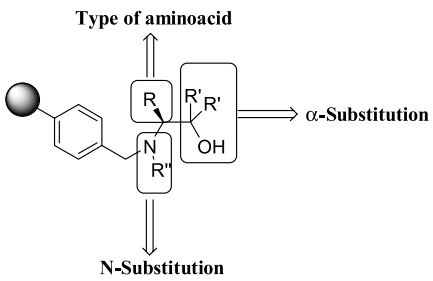


Chart 1.

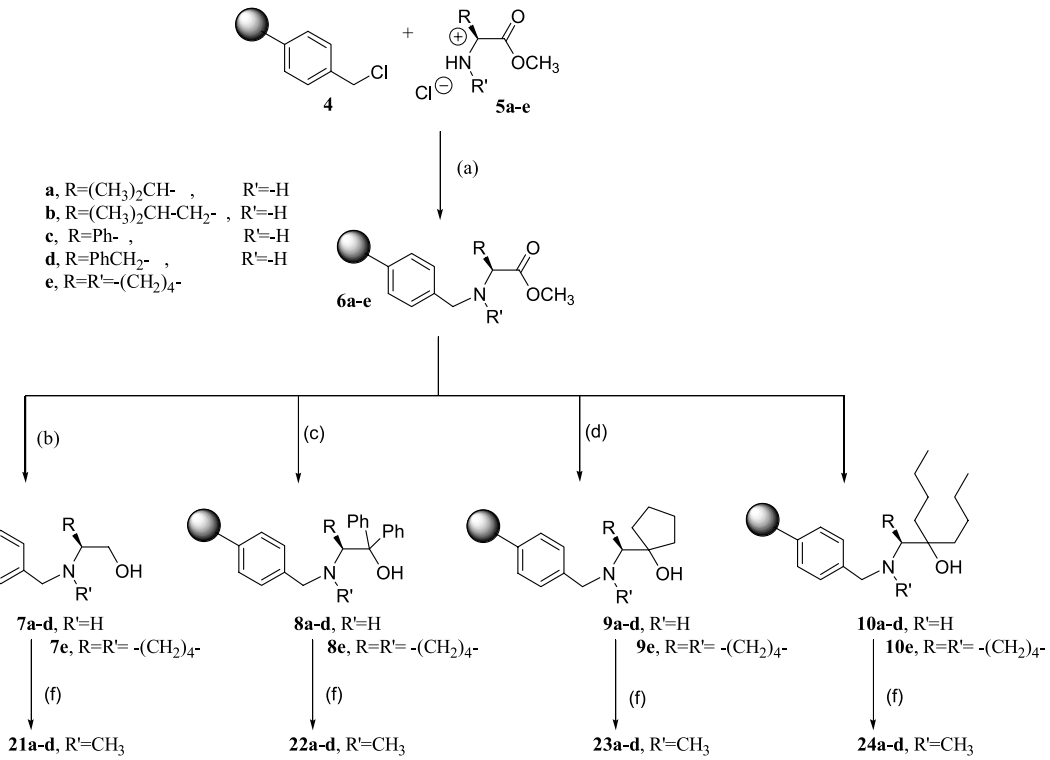
efficiency of the different components of the library in enantioselective processes and different efforts are currently being carried out to provide high throughput techniques in this field.[7]

The preparation of small focused resin-bound libraries of chiral auxiliaries or catalysts, in which the potential structural variations are initially selected according to previous studies in solution, represents a methodology intermediate between the two formerly described. Recently, we have described the use of this methodology for some non-catalytic reactions,[8] and here we describe how this parallel approach can be a powerful tool that allows a better analysis of the effects of the different factors (structural modifications, polymeric matrix) on the efficiency of a given supported catalyst, tuning its catalytic behavior in a given enantioselective reaction, in this case the $ZnEt_2$ addition to benzaldehyde (Scheme 1).[9–11]

2. Results and discussion

Chiral β-amino alcohols have been extensively used as chiral catalysts in both homogeneous and heterogeneous phase in a large number of synthetic transformations.[9–12] The catalytic efficiency of this kind of species is clearly related to the structure they present and different structural modifications need to be evaluated, namely the type of amino acid, and the α,α- and the *N*-substitution (see Chart 1). For supported species, most efforts have been directed towards the preparation and study of proline derivatives.[11] On the other hand, the influence of aliphatic α-substituents has not been considered for those systems, in spite of the fact that solution studies have revealed that, in many instances, this substitution pattern allows very efficient catalysts for the $ZnEt_2$ addition to benzaldehyde be obtained.[14] Accordingly, and taking into account the high diversity potential of the present methodology, we considered for our work amino alcohols derived from different amino acids and containing aliphatic as well as aromatic α-substituents.

The initial preparation of a small library of chiral supported β-amino alcohols was easily carried out as shown in Scheme 2. The direct reaction of the hydrochloride salts of different amino acid methyl esters (**5**) with a chloromethylated polystyrene–divinylbenzene (PS–DVB) polymer provided the corresponding supported amino acid methyl esters **6**. For this reaction, DMF at 50–60°C was



Scheme 2. General synthetic procedure for the preparation of supported amino alcohols. (a) DMF/$NaHCO_3$. (b) LAH/THF. (c) PhMgX/THF. (d) $XMg(CH_2)_4$-MgX/THF. (e) $CH_3(CH_2)_3MgX$/THF. (f) CH_3I/K_2CO_3/THF.

