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([2]Paracyclo[2](5,8)quinolinophan-2-yl)carbinols as catalysts for diethylzinc addition to aldehydes: cooperative effects of planar and central chirality on the asymmetric induction

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Abstract—A systematic study to assess the contribution of planar and central chirality to the asymmetric induction in the diethylzinc addition to aromatic and aliphatic aldehydes has been carried out using planar chiral quinolinophanylcarbinols (R_p)-**1** and (R_p)-**11** and diastereomeric quinolinophanylcarbinols (R_p,*R*)- and (R_p,*S*)-**5**–**8**, exhibiting both planar and central chirality as catalysts. The stereochemistry of the addition process leading to aryl- or 1-alkylpropanols seems to be mostly controlled by the central chirality. Nevertheless, the planar chirality shows a remarkable cooperative effect on the degree of asymmetric induction, which turns out to be positive or negative depending on the configuration of the stereogenic carbon of the catalyst.

1. Introduction

Stereoselective addition of dialkylzinc reagents to aldehydes catalyzed by *N*,*O*-type chiral ligands is one of the most common and effective methods for preparing chiral secondary alcohols.[1–4] Since the pioneering work of Oguni and Omi,[5,6] many researchers have attempted this reaction and, in the process, have developed an impressive number of chiral *N*,*O*-type ligands, mostly β-amino alcohols, thus achieving a very high standard of asymmetric induction. Chiral systems belonging to different chirality classes have been investigated: central, C_2-symmetric and planar chiral ligands, among which ferrocene-derived β- and γ-amino alcohols are the most studied systems.[7–11] In many cases, the planar chirality is associated with the central chirality of a side-chain bearing a stereogenic carbon centre, so the assessment of the contribution made by each chirality element to the enantioselectivity of the process becomes a very intriguing question.[12–16] Among the reported planar chiral catalysts for stereoselective dialkylzinc addition to carbonyl compounds, those derived from [2.2]paracyclophane have received increasing attention over the last few years.[17–26] This is mainly due to a substantial rigidity of the [2.2]paracyclophane backbone and to its marked stability towards oxidation and relatively high temperatures compared with the metallocene-based ligands. Recently, Rozenberg and Bräse reported the first examples of the successful application of chiral salen-type as well as tridentate [2.2]paracyclophane-based *N*,*O*-ligands as catalysts in the enantioselective diethylzinc addition to aliphatic and aromatic aldehydes.[20,21] More recently, Dahmen and Bräse tackled the question of the contribution of the planar and central chirality to the asymmetric induction in the *N*,*O*-type ligand-catalyzed addition of organozinc reagents to aldehydes.[17,23,24] Several hydroxy imine, hydroxy ketimine and amino alcohol ligands based on the [2.2]paracyclophane backbone bearing a stereogenic centre in the side-chain were used in the enantioselective addition of alkyl, alkenyl and alkynyl zinc reagents to aliphatic and aromatic aldehydes.

Two years ago, we began a study to assess the effectiveness of planar chirality in inducing enantioselectivity in the diethylzinc addition to aromatic aldehydes using the novel quinolonophane-based *N*,*O*-type catalyst (*R*)-(+)-(4-methyl-[2]paracyclo[2](5,8)quinolinophan-2-yl)-methanol **1**.[27] The latter was prepared in 45% overall yield, in three steps, by the cyclization of (*R*)-(−)-4-amino-[2.2]paracyclophane **2**[28,29] with 2,4-pentanedione, selective metallation of the resulting (*R*)-(+)-2,4-dimethyl-[2]paracyclo[2](5,8)quinolinophane **3** with butyllithium in diethyl ether and the subsequent reaction of

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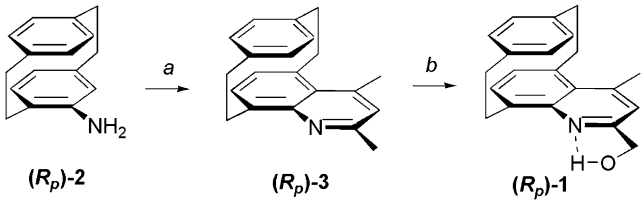
the 2-lithiomethylquinolinophane intermediate with bis(trimethylsilyl)peroxide (Scheme 1).[30]



Scheme 1. Reagents and conditions: (a) 1. Acetylacetone, rt, 2 h; 2. PPA, 75 °C, 48 h, 69%; (b) 1. BuLi, Et_2O, 0 °C; 2. $(Me_3SiO)_2$, −75 °C, 3. H_3O^+, 75%.

