Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 1803–1807

BIOORGANIC &
MEDICINAL
CHEMISTRY
LETTERS

Towards More Chemically Robust Polymer-Supported Chiral Catalysts for the Reactions of Aldehydes with Dialkylzincs

Roger J. Kell, Philip Hodge,* Mohammad Nisar and David Watson

Chemistry Department, University of Manchester, Oxford Road, Manchester, M13 9PL, UK

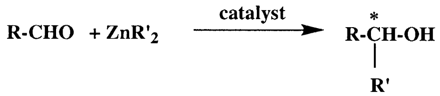
Received 28 November 2001; accepted 19 February 2002

Abstract—*N*-Methyl-α,α-diphenyl-L-prolinol derivatives with *para*-bromo substituents in one or both of the phenyl rings are easily bound to crosslinked polystyrene beads containing phenylboronic acid residues using Suzuki reactions. When the products were used as catalysts for the reactions of aldehydes with diethylzinc in toluene at 20 °C, the alcohols were produced in chemical yields >90% and with ees of upto 94%. The better of the two supported catalysts gave ees only 0–9% lower than those obtained with the corresponding soluble catalyst. One of the supported catalysts was recycled successfully nine times. © 2002 Elsevier Science Ltd. All rights reserved.

Asymmetric syntheses achieved using PS chiral catalysts are a particularly attractive type of synthesis. Thus, (i) at the end of the reaction period the soluble chiral products are easily freed of the PS catalyst by filtration, (ii) at the same time the PS catalyst is recovered for possible reuse, and (iii) because of advantages (i) and (ii) it becomes acceptable to use relatively large amounts of catalyst to obtain high-percentage enantiomeric excesses (% ees) and/or increased reaction rates. Many attempts have been made to prepare PS versions of the better chiral catalysts,[1–3] but it is not a trivial exercise and in many cases the % ees achieved have been significantly lower in the supported systems. Usually this is because not enough attention has been given to the four important factors that need to be considered if a conventional organic reaction is to be converted successfully into a PS one.[4] These are: (i) the reactive site accessibility, (ii) possible site–site interactions, (iii) possible microenvironmental effects, and (iv) the effect of the method of attachment on the 'active site' of the catalyst.[5,6]

An important asymmetric synthesis is the reaction of aldehydes in toluene with dialkylzincs [Reaction 1]. The reaction is catalysed by β-*tertiary*-aminoalcohols.[7,8] Various PS chiral β-amino alcohols have been used as catalysts[6,9–18] and the earlier work has been reviewed.[8] With the reactions of aldehydes with dialkylzincs preparing successful PS catalysts is a particular challenge because the reactions take place slowly without any added catalyst to give racemic products. For example, benzaldehyde in toluene at 20 °C reacts with diethylzinc to give racemic 1-phenylethanol in ca. 15% yield in 18 h.[6] Accordingly, the PS catalysts operate in a competitive situation and unless a sufficient proportion of the PS catalytic sites are readily accessible, the reactions that give racemates will make significant contributions to the overall reactions and consequently relatively low % ees will be obtained.

Reaction 1



$$\text{R-CHO} + \text{ZnR}'_2 \xrightarrow{\text{catalyst}} \text{R-}\underset{\substack{|\\ \text{R}'}}{\overset{*}{\text{C}}}\text{H-OH}$$

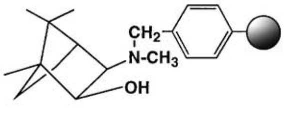
It is often claimed that PS chiral catalysts can be recycled, but recycling is rarely studied in any detail. One factor neccessary for a PS catalyst to be recycled successfully many times is a robust link between the catalyst moieties and the support. Another is that the catalyst moieties themselves must be chemically stable. Very little information is available on this latter point because in practice laboratory chemists rarely re-use catalysts. Recently we showed, however, that PS catalyst **1** slowly loses its activity when used repeatedly to catalyse examples of Reaction 1, and detailed studies *suggest* that this is due to the secondary alcohol group being oxidised, possible reversibly.[18] This decline in performance could, therefore, probably be avoided by using catalysts that contain tertiary rather than secondary alcohol groups. Analogues of catalyst **1** that contain tertiary alcohol groups have not been studied before,