Table 1. Results obtained in the preparation of polymers **6**–**10**

R	R′	Polymeric ester	DF[a]	Loading (mmol/g)	Polymeric amino alcohol (loading, mmol/g)			
$(CH_3)_2CH$	H	**6a**	0.11	0.92	**7a** (0.94)	**8a** (0.82)	**9a** (0.90)	**10a** (0.85)
$(CH_3)_2CHCH_2$	H	**6b**	0.11	0.90	**7b** (0.93)	**8b** (0.81)	**9b** (0.88)	**10b** (0.84)
Ph	H	**6c**	0.11	0.89	**7c** (0.91)	**8c** (0.80)	**9c** (0.87)	**10c** (0.83)
$PhCH_2$	H	**6d**	0.11	0.88	**7d** (0.90)	**8d** (0.79)	**9d** (0.86)	**10d** (0.82)
$-(CH_2)_4-$		**6e**	0.11	0.92	**7e** (0.94)	**8e** (0.82)	**9e** (0.90)	**10e** (0.85)

[a] DF=degree of functionalization as the percentage of aromatic rings in PS–DVB containing the expected functional group.

used as the solvent and anhyd. $NaHCO_3$ as the base.[8] Compounds **5** were easily prepared by treatment of the acids with $SOCl_2$ in methanol. Further treatment of **6** with LAH yielded the supported α,α-unsubstituted chiral β-amino alcohols **7**. On the other hand, the use of different Grignard reagents allowed us to obtain the corresponding supported α,α-substituted amino alcohols **8**–**10**. According to previous results in solution, three different α-substituents were selected. The phenyl group was chosen as an aromatic group representative (compounds **8**),[10c,13] whilst the *n*-butyl group was selected as an aliphatic group representative (compounds **10**).[10i] Finally, α-substitution to introduce an additional cyclic structure was considered. Taking into account previous results with this kind of compounds, cyclopentylidene derivatives **9** were prepared by reaction of **6** with the Grignard reagent prepared from 1,4-dibromobutane.[14]

In all cases, the reactions could be easily followed using FT-IR and FT-Raman spectroscopy.[5a,15] In general, FT-IR spectra showed the appearance of a new band at ca. 1730 cm^{-1} corresponding to the ester group as well as the disappearance of the C–Cl band at 1265 cm^{-1}, which is even clearer in the FT-Raman spectra. Those facts altogether with the elemental analysis confirm that the anchoring of the ester moieties took place in quantitative yield.

^{13}C Gel-phase NMR spectroscopy could also be applied to monitor these synthetic transformations.[5a,16] In addition to the peaks corresponding to the polymeric backbone, the appearance of new peaks for the chiral moiety as well as the disappearance of the peak corresponding to the carbon bound to the chloride group (ca. 46 ppm) were observed. Thus, for instance, for **6e** the NMR spectrum showed the presence of peaks at ca. 20, 27, 38, 49, 50, 56 and 62 ppm corresponding to the proline derivative, in good agreement with the calculated values. The disappearance of the peak at ca. 46 ppm could also be observed.

Further modification of the ester group into the β-amino alcohols **7**–**10** could be easily monitored by the disappearance of the ester group band in the FT-IR spectra at ca. 1730 cm^{-1} as well as by the disappearance of the methyl ester peak at ca. 50 ppm in the ^{13}C NMR spectra. Elemental analysis gave the expected results, with loadings ranging from 0.94 to 0.80 mmol g^{-1} (see Table 1).

The different supported β-amino alcohols (**7**–**10**) were tested as chiral ligands for the diethylzinc addition to benzaldehyde using a catalytic amount (10 mol%) of the polymer supported species to give the corresponding (*R*)-alcohol. The results obtained with the compounds of the sub-library bearing a cyclopentylidene group in the α-position are shown in Table 2. Similar trends were obtained for the other amino alcohols of the library. The *R* enantiomer of alcohol **2** was the major isomer obtained in all cases starting from the natural amino acid. As can be seen in the table, only the (*S*)-proline derivative **9e** showed good catalytic behavior in terms of both selectivity and enantioselectivity (see entry 6, Table 2). Substitution of the cyclopentylidene ring by a cyclohexylidene ring (polymer **15**) did not provide any increase in selectivity (83%) or enantioselectivity (45% ee), whilst the use of a derivative containing a cycloheptylidene ring (**16**) afforded lower selectivity (70%) and enantioselectivity (35% ee).[14a]

Although the activity of **9e** was not very high, the results obtained were interesting in terms of enantioselectivity. Previous results in the literature have shown that a significant drop in enantioselectivity is very often observed when a monomeric chiral catalyst is grafted onto a polymeric backbone. This general behavior is followed by the different (*S*)-proline derivatives **11**–**17** (Chart 2).[9,11b,c] Nevertheless, in the case of **9e** the heterogeneous catalyst gave a better enantioselectivity (45% ee) than the

Table 2. Results obtained for the addition of $ZnEt_2$ to benzaldehyde at 25°C using supported catalysts **9**

Entry	Ligand[a]	Yield (%)[b]	Selectivity (%)[c]	ee (%)[d]
1	**9a**	56	53	11 (*R*)
2	9a[a]	65	86	6 (*R*)
3	**9b**	58	65	7 (*R*)
4	**9c**	54	48	5 (*R*)
5	**9d**	60	78	10 (*R*)
6	**9e**	62	83	45 (*R*)

[a] 10% (Molar) of **9** was used in all cases, except for entry 2 (20%).
[b] Determined by NMR.
[c] Determined by NMR. Selectivity=(([*R*−2]+[*S*−2])/([*R*−2]+[*S*−2]+[3]))×100.
[d] Determined by HPLC (Chiracel OD), major isomer: *R*.