On the basis of this investigation, it was hypothesized that the close proximity of a metal reaction centre to the ethylene bridge of the [2.2]paracyclophane moiety in the transition state of the addition process was crucial for enantioselection. This hypothesis arose from the finding that the *N*-acetyl- and *N*-propanoyl derivative of (+)-(*R*)-[2.2]paracyclophano[4,5-*d*]-oxazol-2(3*H*)-one, used as chiral auxiliary, generated good enantioselectivities (up to 90% ee) in the Bu_2BOTf/Et_3N-promoted aldol condensation of α-metallated amides with benzaldehyde.[31,32] The result was interpreted to be the consequence of the steric interaction of the phenyl ring with the ethylene bridge of the [2.2]paracyclophane moiety precluding the attack by the α-lithiated amide at one of the two enantiotopic faces of the aldehydic carbonyl group.

Addition of diethylzinc to various aldehydes in the presence of (*R*)-(+)-**1** (0.1 equiv) in toluene at 25 °C afforded the corresponding (*S*)-1-aryl-1-propanols in good yields with ees ranging from 30% to 75%. Enantioselectivity was increased to a certain degree by increasing the Et_2Zn/aldehyde molar ratio, the optimal one being 5:1. This is in keeping with the findings of Noyori regarding the presence of different catalytic species in equilibrium in the reaction mixture, the most effective one predominating at a higher concentration of the reagent. Complexes formed at lower Et_2Zn/aldehyde ratios were less effective in ethylating aldehydes and formed slowly benzyl alcohol.[33] Moreover, low temperatures decreased the yield and reduced the enantioselectivity, while lengthening the reaction time favoured the competing reduction of the aldehyde to the corresponding benzyl alcohol. The predominance of the enantiomer (*S*)-1-aryl-1-propanol and the similar values of the specific rotation observed in all cases led us to envisage the two transition states TS1 and TS2 (Fig. 1), where the steric interaction between the aldehydic hydrogen and the ethyl group bonded to the chelated zinc atom seemed to play a determinant role in the enantioselectivite transfer of ethyl from a second coordinate molecule of diethylzinc to the formyl group.

Despite the low enantioselectivity registered with this kind of ligand, which was far from the high standards achieved nowadays in this process, we thought that the performance of such catalysts could be considerably

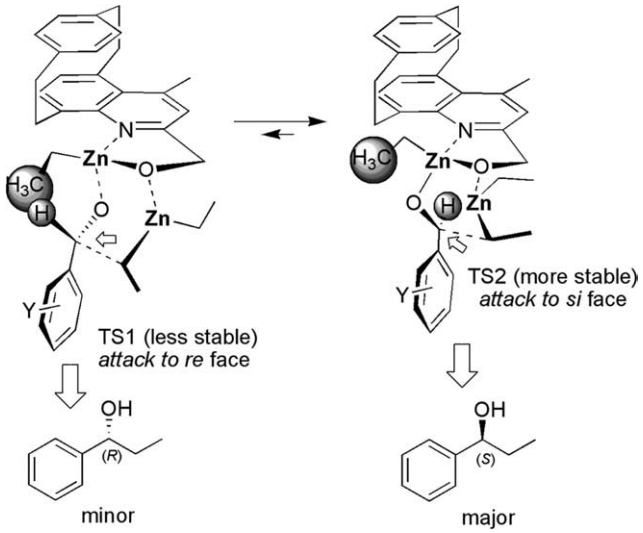


Figure 1. Transition states for the (*R*)-(+)-**1**-catalyzed diethylzinc addition to aromatic aldehydes.