---

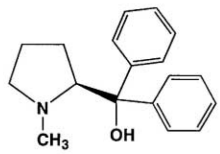
*Corresponding author. Tel.: +44-161-275-4707; fax : +44-161-275-4273; e-mail: philip.hodge@man.ac.uk

0960-894X/02/$ - see front matter
PII: S0960-894X(02)00276-7

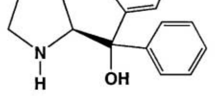
but derivatives of *N*-methyl-α,α-diphenylprolinol (**2**) satisfy the structural requirement and have been shown to be excellent catalysts in many asymmetric syntheses including examples of Reaction 1.[7,8] Accordingly the preparation of PS *N*-methyl-α,α-diphenylprolinol derivatives was investigated.



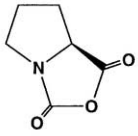
1



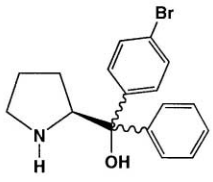
2



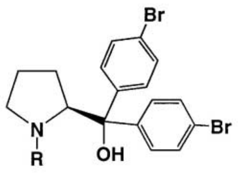
5



6



7



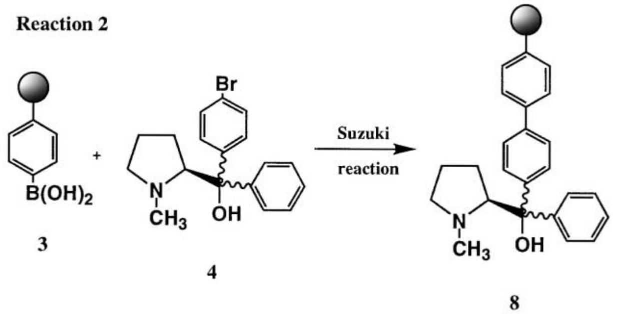
9 : R = H

10 : R = CH$_3$

Three approaches for attaching *N*-alkyl-α,α-diphenylprolinol moieties to polymer beads are via the 4-hydroxyl group of a derivative prepared from hydroxyproline,[16] via the *N*-substituent,[6,15] or via the phenyl groups. Attachment via the 4-hydroxyl group will often result in sensitive linkages and attachment via the *N*-substituent has been shown to interfere with the 'active site',[6,15] but attachment via the phenyl groups, which does not appear to have been studied before, would not be expected to interfere.

Recently, we described the attachment of various achiral moieties to polystyrene beads using Suzuki couplings between appropriate aryl bromides and PS boronic acid **3**.[19] We now report that this same method can be used successfully to attach *N*-methyl-α,α-diphenyl-L-prolinol diastereoisomers **4** with a *para*-bromo substituent in one of the phenyl rings to crosslinked polystyrene beads [see Reaction 2]. The method has the attractive features that (i) it is a one-pot procedure, (ii) since the Suzuki reaction is tolerant of many functional groups[20] the catalyst moiety can be attached without any need for protecting groups and the reaction system need not be dry, (iii) the catalyst moieties are bound by a very robust bond, and (iv) by using extended reaction times the beads are easily freed by hydrolysis of the boronic acid residues **3** that do not take part in the Suzuki couplings.

Reaction 2



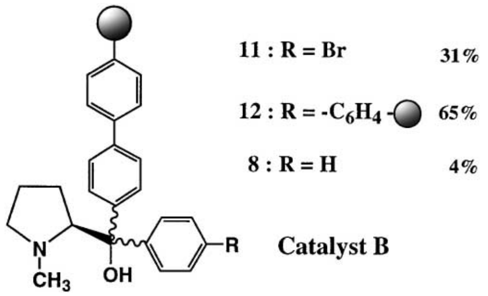
Catalyst A

α,α-Diphenyl-L-prolinol (**5**) is conveniently prepared without any racemisation problems by the reaction of α-*N*-carbonic anhydride **6**[21] with phenylmagnesium bromide.[22] This synthesis was repeated successfully (44% yield based on proline) to give α,α-diphenyl-L-prolinol (**5**) and the product was *N*-methylated (55% yield) by the Eschweiler–Clark method[23] to give compound **2**.