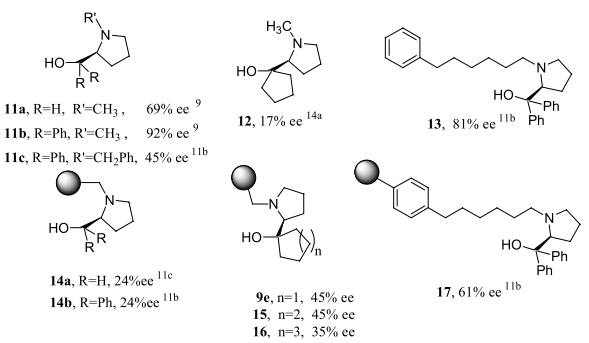
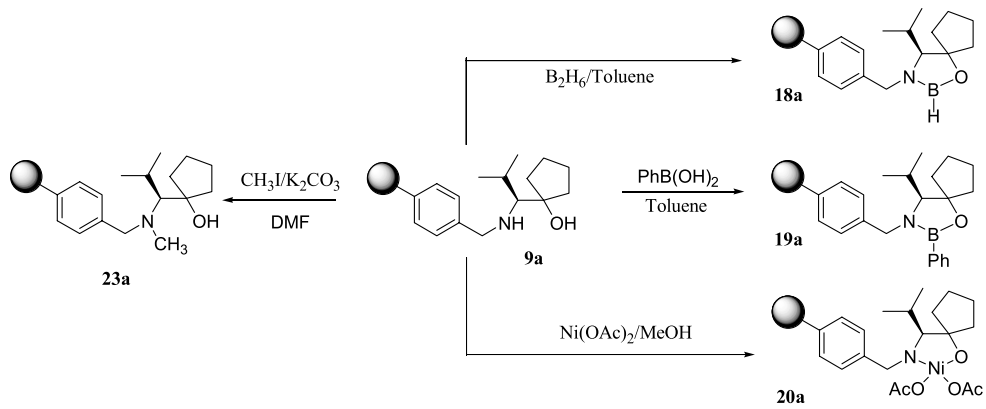


Chart 2.



Scheme 3. Synthesis of supported β-amino alcohols **18**–**21a**. (a) CH_3I/K_2CO_3, DMF. (b) BH_3, toluene. (c) $PhB(OH)_2$, toluene. (d) $Ni(OAc)_2$.

homogeneous analogue **12** (17% ee). This fact should not be related to the different *N*-substitution pattern of the supported proline derivative **9e**. As a matter of fact, it is well established that amino alcohols containing *N*-methylated moieties provide higher enantioselectivities than *N*-benzylated amino alcohols (compare, for instance, **11b** and **11c** in Chart 2). Taking this into account, this is one of the few examples reported to date in which the immobilization of the chiral ligand leads to a significantly higher asymmetric induction.

The poor catalytic behavior of the other amino alcohols must be clearly related with the presence of the NH group in those supported species. This fact is in good agreement with results previously reported, for instance, by Fréchet and Itsuno.[11c] The use of a larger amount of ligand (20% mol, entry 2, Table 2) did not afford an improvement in the enantioselectivity, although a higher selectivity was achieved.

Thus, it seems clear that the presence of the NH fragment should be avoided to improve the catalytic efficiency of those supported species. Three different strategies were evaluated in order to achieve this goal (Scheme 3). The supported β-amino alcohol **9a** derived from (*S*)-valine and bearing a cyclopentylidene group at the α-position, giving moderate results in activity, selectivity and enantioselectivity, was selected for this purpose.

The first approach was the preparation of the oxazaborolidine derivatives formed by reaction with borane (**18a**) or phenylboronic acid (**19a**). Similar derivatives have been used in solution for the diethyl zinc addition to different aldehydes and their catalytic efficiency seems to show a great dependence on the substitution pattern of the boron atom.[17] The results obtained with the supported oxazaborolidine derivatives showed a similar dependence and in both cases the selectivity was increased (see Table 3). A greater improvement of the enantioselectivity was obtained with compound **19a** bearing a phenyl group on the boron atom (50% ee, entry 3, Table 3) but this result is still far away from those obtained with similar catalysts in homogenous phase.[9]

Table 3. Results obtained for the addition of $ZnEt_2$ to benzaldehyde at 25°C using supported catalysts derived from amino alcohol **9a**

Entry	Ligand[a]	Yield (%)[b]	Selectivity (%)[c]	ee (%)[d]
1	**9a**	56	53	11 (*R*)
2	**18a**	90	93	6 (*R*)
3	**19a**	95	85	50 (*R*)
4	**20a**	90	71	2 (*R*)
5	**23a**	99	86	80 (*R*)

[a] 10% (molar) of **9** was used in all cases.
[b] Determined by NMR.
[c] Determined by NMR. Selectivity=(([*R*−2]+[*S*−2])/([*R*−2]+[*S*−2]+[3]))×100.
[d] Determined by HPLC (Chiracel OD), major isomer: *R*.