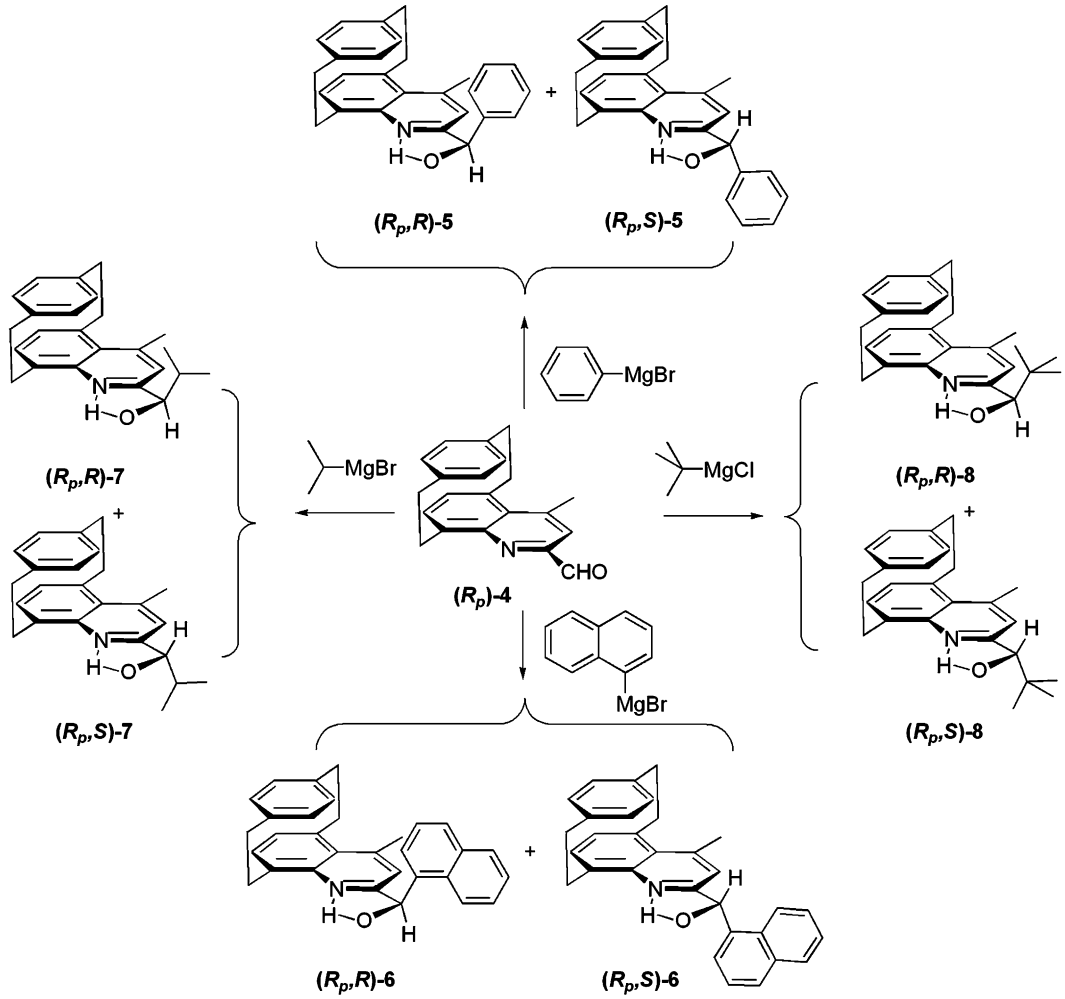
improved upon by the cooperative effect of planar and central chirality produced by structural changes in the side-chain.

To put this idea in concrete form, a systematic investigation was therefore undertaken to determine the mutual role of the planar and central chirality on the enantioselectivity of the diethylzinc addition to aldehydes. The results of this research are reported herein.

2. Results and discussion

Carbinols **5**–**8**, exhibiting both planar and central chirality, were synthesized starting from the common precursor (R_p)-(+)-**1**. Thus, oxidation of the latter with pyridinium dichromate at room temperature in CH_2Cl_2 afforded (R_p)-(-)4-methyl-[2]paracyclo[2](5,8)quinolinophane-2-carbaldehyde (R_p)-**4** in 75% yield. Aldehyde (R_p)-**4** was made to react in turn with the Grignard reagents prepared from bromobenzene, 1-bromonaphthalene, isopropyl bromide and *tert*-butyl chloride (Scheme 2). A diastereomeric mixture of alcohols (R_p,*S*)- and (R_p,*R*)-**5**–**8** was obtained each time in the following yields and (R_p,*S*)/(R_p,*R*) molar ratios: **5**, 53%, 60/40; **6**, 56%, 70/30; **7**, 23%, 56/44; and **8**, 42%, 54/46. The low yield of **7** was mainly due to the competing Merwein–Pondorff–Verley reduction of the aldehyde by ^{i}PrMgBr giving the alcohol (R_p)-**1** (56%). Carbinols (R_p,*R*)-**8** and (R_p,*S*)-**8** had to be converted into the corresponding benzoate esters before being separated by HPLC; (R_p,*R*)-**7** and (R_p,*S*)-**7** were directly separated by HPLC, while all the other diastereomeric mixtures were easily resolved by simple chromatography of the crude on silica gel using petroleum ether/diethyl ether mixtures as eluent.

The absolute configuration of the new stereogenic centre was easily assigned by NOESY experiments. In fact, due to the intramolecular hydrogen bond between the



Scheme 2. Synthesis of the ligands (R_p,R)- and (R_p,S)-**5**–**8**.

hydroxylic proton and the nitrogen atom of the quinoline moiety, the diastereomeric alcohols, at least in the weakly polar solvents such as chloroform, form conformationally rigid five-membered heterocyclic rings. Thus, in the (R_p,R)-diastereomer, a substantial NOE can be observed between the protons of the paracyclophane moiety overlying the heterocyclic ring (the AB system between δ 5.0 and 6.0) and the protons of the substituent on the stereogenic hydroxylic carbon (Fig. 2), in particular: the ortho protons of the phenyl ring in (R_p,R)-**5**; H-2, H-8 and to a lesser extent, H-3 and H-7 protons of the 1-naphthyl group in (R_p,R)-**6**; the protons of the isopropyl group in (R_p,R)-**7** and those of the *tert*-butyl group in (R_p,R)-**8**.