An analogous synthesis was then carried out by reacting the anhydride **6** with a mixture of phenylmagnesium bromide and 4-bromophenylmagnesium bromide[24] (mol ratio, 60:40). The viscous oil obtained (Product I) was, as expected, a mixture of compounds **5** and **7**. The mass spectrum (chemical ionisation) had a peak at 253 due to the unbrominated product and peaks at 331 and 333 corresponding to monobromo products **7** with ^{79}Br and ^{81}Br. By elemental analysis it contained 2.7% of Br. Attempts to separate the mixture by column chromatography failed, so it was directly *N*-methylated using the Eschweiler–Clark method[23] to give Product II containing compound **2** and the monobromo diastereoisomers **4**. By GC, the mol ratio was 85:15. As only the bromo compounds **4** are capable of taking part in a Suzuki coupling, the coupling was carried out using Product II. Whilst it is intended to subsequently develop separate syntheses of each isomer of **4**, in these initial studies the mixture was considered to be satisfactory as it is not expected that the isomers will result in either very different reactivities or % ees.

The PS boronic acid **3** was prepared via the direct lithiation of 1% crosslinked polystyrene beads.[25] The final beads contained 2.39% of B, corresponding to 2.21 mmol/g of residues **3**. A suspension of the beads was then reacted with Product II and a mixture of 2 M sodium carbonate, 1,2-dimethoxyethane and tetrakistriphenylphosphinepalladium[0] at 80–85 °C for 4 days, using the general procedure described previously,[19] to bring about the Suzuki coupling shown in Reaction 2. This afforded PS Catalyst A that, by elemental analysis contained 1.82% of nitrogen, corresponding to a loading of 1.30 mmol of the diastereoisomeric α,α-diaryl-L-prolinol residues **8** per gram, and 0.00% of boron indicating the complete removal of residues **3**.

PS Catalyst B was prepared in order to assess the effect on catalyst performance of binding the catalyst moieties through both phenyl groups.[4] The preparative method was similar to that used with PS Catalyst A. First the anhydride **6** was reacted with 4-bromophenylmagnesium bromide.[24] This reaction surprisingly afforded a mixture (Product III) (25% yield based on proline) that not only contained the dibromo compound **9** but also the monobromo diastereoisomers **7**. The mass spectrum (chemical ionisation) had peaks at 409, 411 and 413 corresponding to dibromo products with $2\times{}^{79}$Br, ^{79}Br + ^{81}Br, $2\times{}^{81}$Br, and at 331 and 333 corresponding to monobromo products with ^{79}Br and ^{81}Br. By elemental analysis it had N 3.7% and Br 35.8% (expected for $C_{17}H_{17}Br_2NO$ N 3.4% and Br 38.9%). Attempts to achieve crystallisation of the oil or significant resolution by column chromatography failed. It is not clear how the debromination occurred but it was probably the result of a further Grignard reaction followed by quenching with water. Product III was *N*-methylated (70% yield) using the Eschweiler–Clark reaction[23] to give Product IV containing, by GC analysis, the dibromo compound **10** and the monobromo diastereoisomers **4** in the ratio 78:22. Product IV was reacted with beads containing residues **3**, under Suzuki conditions similar to those used previously, to give PS Catalyst B. By elemental analyses the catalyst contained 1.64% nitrogen, 2.90% bromine and 0.00% of boron. This corresponds to a loading of 1.17 mmol of *N*-methyl-α,α-diaryl-L-prolinol residues per g and a degree of substitution of 0.18, 31% of which bore a bromo group and were therefore residues **11**. Assuming all the bromo groups in the starting material were equally reactive and bearing in mind the composition of the feedstock, this suggests that ca. 35% of the *N*-methyl-α,α-diaryl-L-prolinol residues were 'single bound' and 65% 'double bound'. The latter residues **12** correspond to a significant increase in crosslinking (ca. 12%) and therefore will lead to reduced access to the 'active sites'.[4] In summary, therefore, Catalyst B was considered to have 65% of the *N*-methyl-α,α-diaryl-L-prolinol moieties as residues **12**, 31% as residues **11** and 4% as residues **8**.