Alternatively, the complexation with nickel (II) (**20a**) and the formation of the *N*-methyl derivative (**23a**) were also evaluated.[18] The results obtained with the supported metal-complex **20a** were disappointing both in terms of selectivity and enantioselectivity (entry 4, Table 3). The best results were obtained with the *N*-methylated derivative **23a** that allowed us to obtain a large improvement in the catalytic behavior, in particular enantioselectivity (80% ee, entry 5, Table 3). Two different alternatives were considered for the preparation of polymer **23a**. The first one was the methylation of **9a** with CH_3I in DMF containing K_2CO_3 as shown in Scheme 3. In a second approach, the corresponding polymeric amino ester **6a** was *N*-methylated using the same methodology and then reacted with the corresponding Grignard reagent to obtain **23a**. In both cases the results were similar, with quantitative conversions, and no differences were observed when used for the $ZnEt_2$ addition.

In view of the large improvement obtained with the *N*-methyl supported derivative **23a**, the synthesis of the corresponding *N*-methylated derivatives (**21**–**24**) of the β-amino alcohols **7**–**10** was carried out (Scheme 2). The results obtained with those heterogeneous catalysts for the diethyl addition reaction are summarized in Table 4 and Figure 1.

As can be seen, an increase in selectivity is accompanied, in general, by an increase in the enantioselectivity observed. In all cases, α,α-unsubstituted polymeric amino alcohols (**21**) gave the lowest selectivities and enantioselectivities. On the contrary, the highest selectivities were always found when the α-substituent was butyl or cyclopentylidene. Phenyl substituents at the α-position gave rise to the appearance of moderate or poor asymmetric inductions and selectivities. This is rather surprising, as the presence of such

Table 4. Results obtained for the addition of $ZnEt_2$ to benzaldehyde at 25°C using supported catalysts **21**–**24**

Entry	Polymer[a]	Yield (%)[b]	Selectivity (%)[c]	ee (%)[d]
1	**21a**	89	55	10
2	**21b**	94	65	15
3	**21c**	93	56	7
4	**21d**	82	48	2
5	**22a**	89	63	15
6	**22b**	90	70	24
7	**22c**	83	58	11
8	**22d**	97	70	24
9	**23a**	99	86	80
10	**23b**	81	53	22
11	**23c**	90	68	23
12	**23d**	92	70	20
13	**24a**	92	73	34
14	**24b**	98	91	74
15	**24c**	94	86	17
16	**24d**	95	85	45

[a] 10% (molar) of catalyst was used in all cases.
[b] Determined by NMR.
[c] Determined by NMR. Selectivity=(([*R*−2]+[*S*−2])/([*R*−2]+[*S*−2]+[3]))×100.
[d] Determined by HPLC (Chiracel OD), major isomer: *R*.

α-substituents has very often been considered as a central structural feature for the development of related homogeneous chiral auxiliaries in this reaction. However, such a detrimental effect of α-phenyl substituents has been recently observed for the LAH reduction of acetophenone mediated by supported *N*-tosyl amino alcohols.[8c]

The nature of the amino acid (R substituent in **21**–**24**) plays a very important role in the outcome of the reaction. Best results were obtained, in general, for leucine and valine derived amino alcohols. This clearly confirms that the observation of better enantioselectivities for proline derivatives in the first series of experiments (Table 2) is related to the absence, in those derivatives, of the N–H fragment. For resin-bound amino alcohols prepared from valine (**21a**–**24a**), the best results were observed for compound **23a** containing a cyclopentylidene substituent at the α-position (see entry 9, Table 4). In the case of leucine derivatives, compound **24b**, substituted at the α-position with two *n*-butyl groups, was clearly the most efficient. This compound afforded a slightly higher selectivity (91 vs 86% for **23a**) and a somewhat lower enantioselectivity (74 vs 80% ee for **23a**) (compare entries 9 and 14 in Table 4).

3. Conclusions

The present parallel approach for the preparation of small, focused libraries of polymer-supported amino alcohols allows a simple and rapid search for efficient heterogeneous chiral auxiliaries of interest for catalytic and non-catalytic enantioselective processes. Thus, in this case it has been possible to easily analyze, in a few steps, the structural parameters that control the efficiency of a family of structurally simple amino alcohols for the $ZnEt_2$ addition to benzaldehyde. The value of this approach is greatly enhanced when, as is the case here, a sound knowledge of the main parameters of the reaction under study is known from previous solution studies. The results obtained in this work for the more efficient structures, compare well with other previously reported supported species derived from simple aminoacids in terms of the selectivities (86–91%) and enantioselectivities (74–80%) attained. In general, in this field, higher selectivities or enantioselectivities have been described only for the use of structurally much more complex amino alcohols.[11] On the other hand, the final structures here obtained could also be used as starting points for a second optimization procedure, in an iterative way. Within the general trends detected, it is worth mentioning that a combination of aliphatic substituents both at the α- and at the β-position gives rise, in general to the best results in terms of the activity, chemoselectivity and enantioselectivity observed for the reaction under study.