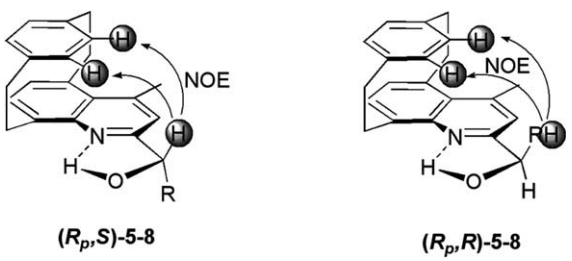
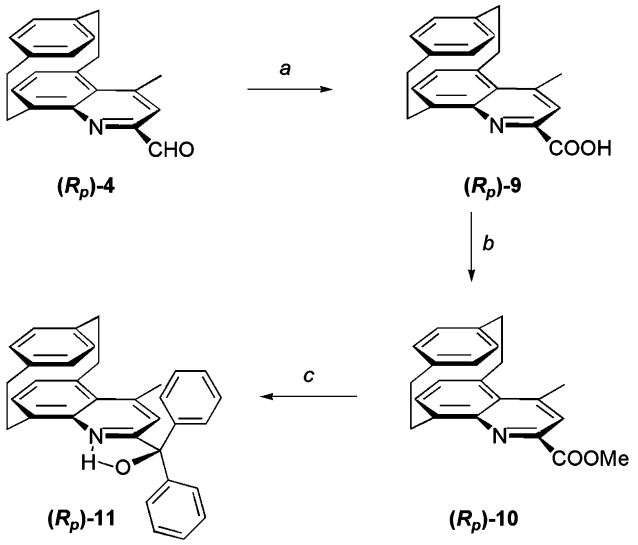


Figure 2. NOE interactions in the (quinolinophanyl)carbinols **5**–**8**.

As expected, no NOE was observed for the corresponding protons in the (R_p,S)-diastereomer, while a substantial NOE was registered between the proton at the stereogenic carbon and the protons of the overlying aromatic ring.

For comparisons, planar chiral (R_p)-diphenyl-(4-methyl-[2]paracyclo[2](5,8)quinolinophan-2-yl)methanol (R_p)-**11** was also prepared. Thus, (R_p)-(−)-4-methyl-[2]paracyclo[2](5,8)quinolinophane-2-carboxylic acid (R_p)-**9**, obtained by H_2O_2-promoted oxidation of the aldehyde **4** in formic acid, was quantitatively transformed into the corresponding methyl ester (R_p)-**10** by reaction with diazomethane in diethyl ether (Scheme 3). Finally, ester (R_p)-**10** was made to react with 2 equiv of phenylmagnesium bromide in THF to give the expected diphenyl carbinol (R_p)-**11** in 87% yield.

Ligands **5**–**8** were used as the catalysts in the addition of diethylzinc to aldehydes. A cooperative effect of (R_p)-planar and (S)-central chirality was immediately evident when these ligands were employed as the catalyst in the reaction of diethylzinc addition with 2-naphthaldehyde (Table 1), the latter having been selected as a probe in our enantioselectivity tests. In all cases, (S)-1-(2-naphthyl)propanol was formed in good yield and with



Scheme 3. Reagents and conditions: (a) H_2O_2, HCOOH, 4 °C, 12 h; (b) CH_2N_2, DDE, 25 °C; (c) C_6H_5MgBr (2.5 equiv), THF, 25 °C.

excellent enantioselectivities, the ee values ranged from 83% to 90% with the aryl-substituted carbinols (R_p,*S*)-**5** and (R_p,*S*)-**6**, and up to 99% with carbinols (R_p,*S*)-**7** and (R_p,*S*)-**8** bearing a bulky alkyl group on the stereogenic centre (compare entry 1 with entries 3, 5, 7 and 9 in Table 1).

A synergic effect of planar and central chirality on the asymmetric induction was also observed with the diastereomeric aryl(quinolinophan-2-yl)carbinols (R_p,*R*)-**5** and (R_p,*R*)-**6** (compare entry 1 with entries 2 and 4 in Table 1). However, a negative cooperative effect was registered when the aryl group was replaced by an isopropyl or *tert*-butyl group in the diastereomers of an (*R*)-configuration (compare entry 1 with entries 6 and 8). In all cases, the inversion of the configuration at the stereogenic carbon of the catalyst caused the inversion of the configuration of the adduct 1-arylpropanol.

The above results provide valuable information for elucidating the mechanism of the diethylzinc addition to aldehydes catalyzed by these particular ligands. The mechanistic hypotheses that best fit the observed enantioselectivities are illustrated by the transition states outlined in Figure 3 referring to the reactions catalyzed by (R_p,*R*)-**8** and (R_p,*S*)-**8**. These were based on the following sound considerations: (a) in the previously formed *N*,*O*-chelate zinc complex, the ethyl group on the zinc atom prefers an *anti* arrangement with respect to the alkyl (or aryl) group bound to the stereogenic carbon of the ligand; (b) the energy difference between the plausible transition states comes in part from the steric interactions between the aldehydic proton and the ethyl group on the *N*,*O*-chelate zinc atom and mostly from the steric interaction of the aryl (or alkyl) group of the aldehyde while axially oriented in a by now agreed six-membered boat-like cyclic transition state;[34–36] and (c) for obvious steric reasons, the coordination of the carbonyl oxygen at the chelated zinc atom occurs so as to get the aryl group trans to the metal. On this basis, transition state **TS3** seems quite improbable because of the steric crowding caused by the *syn* arrangement of the ethyl and *tert*-butyl groups. Due to the lack of steric interactions between the aldehydic hydrogen and the ethyl group on the chelate zinc atom and especially between the aryl group and the substituent on the stereogenic carbon, **TS5** is by far more stable than **TS4** and gives the expected (*S*)-1-arylpropanol in very high ee.