Catalyst B

The examples of Reaction 1 investigated were carried out for 20 h in toluene at 20 °C under nitrogen with an aldehyde to dialkylzinc ratio of 1.00:1.10: see ref 26 for details. For the reactions using the PS catalysts the reaction vessel was a tube and after an appropriate amount of catalyst had been placed in the tube it was sealed with a septum cap. All solutions were then added or removed using a syringe. In this way once one reaction was complete the catalyst left in the tube could be re-used easily. One charge of PS catalyst was used for a series of reactions: see below and Table 1. Yields of the recovered materials were >95% and, when diethylzinc was used, >95% of the recovered materials were the chiral alcohols. The % ees were determined by GC over a chiral stationary phase as in previous studies.[6,17,18]

To determine what mol% of PS catalyst A was appropriate to use, three tubes were set up for reactions using 5, 10 and 30 mol% of catalyst and they were used for a series of reactions between various aldehydes and diethylzinc. It is evident from the results summarised in Table 1, entries 1, 3 and 5–9, that whilst in general good % ees were obtained with a range of aldehydes the % ees generally improved as the mol% of the catalyst increased. Since 5 mol% of the soluble catalyst **2** is usually sufficient to obtain the optimal % ees, this result suggests that perhaps only ca. 20% of the PS sites are

Table 1. The % ees obtained from reactions of various aldehydes with dialkylzincs catalysed by compound **2** or PS derivatives[a]

Entry	Aldehyde	Reagent[b]	% ee of alcohol product using various catalysts[c]				
			PS Catalyst A			PS Catalyst B 30 mol%[d]	Catalyst **2** 5 mol%
			5 mol%[d]	10 mol%[d]	30 mol%[e]		
1	Benzaldehyde	E	78	79	88	83	93
2	Benzaldehyde	M	—	—	23[f]	—	70[g]
3	4-Chlorobenzaldehyde	E	85	88	94	80	94
4	4-Chlorobenzaldehyde	M	—	—	83	—	—
5	4-Carbomethoxybenzaldehyde	E	83	85	86	81	95
6	4-Carbomethoxybenzaldehyde	M	—	—	46	—	—
7	β-Naphthaldehyde	E	—	80	81	—	84
8	Cinnamaldehyde	E	—	71	78	65	—
9	Cyclohexanecarboxaldehyde	E	—	51	—	—	—

[a] Reactions carried out in toluene at 20 °C with an aldehyde to dialkylzinc ratio of 1.00:1.10.

[b] E, diethylzinc; M, dimethylzinc.

[c] The % ee was determined by analytical GC using a chiral column — see refs 6, 17 and 18 for details.

[d] All reactions were carried out with the same sample of PS catalyst. The reactions were carried out in the order listed.

[e] All the eight reactions listed in this column were carried out with the same sample of PS catalyst. The five reactions carried out using diethylzinc were carried out first in the order given, then the three reactions with dimethylzinc were carried out in the order given. Re-use of the catalyst a ninth time in a repeat of the first entry gave alcohol product with 87% ee.

[f] Yield only 44% — remainder of the product includes benzyl alcohol (20%), acetophenone (6%), starting material (9%) and unidentified compounds (21%).

[g] Yield only 41% — remainder of the product includes benzyl alcohol (42%), acetophenone (7%), starting material (8%) and unidentified compounds (2%).

readily accessible. Such a low percentage may arise because there are interactions between the 'active sites' which the amount of diethylzinc present can not completely break up (see mechanistic discussion in ref 17). That is, there is a further type of crosslinking.