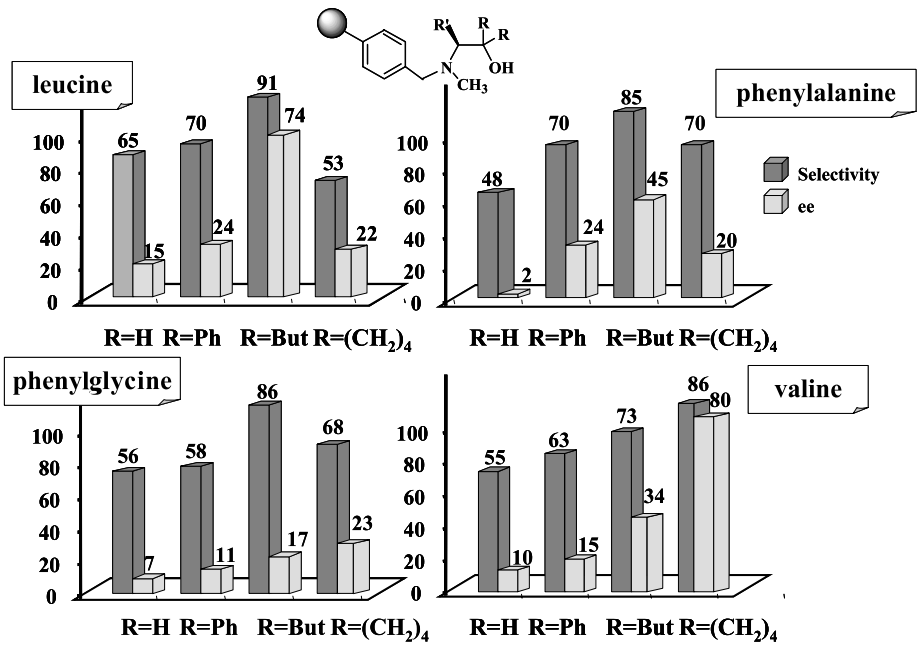


Figure 1. Results for the $ZnEt_2$ addition to benzaldehyde catalyzed by **21**–**24**.

One of the main advantages of this methodology is that, for the search process, not only the factors related with the structural modification on the chiral auxiliary are considered, but also, and simultaneously, the factors related to the polymeric matrix. It is again clear, from the present results that the polymeric network can play a very important role, and the trends observed in solution for the variation of the different structural parameters in the chiral auxiliary are not strictly followed when the resin-bound compounds are studied. Using this methodology we have been able to detect heterogeneous species for which the observed enantioselectivity was much higher than that reported in solution.

4. Experimental

4.1. Data for compounds

4.1.1. General procedure for the preparation of polymer-supported amino esters 6: synthesis of 6a. A chloromethylated resin (1 mmol Cl/g, 1% DVB, 2 g, 2 mmol) (DF=0.11, $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_9H_9Cl)_{0.11}$) was added, under an argon atmosphere, to a solution containing a mixture of the (*S*)-valine methyl ester hydrochloride (1.005 g, 6 mmol) and anhyd. $NaHCO_3$ (1.008 g, 12 mmol) in dry DMF (50 mL). After stirring at 65°C for 24 h, the resin was filtered and washed with DMF (2×), MeOH–H_2O (2:1)(3×), MeOH–H_2O (1:1)(3×), MeOH–H_2O (1:2)(3×), MeOH (3×) and vacuum dried to give polymer **6a** showing a quantitative transformation of the chloromethyl groups. DF=0.11, 0.92 mmol/g. IR (KBr): peak absent at 1260 cm^{-1}, peak present at 1733 cm^{-1}. ^{13}C NMR (300 MHz, gel phase) ($CDCl_3$, δ): 17.9, 30.3, 50.4, 65.3, 78.2, 127.5, 143.0. Anal. calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_{15}H_{21}O_2N)_{0.11}$: N, 1.3. Found: N, 0.9.

4.1.2. General procedure for the preparation of polymer-supported amino alcohols 7: synthesis of 7a. Polymer **6a** (0.5 g, ca. 0.455 mmol) was treated with an excess of $LiAlH_4$ (52 mg, 1.365 mmol) in dry THF (30 mL) at room temperature for 48 h, under an argon atmosphere. The polymer was then filtered, washed with THF (2×), THF–H_2O (1:1) (3×), diluted HCl (2×), H_2O (2×), MeOH (3×), and CH_2Cl_2 (3×) and vacuum dried to give resin **7a** showing a quantitative transformation of the ester groups. DF=0.11, 0.94 mmol/g. IR (KBr): peak absent at 1733 cm^{-1}. ^{13}C NMR (300 MHz, gel phase) ($CDCl_3$, δ): 17.9, 30.3, 39.5, 65.3, 78.2, 127.5, 143.0. Anal. calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_{14}H_{21}ON)_{0.11}$: N, 1.3. Found: N, 1.0.

4.1.3. General procedure for the preparation of polymer-supported amino alcohols 8: synthesis of 8a. Polymer **6a** (0.5 g, 0.455 mmol) was suspended in dry THF (30 mL) and treated with an excess of a 2 M solution of PhMgCl (1.82 mL, 3.64 mmol) in THF. The mixture was refluxed for 24 h, under an argon atmosphere, and the polymer was filtered, washed with THF (2×), diluted HCl, H_2O (3×), MeOH (3×) and CH_2Cl_2 (3×) and vacuum dried to give resin **8a** showing a quantitative transformation of the ester groups. DF=0.11, 0.82 mmol/g. IR (KBr): peak absent at 1733 cm^{-1}. ^{13}C NMR (300 MHz, gel phase) ($CDCl_3$, δ): 18.1, 23.6, 54.0, 86.3, 125.7, 128.0, 130.0, 143.0. Anal. calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_{26}H_{29}ON)_{0.11}$: N, 1.1. Found: N, 0.7.