The same considerations hold true for the reactions catalyzed by the (R_p,*R*)-**8** ligand. Thus, due to the absence of steric interactions between the aldehydic hydrogen and the ethyl group on the chelated zinc atom (Fig. 3), **TS7** turns out to be more stable than **TS6** and provides (*R*)-1-arylpropanol as the major enantiomer. However, owing to an increased rotational freedom around the C–Zn bond in **TS6** the steric interactions between the axially oriented ethyl group and the aldehydic proton become less severe. This in turns causes a decrease in the energy difference between **TS6** and **TS7**, with a consequent drop in enantioselectivity.

It should be noted that, as reported by Chelucci[37] and Hoshino,[38,39] (*R*)-2,2-dimethyl-1-(2-pyridyl)propanol (*R*)-**12**, an analogue ligand exhibiting central chirality only, induces an enantioselectivity, in the diethylzinc addition to benzaldehyde, that is very similar to that observed with (R_p,*R*)-**8** providing 1-phenylpropanol with the same (*R*)-configuration (82% ee in hexane–ether

Table 1. Enantioselective addition of diethylzinc (5 equiv) to 2-naphthaldeyde catalyzed by the planar chiral carbinols (R_p)-**1**, (R_p)-**11** and the diastereomeric carbinols (R_p,*R*)- and (R_p,*S*)-**5**–**8**, in toluene at 0 °C

Entry	Catalyst (0.1 equiv)	Time (h)	1-(2-Naphthyl) propanol yield (%)	(2-Naphthyl)methanol yield (%)	Ee of **6** (%)[a] (config.)
1	(S_p)-**1**	110[b]	33	50	61 (*R*)
2	(R_p,*R*)-**5**	6	98	Traces	84 (*R*)
3	(R_p,*S*)-**5**	6	98	Traces	83 (S)
4	(R_p,*R*)-**6**	6	97	~1	88 (*R*)
5	(R_p,*S*)-**6**	6	97	~1	90 (*S*)
6	(R_p,*R*)-**7**	6	47	4	40 (*R*)
7	(R_p,*S*)-**7**	6	86	2	99 (*S*)
8	(R_p,*R*)-**8**	6	44	4	52 (*R*)
9	(R_p,*S*)-**8**	6	87	2	99 (*S*)
10	(R_p)-**11**	3	100	—	67 (*S*)

[a] Determined by GLC analysis of the crude on a 30 m × 0.25 mm × 0.25 μm BETADEX™ Supelco.
[b] Ref. 27.