Using 30 mol% of PS catalyst, benzaldehyde, 4-chlorobenzaldehyde and 4-carbomethoxy-benzaldehyde were treated with dimethylzinc. As has been found in other studies,[10,13,27] these reactions were generally less satisfactory than those with diethylzinc. It is not clear why this should be. Thus, the % ees of the alcohol products were significantly lower and the reactions were less clean: see Table 1 entries 2, 4 and 6 and footnotes f and g. Whilst, by GC–MS, the reaction with diethylzinc gave $<1\%$ each of benzyl alcohol and propiophenone, the reactions with dimethylzinc gave substantial amounts of benzyl alcohol and acetophenone. How such large amounts of benzyl alcohol are formed is not clear, but the acetophenone presumably arises from by hydride transfer from the initial product of addition of dimethylzinc to benzaldehyde. We have suggested before that reactions of this type cause PS catalysts such as **1** to lose activity on repeated use.[18] Such a side reaction would not be possible with the PS *N*-methyl-α,α-diaryl-L-prolinols used here.

Attention was next turned to PS Catalyst B. A series of reactions was carried out between various aldehydes and diethylzinc using one charge of 30 mol% of PS Catalyst B. It is evident from the results in Table 1 that with this catalyst the % ees were 9% less on average than those obtained with PS Catalyst A. This is undoubtedly due to the fact that many of the catalyst moieties are 'double bound'. Apart from increasing the extent of crosslinking, 'double binding' also means the catalytic sites are on crosslinks and so are generally less accessible than those on simple side chains.

It was hoped that the PS catalysts would recycle well. The most extensively recycled sample was the charge of PS Catalyst A which was used for all the eight reactions carried out using 30 mol% of the catalyst: see Table 1 and footnote e. After the eighth reaction, the reaction summarised in entry 1 was repeated. It gave an ee of 87% compared with an ee of 88% for the first reaction. This is encouraging and suggests that the present catalyst moieties are more robust than those used in the PS catalyst **1** studied previously.[17,18]

For comparison purposes reactions were also carried out with soluble catalyst **2**: see reference 28. When diethylzinc was used the chemical yields, like those with the PS catalysts, were $>90\%$. The % ees obtained with this catalyst are given in Table 1 and are in excellent agreement with those reported in the literature[8,23] bearing in mind that the present reactions were carried out in toluene at 20 °C whereas most of the literature reactions were carried out in hexane at 0 °C. The % ees obtained with catalyst **2** should be compared with those obtained using 30 mol% of PS Catalyst A. It is evident that whilst the reactions catalysed by compound **2** in some cases afford the same % ees, in other cases they are upto 9% higher. The explanation may in part be due to site–site interactions producing crosslinks that limit swelling and hence limit access to the 'active sites',[4] but there are other possible explanations. Thus, the reactions that give racemates can take place both in the beads and in the surrounding solvent, whereas the PS catalyst can only influence the course of the reaction when the soluble reactants (i.e., the aldehydes and dialkylzincs) are within the beads. As a consequence the relative rates of the catalysed and uncatalysed reactions depend crucially on the distribution of the soluble reactants between the bead phase and the solution phase. The present results suggest a substantial fraction of the soluble reactants are outside the beads.

In summary, using the approach summarised in Reaction 2, PS catalysts containing *N*-methyl-α,α-diphenyl-L-prolinol residues were easily prepared. The catalyst moieties were bound through one or both phenyl residues. When PS catalyst A was used at 30 mol% in toluene at 20 °C for examples of Reaction 1 involving diethylzinc, the expected alcohols were obtained in 78–94% ees. The PS catalysts recycle well and PS Catalyst A was used successfully nine times. Where comparisons can be made with the results obtained with the soluble analogue **2**, the PS catalysts usually afford somewhat lower % ees. In part, this is due to the PS catalysts having to compete with the background reactions that give racemic alcohol products. Given the success of the present study, in future work we propose to prepare PS catalysts using the pure isomers of compounds **4** and to use them for extended periods in flow systems.[18]

Acknowledgements

We thank the EPSRC for Ph.D. (R.J.K.) and M.Sc. (M.N.) Studentships.