4.1.4. General procedure for the preparation of polymer-supported amino alcohols 9: synthesis of 9a. Polymer **6a** (0.5 g, 0.455 mmol) was suspended in a solution of the Grignard reagent prepared from 1,4-dibromobutane (393 mg, 1.82 mmol) and Mg (88.5 mg, 3.64 mmol) in dry THF (30 mL). The mixture was refluxed for 24 h, under an argon atmosphere, and the polymer was filtered, washed with THF (2×), diluted HCl, H_2O (3×), MeOH (3×) and CH_2Cl_2 (3×) and vacuum dried to give resin **9a** showing a quantitative transformation of the ester groups. DF=0.11, 0.90 mmol/g. IR (KBr): peak absent at 1733 cm^{-1}. ^{13}C NMR (300 MHz, gel phase) ($CDCl_3$, δ): 18.0, 23.8, 54.0, 72.3, 82.3. Anal. calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_{18}H_{27}ON)$ 0.11: N, 1.1. Found: N, 1.0.

4.1.5. General procedure for the preparation of polymer-supported amino alcohols 10: synthesis of 10a. Polymer **6a** (0.5 g, 0.455 mmol) was suspended in a solution of the Grignard reagent prepared from 1-bromobutane (0.5 g, 1.83 mmol) and Mg (89 mg, 3.66 mmol) in dry THF (30 mL). The mixture was refluxed for 24 h, under an argon atmosphere, and the polymer was filtered, washed with THF (2×), diluted HCl, H_2O (3×), MeOH (3×) and CH_2Cl_2 (3×) and vacuum dried to give resin **10a** showing a quantitative transformation of the ester groups. DF=0.11, 0.85 mmol/g. IR (KBr): peak absent at 1733 cm^{-1}. ^{13}C NMR (300 MHz, gel phase) ($CDCl_3$, δ): 14.3, 18.0, 24.0, 54.2, 72.1, 77.0. Anal. calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_{18}H_{27}ON)_{0.11}$: N, 1.1. Found: N, 1.1.

4.1.6. Synthesis of polymer-supported oxazaborolidine 19a. Polymer **9a** (3 g, 2.7 mmol) was suspended in a solution of phenylboronic acid (0.83 g, 6.84 mmol) in dry toluene (45 mL). The mixture was heated at reflux in a system equipped with a Dean–Stark collector accessory until 20 mL of toluene were collected. The resulting polymer was filtered, washed with toluene (2×), THF (3×), CH_2Cl_2 (3×) and MeOH (3×) and vacuum dried to give resin **19a**. DF=0.11, 0.83 mmol/g. Anal. calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_{24}H_{30}BON)_{0.11}$: N, 1.1. Found: N, 0.9.

4.1.7. Synthesis of polymer-supported nickel complex 20a. Polymer **9a** (1 g, 0.9 mmol) was suspended in dry methanol (10 mL) and a solution of $Ni(OAc)_2$ (0.4 g, 2.28 mmol) in methanol (25 mL) was then added. The mixture was refluxed for 24 h and the resulting polymer was filtered, washed with toluene (2×), THF (3×), CH_2Cl_2 (3×) and MeOH (3×) and vacuum dried to give resin **20a**. DF=0.11, 0.77 mmol/g. Anal. calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_{22}H_{31}NiO_5N)_{0.11}$: N, 1.2. Found: N, 1.0.

4.1.8. General procedure for the preparation of *N*-methylated polymer-supported amino alcohols 21–24: synthesis of 23a. Polymer **9a** (1.1 g, 1 mmol) was suspended in dry DMF (10 mL) containing anhyd. K_2CO_3 (294 mg, 3 mmol) and then methyl iodide (425 mg, 3 mmol) was added. The mixture was refluxed for 24 h, under an argon atmosphere, and the polymer was filtered, washed with DMF (2×), methanol (3×) and acetone (3×)

and vacuum dried to give resin **23a**. DF=0.11, 0.88 mmol/g. Anal. calcd for $(C_{10}H_{10})_{0.01}(C_8H_8)_{0.88}(C_{19}H_{29}ON)_{0.11}$: N, 1.2. Found: N, 1.1.

4.1.9. General procedure for the addition of $ZnEt_2$ to benzaldehyde. The corresponding polymer-supported amino alcohol (0.5 mmol) was suspended in dry toluene (10 mL), under an argon atmosphere, at −40°C and a 1.1 M solution of Et_2Zn in toluene (10 mL, 11 mmol) was added dropwise (addition time: 10 min). The mixture was stirred at this temperature for 30 min and then, at room temperature, a solution of freshly distilled benzaldehyde (0.54 g, 5 mmol) in dry toluene (20 mL) was added over 30 min. Stirring was continued for 24 h and then the reaction was quenched at 0°C by addition of a 2 M solution of HCl (60 mL). The mixture was extracted with diethyl ether (3×40 mL), the organic phase was washed with a saturated solution of $NaHCO_3$, dried with anhyd. $MgSO_4$ and vacuum evaporated to give an oily residue. The ^1H NMR ($CDCl_3$) of this residue allows to obtain the yield and selectivity of the reaction using the following signals (δ): benzaldehyde (1) (9.9, s, 1H); 1-phenyl-1-propanol (2) (4.45, t, 1H); benzyl alcohol (3) (4.65, s, 2H). The enantiomeric excess was determined by the use of HPLC (Chiralcel OD) using a mixture *n*-hexane–*i*-propanol (97:3) as the eluent (1 mL/min): (*R*)-1-phenyl-1-propanol, room temperature 10.48 min; (*S*)-1-phenyl-1-propanol, room temperature 12.64 min.