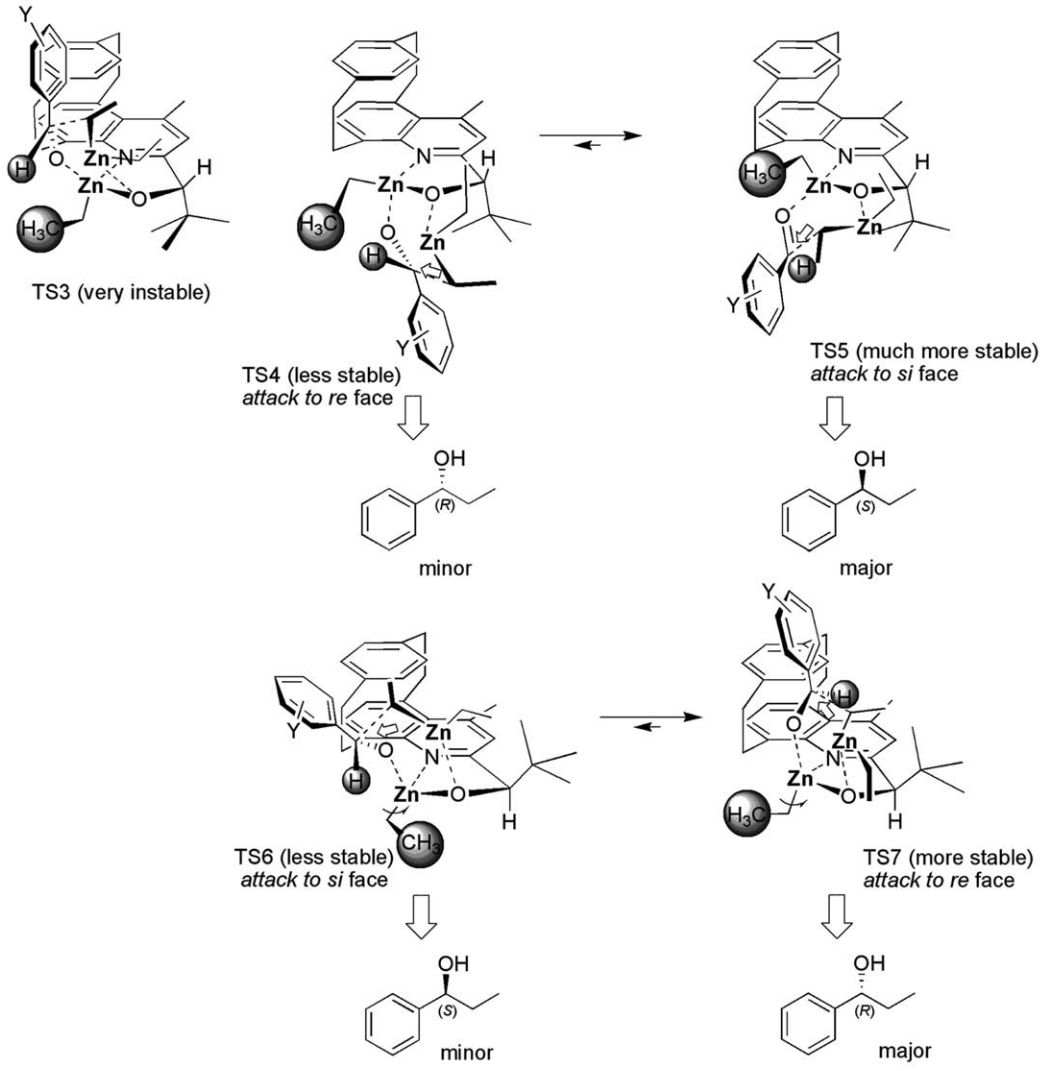


Figure 3. Plausible transition states for the (R_p,*R*)- and (R_p,*S*)-**8**-catalyzed addition of diethylzinc to benzaldehydes.

Table 2. Addition of diethylzinc (5 equiv) to aldehydes catalyzed by (R_p,*S*)-**7** and (R_p,*S*)-**8** in toluene at 0 °C after 6 h

Aldehyde	Ligand (10%)	1-Arylpropanol yield (%)	Arylmethanol yield, %	Ee[a] (config.)
2-Naphthaldehyde	(R_p,*S*)-**7**	86	2	99 (*S*)
	(R_p,*S*)-**8**	87		99 (*S*)
1-Naphthaldehyde	(R_p,*S*)-**7**	90	1	97 (*S*)
	(R_p,*S*)-**8**	84	3	98 (*S*)
Benzaldehyde	(R_p,*S*)-**7**	88	1	96 (*S*)
	(R_p,*S*)-**8**	84	1	97 (*S*)
o-Tolualdehyde	(R_p,*S*)-**7**	79	3	96 (*S*)
	(R_p,*S*)-**8**	80	1	98 (*S*)
m-Anisaldehyde	(R_p,*S*)-**7**	83	3	96 (*S*)
	(R_p,*S*)-**8**	82	2	98 (*S*)
p-Anisaldehyde	(R_p,*S*)-**7**	35	6	92 (*S*)
	(R_p,*S*)-**8**	32[b]	8	96 (*S*)
Cyclohexen-3-carbaldehyde	(R_p,*S*)-**7**	99	—	98 (*S*)
	(R_p,*S*)-**8**	98	—	>99 (*S*)
3,5-Bis(trifluoromethyl)benzaldehyde	(R_p,*S*)-**8**	98	—	99 (S)
3-Pyridincarbaldehyde	(R_p,*S*)-**8**	92	—	74 (*S*)
Cinnamaldehyde	(R_p,*S*)-**8**	49	2	84 (*S*)

[a] Determined by GLC analysis of the crude on a 30 m × 0.25 mm × 0.25 μm BETADEX™ Supelco.
[b] 56% of the starting aldehyde was recovered.

mixture,[37] 66% ee in hexane[38]). This suggests that transition states such as **TS6** and **TS7** could also be envisaged for the (*R*)-**12**-catalyzed process.

The ee values and the configuration of the 1-arylpropanols obtained in the reactions catalyzed by the planar chiral diphenyl(quinolinophan-2-yl)carbinol (R_p)-**11** are practically the same as those obtained for carbinol (R_p)-**1**. This means that the crowding at the stereogenic carbon has a trifling effect on the enantioselectivity induced by the planar chirality of the catalyst (entries 1 and 10 in Table 1). Nevertheless, a substantial increase in the reaction rate was observed.

The excellent results obtained in the (R_p,*S*)-**7**- and (R_p,*S*)-**8**-catalyzed additions of diethylzinc to 2-naphthaldehyde were confirmed with a variety of aromatic and aliphatic aldehydes with the highest ee value obtained with cyclohexen-3-carbaldehyde (Table 2).