References and Notes

1. Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637.
2. Hodge, P. In *Innovation and Perspectives in Solid Phase Synthesis*; Epton, R., Ed; SPCC, Birmingham, 1990; p. 273.
3. De Miguel, Y. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4213.
4. Hodge, P. *Chem. Soc. Rev.* **1997**, *26*, 417.
5. Hodge, P.; Khoshdel, E.; Waterhouse, J.; Frechet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2327.
6. Hodge, P.; Kell, R. J.; Ma, J.; Morris, H. *Aust. J. Chem.* **1999**, *52*, 1041.
7. Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.
8. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
9. Itsuno, S.; Frechet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4140.
10. Soai, K.; Niwa, S.; Watanabe, M. *J. Org. Chem.* **1988**, *53*, 927.
11. Soai, K.; Niwa, S.; Watanabe, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 109.
12. Soai, K.; Watanabe, M. *J. Chem. Soc., Chem. Comm.* **1990**, *43*.
13. Itsuno, S.; Sakurai, Y.; Ito, K.; Maruyama, T.; Nakahama, S.; Frechet, J. M. J. *J. Org. Chem.* **1990**, *55*, 304.

14. Zhang, Z.; Hodge, P.; Stratford, P. W. *Reactive Polym.* **1991**, *15*, 71.

15. Watanabe, M.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 837.

16. Liu, G.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 7712.

17. Sung, D. W. L.; Hodge, P.; Stratford, P. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1463.

18. Hodge, P.; Sung, D. W. L.; Stratford, P. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2335.

19. Kell, R. J.; Hodge, P.; Nisar, M.; Williams, R. T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3403.

20. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

21. Daly, W. H.; Poche', D. *Tetrahedron Lett.* **1988**, *29*, 5859.

22. Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blackstock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751.

23. Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.

24. Schiemenz, G. P. *Org. Synth. Collec. Vol. V* **1973**, 496.

25. Farrall, M. J.; Frechet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877.

26. The PS catalyst (5, 10, or 30% with respect to the aldehyde) and a small magnetic stirrer bar were placed in a tube (100×20 mm) sealed with a septum cap. Nitrogen was passed through the tube via syringe needles. Dry toluene (5 mL) was syringed into the tube and the mixture was left for 30 min for the beads to swell. The mixture was chilled using an ice bath and a 1.1 M solution of diethylzinc in toluene (5.0 mL, 5.5 mmol) [or a 2.0 M solution of dimethylzinc in toluene (2.75 mL, 5.5 mmol)] was added dropwise, again using a syringe. When the addition was complete the mixture was stirred for 60 min at 20 °C. The aldehyde (5.0 mmol, freshly distilled if a liquid) in toluene (5 mL) was then added dropwise over 15 min and when the addition was complete stirring was continued at 20 °C for 20 h. At the end of this period the organic layer was syringed off. The beads were washed twice with toluene (2×10 mL). The combined organic solutions were washed successively with hydrochloric acid (50 mL of 1 M) and distilled water (100 mL), then dried over anhydrous magnesium sulphate. Evaporation of the solvent gave the crude product as a yellow oil (recoveries were >95%). As in previous studies,[6,17,18] an ^{1}H NMR spectrum was recorded and a GC run to determine both the % ee and the chemical yield (the percentage of aldehyde in the recovered product converted into the desired alcohol: this was >95% when diethylzinc was used but see footnotes in Table 1 for reactions using dimethylzinc). The PS catalyst in the tube was then used for the next reaction.

27. Noyori, R.; Kitamura, M. *Angew. Chem., Intl. Ed. Engl.* **1991**, *30*, 49.

28. The catalyst 2 (5% mol) was dissolved in toluene (5 mL) and the solution cooled in an ice bath. A 1.1 M solution of diethylzinc solution in toluene (5.0 mL) [or a 2.0 M solution of dimethylzinc in toluene (2.75 mL, 5.5 mmol)] was added dropwise over 30 min. The aldehyde (2.5 mmol) in toluene (5 mL) was added and the mixture was stirred at 20 °C for 20 h. At the end of the reaction period the reaction was quenched with 1 N hydrochloric acid, and the organic products were extracted with ethyl acetate (50 mL). The extract was washed with water and dried over anhydrous magnesium sulphate. The residue left after evaporation of the solvent under reduced pressure was fractionally distilled in vacuum (1 mm of Hg) from bulb-to-bulb to give a mixture of the enantiomeric alcohols. The % ee was determined by GC analysis as described above.