Acknowledgements

Financial support for this work has been provided by the Spanish CICYT (project MAT99-1176) and by Fonds der Chemischen Industrie, Frankfurt am Main/Germanyand. Amino acids have been donated by Degussa AG.

References

1. (a) Brown, C. *Chirality in Drug Design and Synthesis*; Academic: New York, 1990. (b) Seri-Levy, A.; Richards, W. G. *Tetrahedron: Asymmetry* **1993**, *4*, 1917. (c) Nugent, W. A.; RajanBadu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479. (d) Amato, I. *Science* **1992**, *256*, 964.
2. (a) Brown, J. M. *Tetrahedron: Asymmetry* **1991**, *2*, 481. (b) Bosnich, B. *Chem. Br.* **1984**, 809. (c) In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 2nd ed., 1993. (d) ApSimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *19*, 5157. (e) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
3. (a) In *Synthesis and Separations Using Functional Polymers*; Sherrington, D. C., Hogde, P., Eds.; Wiley: Chichester, 1988. (b) Shuttlenworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217. (c) Hodge, P. *Chem. Soc. Rev.* **1997**, *26*, 417. (d) Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, 21. (e) Sherrington, D. C. *Chem. Commun.* **1998**, 2275. (f) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815. (g) de Miguel, Y. R.; Brulé, E.; Margue, R. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3085. (h) Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637.
4. (a) Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compounds Libraries*; Elsevier: Oxford, 1998. (b) Seneci, P. *Solid-Synthesis and Combinatorial Technologies*; Wiley: New York, 2000. (c) Burgess, K. *Solid Phase Organic Synthesis*; Wiley: New York, 2000.
5. (a) Altava, B.; Burguete, M. I.; Escuder, B.; Luis, S. V.; Salvador, R. V.; Fraile, J. M.; Mayoral, J. A.; Royo, A. J. *J. Org. Chem.* **1997**, *62*, 3126. (b) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147. (c) Altava, B.; Burguete, M. I.; Collado, M.; García-Verdugo, E.; Luis, S. V.; Salvador, R. V.; Vicent, M. J. *Tetrahedron* **1999**, *55*, 12897. (d) Adrián, F.; Burguete, M. I.; Luis, S. V.; Fraile, J. M.; Mayoral, J. A.; Royo, A. J.; García, J. I.; García, J.; García-España, E.; Sánchez, M. C. *Eur. J. Inorg. Chem.* **1999**, 2347. (e) Altava, B.; Burguete, M. I.; García, J. I.; Luis, S. V.; Fraile, J. M.; Mayoral, J. A.; Vicent, M. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 1503. (f) Burguete, M. I.; García, J. I.; García-Verdugo, E.; Luis, S. V.; Fraile, J. M.; Mayoral, J. A. *Org. Lett.* **2000**, *2*, 3905. (g) Hu, J.; Zhao, G.; Ding, Z. *Angew. Chem. Int. Ed.* **2001**, *40*, 1109. (h) Burguete, M. I.; Fraile, J. M.; García, J. I.; García-Verdugo, E.; Herrerías, C. I.; Luis, S. V.; Mayoral, J. A. *J. Org. Chem.* **2001**, *66*, 8893.
6. For some examples and leading references see: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Gilbertson, S. R.; Collibee, S. E.; Agarkov, A. *J. Am. Chem. Soc.* **2000**, *122*, 6522. (c) Reetz, M. T. *Angew. Chem. Int. Ed.* **2001**, *40*, 284. (d) Dahmen, S.; Bäse, S. *Synthesis* **2001**, 1431.
7. (a) Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180. (b) Reetz, M. T.; Becker, M. H.; Kuhling, K. M.; Holzwarth, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2647. (c) Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 497. (d) Guo, J.; Wu, J.; Siuzdak, G.; Finn, M. G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1755. (e) Reetz, M. T.; Becker, M. H.; Klein, H.-W.; Stockigt, D. *Angew. Chem. Int. Ed.* **1999**, *38*, 1758. (f) Reetz, M. T.; Kuhling, K. M.; Deege, A.; Hinrichs, H.; Belder, D. *Angew. Chem. Int. Ed.* **2000**, *39*, 3891. (g) Korbel, G. A.; Lalic, G.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 361. (h) Abato, P.; Seto, C. T. *J. Am. Chem. Soc.* **2001**, *123*, 9206. (i) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496.
8. (a) Altava, B.; Burguete, M. I.; Collado, M.; Luis, S. V.; Pozo, O.; Salvador, R. V. *An. Quím., Int. Ed.* **1997**, *93*, 260. (b) Altava, B.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V.; Pozo, O.; Salvador, R. V. *Eur. J. Org. Chem.* **1999**, 2263. (c) Altava, B.; Burguete, M. I.; Collado, M.; García-Verdugo, E.; Luis, S. V.; Salvador, R. V.; Vicent, M. J. *Tetrahedron Lett.* **2001**, *42*, 1673.
9. Reviews: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (c) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757.
10. For examples of homogeneous catalysts in $ZnEt_2$ additions see: (a) Tanaka, K.; Ushio, H.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1700. (b) Hayashi, M.; Kaneko, T.; Oguni, N. *J. Chem. Soc., Perkin Trans. 1* **1991**, 25. (c) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111. (d) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 25. (e) Peper, V.; Martens, J. *Chem. Ber.* **1996**, *129*, 691. (f) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902. (g) Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108. (h) Vázquez, J.; Pericàs, M. A.; Maseras, F.; Lledós, A. *J. Org.*