3. Conclusions

In an attempt to sort out the mutual role of different chirality classes in stereoselective processes, we have tested the ability of diastereomeric (quinolinophan-2-yl)carbinols (R_p,*R*)- and (R_p,*S*)-**5**–**8**, exhibiting both planar and central chirality, as catalysts of the enantioselective addition of diethylzinc to aldehydes.

The above *N*,*O*-type ligands were easily obtained, in enantiomerically pure form, from a common precursor (*R*)-2,4-dimethyl-[2]paracyclo[2](5,8)quinolinophane **3** prepared in our laboratory on a multigram scale. The performances of (R_p,*R*)- and (R_p,*S*)-**5**–**8** in inducing asymmetry were compared with those of only planar (R_p)-**1** and (R_p)-**11** or of only central chiral 2,2-dimethyl-1-(2-pyridyl)propanol (*R*)-**12** analogues. The following conclusions were drawn: the configuration at the stereogenic carbon of the adduct 1-arylpropanol seems to be exclusively controlled by the central chirality of the catalyst. Accordingly, (*R*)-1-arylpropanol is obtained from the (*R*)-ligand as the major enantiomer, while the (*S*)-ligand provides (*S*)-1-arylpropanols almost exclusively. Planar chirality does not seem to play a significant role in determining the configuration of the product 1-arylpropanol, but it does show a remarkable cooperative effect on the asymmetric induction, which turns out to be positive or negative depending on the configuration at the stereogenic centre of the catalyst. In this particular case, the role of the cyclophane moiety is to orientate the coordination of the aldehyde on the chelated zinc atom on the opposite side with respect to the aromatic ring overlying the quinoline moiety. Consequently, enantioselectivity induced by the planar chirality is derived, at least in part, from the steric interaction between the aldehydic proton and the ethyl group suitably oriented by the adjacent ethylenic bridge between the two aromatic systems. It is noteworthy that the diastereomeric aryl(quinolinophanyl)carbinols (R_pR)- and (R_p,*S*)-**5,6** provide 1-arylpropanols of opposite configuration in high enantiomeric excesses, at least comparable with those observed with enantiomeric aryl(2-pyridyl)carbinols. Nevertheless, they have the undoubted advantage of being obtained in enantiomeric excess by simple chromatography of the diastereomeric mixture on silica gel by avoiding wearisome resolution procedures.

4. Experimental

If not specified otherwise, ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solution using tetramethylsilane as an internal standard. IR spectra were recorded on a FT-IR instrument in $CHCl_3$ solution in the 4000–400 cm^{-1} range. Gas-chromatographic analyses were performed using 30 m × 0.32 mm capillary columns loaded with two different stationary phases: HP-5 MS (5% phenyl-methylpolysiloxane) and HP-35 MS (5% phenyl-methylpolysiloxane) at 70–310 °C. Mass spectra were obtained at 70 eV. Optical activity was measured at 20 °C in $CHCl_3$ solution. The enantiomeric excesses of 1-aryl-1-propanols were determined by GLC analysis of the mixture on 30 m, 0.25 mm, 0.25 μm BETADEX™ Supelco column using the same conditions as reported in the literature.[40]

Reagents. Commercial [2.2]paracyclophane (parylene) and trifluoroacetic anhydride were used as received. Racemic 4-carboxy[2.2]paracyclophane was prepared in 70% overall yield by Friedel–Craft acylation of [2.2]paracyclophane with trifluoroacetic anhydride followed by alkaline hydrolysis of the resulting trifluoroacetyl derivative in refluxing 17% aqueous KOH.[41] (R_p)-(−)- and (S_p)-(+)-4-carboxy[2.2]paracyclophane were obtained from the racemic mixture by fractional crystallization of the diastereoisomeric salts with (*S*)-(−)- and (*R*)-(+)-α-methylbenzylamine, respectively. (*R*)-(−)-4-Carboxy[2.2]paracyclophane {$[\alpha]_D^{20} = -164$ (*c* 0.6, $CHCl_3$); lit.,[42] −164}; (*S*)-(+)-4-carboxy[2.2]paracyclophane {$[\alpha]_D^{20} = +164$ (*c* 0.61, $CHCl_3$); lit.,[42] +164}. (*R*)-4-amino[2.2]paracyclophane **1** was prepared from (R_p)-(−)-4-carboxy[2.2]paracyclophane in 90% overall yield through a four-step sequence as previously reported.[27]