Chem. **2000**, *65*, 7303. (i) Kawanami, Y.; Miki, M.; Sakamoto, T.; Nishitami, K. *Tetrahedron* **2000**, *56*, 175. (j) Long, J.; Ding, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 544. (k) Dangel, B. D.; Plot, R. *Org. Lett.* **2000**, *2*, 3003.

11. For some examples of heterogeneous catalysts in $ZnEt_2$ additions see: (a) Soai, K.; Watanabe, M. *Tetrahedron: Asymmetry* **1991**, *2*, 97. (b) Soai, K.; Watanabe, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 837. (c) Itsuno, S.; Fréchet, J. M. J. *J. Org. Chem.* **1987**, *52*, 41. (d) Itsuno, S.; Sakurai, Y.; Ito, K.; Marayuma, T.; Nakahama, S.; Fréchet, J. M. J. *J. Org. Chem.* **1990**, *55*, 304. (e) Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712. (f) Halm, C.; Kurth, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 510. (g) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericás, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309. (h) Sung, D. W. L.; Hodge, P.; Stratford, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1463. (i) Sung, D. W. L.; Hodge, P.; Stratford, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2335. (j) Holte, P.; Wijgergangs, J.-P.; Thijs, L.; Zwanenburg, B. *Org. Lett.* **1999**, *1*, 1095. (k) Yang, X. W.; Sheng, J.-H.; Da, C.-S.; Wang, H.-S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295. (l) Yang, X. W.; Sheng, J.-H.; Da, C.-S.; Wang, H.-S.; Su, W.; Wang, R.; Chan, A. S. C. *Tetrahedron* **2000**, *56*, 3511. (m) Brouwer, A. J.; Linden, H. J.; Liskamp, R. M.; J, *J. Org. Chem.* **2000**, *65*, 1750. (n) Degni, S.; Wilén, C.-E.; Leino, R. *Org. Lett.* **2001**, *3*, 2551. (o) Huttenloch, O.; Laxman, E.; Waldmann, H. *Chem. Commun.* **2002**, 673. (p) Kell, R. J.; Hodge, P.; Nisar, M.; Watson, D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1803.

12. (a) Kiyooka, S.; Kaneko, Y.; Kume, K. *Tetrahedron Lett.* **1992**, *33*, 4927. (b) Nevalainen, V. *Tetrahedron: Asymmetry* **1997**, *8*, 2241. (c) Trentmann, W.; Mehler, T.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2033. (d) Sibi, M. P.; Cook, G. R.; Liu, P. *Tetrahedron Lett.* **1999**, *40*, 2477. (e) Yang, G. S.; Hu, J. B.; Zhao, G.; Ding, Y.; Tang, M. H. *Tetrahedron: Asymmetry* **1999**, *10*, 4307. (f) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1629. (g) Kamahori, K.; Tada, S.; Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1995**, *6*, 2547. (h) Itsuno, S.; Matsumoto, T.; Sato, D.; Inoue, T. *J. Org. Chem.* **2000**, *65*, 5879.

13. Braun, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 519.

14. (a) Wilken, J.; Kossenjans, M.; Gröger, H.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2007. (b) Kossenjans, M.; Martens, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1409. (c) Wilken, J.; Erny, S.; Wassmann, S.; Martens, J. *Tetrahedron: Asymmetry* **2000**, *11*, 2143.

15. (a) Altava, B.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V.; Vicent, M. J. *Tetrahedron* **2001**, *57*, 8675. (b) Altava, B.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V.; Vicent, M. J. *Tetrahedron Lett.* **2001**, *42*, 8459.

16. (a) Ford, W. T.; Yacoub, S. A. *J. Org. Chem.* **1981**, *46*, 819. (b) Giralt, E.; Rizo, J.; Pedroso, E. *Tetrahedron* **1984**, *40*, 4141.

17. (a) Joshi, N. N.; Srebnik, M.; Brown, H. C. *Tetrahedron Lett.* **1989**, *30*, 5551. (b) El Monakj, N.; Caze, C. *Eur. Polym. J.* **1995**, *31*, 193.

18. (a) Soai, K.; Yakoyama, S.; Ebihara, S.; Hayasaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690. (b) Kijima, M.; Miyamori, K.; Sato, K. *J. Org. Chem.* **1988**, *53*, 4148. (c) Soai, K.; Hayasaka, T.; Ugajin, S. *J. Chem. Soc., Chem. Commun.* **1989**, 516. (d) Fujii, T.; Saito, T.; Mori, S.; Chikazawa, J. *Tetrahedron Lett.* **1991**, *32*, 97.