4.1. (R_p)-(+)-2,4-Dimethyl-[2]paracyclo[2](5,8)quinolinophane (R_p)-3

(*R*)-(−)-4-Amino-[2.2]paracyclophane (5.0 g, 22.4 mmol) and 2,4-pentanedione (5 mL, 4.9 g, 48 mmol) were heated at 90 °C for 6 h with stirring. After cooling, petroleum ether (10 mL) was added, the mixture filtered and the resulting white solid added to polyphosphoric acid (300 g). The mixture was made to react at 70 °C for 48 h while being gently stirred mechanically. The viscous yellow mass was rapidly poured in iced water (500 mL) and the resulting slurry was basified with 25% aqueous NaOH. The organic product was extracted with CH_2Cl_2 (3 × 50 mL), the collected organic phases dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. Chromatography of the remaining crude on SiO_2 (eluent, petroleum ether/diethyl ether 9:1) allowed a yellow solid to be collected, which was re-crystallized from

octanes to obtain pale yellow needles (3.2 g, 62%). The product was identified as (R_p)-(+)-2,4-dimethyl-[2]paracyclo[2](5,8)quinolinophane (100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 97:3 hexane/isopropanol) on the basis of its spectral and analytical characteristics: mp 124–125 °C; $[\alpha]_D^{25} = +38$ (*c* 0.52, $CHCl_3$); ^{1}H NMR δ 6.98 (s, 1H), 6.87–6.74 (AB system, J_{AB} = 7.2 Hz, 2H), 6.48 (s, 2H), 5.75 (d, *J* = 7.8 Hz, 1H), 5.50 (d, *J* = 7.8 Hz, 1H), 4.35–4.22 (m, 1H), 3.84 (dd, *J* = 14.0 and 9.1 Hz, 1H), 3.16 (dd, *J* = 13.0 and 9.7 Hz, 1H), 3.10–2.91 (m, 4H), 2.70 (s, 3H), 2.68 (s, 3H), 2.57 (dt, *J* = 13.1 and 9.1 Hz, 1H); ^{13}C NMR δ 155.5, 150.1, 142.9, 139.7, 139.0, 137.8, 136.8, 133.0, 132.4, 132.2, 131.1, 128.4, 128.3, 128.0, 123.5, 38.0, 35.3, 34.6, 31.9, 25.0, 22.6; IR (CCl_4) ν_{max} 3063 (w), 3014, 2961–2852, 1594, 1503, 1434, 1377, 860 cm^{-1} MS *m*/*z* (%) 287 (M^+, 66), 183 (100), 104 (9). Anal. Calcd for $C_{21}H_{21}N$: C, 87.76; H, 7.36; N, 4.87. Found: C, 87.51; H, 7.47; N, 5.01.

4.2. (R_p)-(+)-2-Hydroxymethyl-4-methyl-[2]paracyclo-[2](5,8)quinolinophane (*R*)-1

Butyllithium (4.6 mL 1.54 M in hexane, 7.1 mmol) was added to a solution of 2,4-dimethyl-[2]paracyclo-[2](5,8)quinolinophane (2.0 g, 7.0 mmol) in anhydrous diethyl ether (10 mL), at 0 °C under nitrogen atmosphere. After 1 h, the red mixture was cooled to −75 °C and freshly prepared bis(trimethylsilyl)peroxide[30] (1.5 g, 8.6 mmol) was then added. The cold bath was removed and the mixture made to react at 25 °C for 3 h. The solution was acidified with concd HCl (30 mL), stirred for 15 min and basified until pH 9, before it was extracted with dichloromethane (3 × 150 mL). The collected organic phases were dried over Na_2SO_4 and the solvent evaporated at reduced pressure. Chromatography of the remaining crude on SiO_2 (eluent, petroleum ether/diethyl ether 7:3) allowed a pale yellow solid to be collected in 75% yield and was identified as (R_p)-(+)-2-hydroxymethyl-4-methyl-[2]paracyclo[2](5,8)quinolinophane (100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 98:2 hexane/isopropanol) on the basis of the following spectroscopic and analytical data: mp 116–118 °C (from diethyl ether); $[\alpha]_D^{20} = +16.0$ (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 6.96 (s, 1H), 6.93–6.82 (AB system, J_{AB} = 7.2 Hz, 2H), 6.49 (s, 2H), 5.73 (d, *J* = 7.6 Hz, 1H), 5.48 (d, *J* = 7.6 Hz, 1H), 4.95–4.82 (AB system, J_{AB} = 15.0 Hz, 2H), 4.86 (broad s, 1H), 4.33–4.22 (m, 1H), 3.87 (dd, *J* = 14.0 and 9.2, 1H), 3.18 (dd, *J* = 13.0 and 9.9 Hz, 1H), 3.12–2.94 (m, 4H), 2.72 (s, 3H), 2.58 (dt, *J* = 13.1 and 9.0 Hz, 1H); ^{13}C NMR δ 155.0, 148.4, 144.2, 139.4, 138.7, 137.7, 137.2, 133.7, 132.8, 132.5, 131.3, 129.6, 128.2, 127.7, 119.8, 63.4, 37.6, 35.2, 34.4, 31.9, 22.8; IR ($CHCl_3$) 3417 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.20; H, 6.99; N, 4.54.

4.3. (R_p)-(−)-4-Methyl-[2]paracyclo[2](5,8)quinolinophane-2-carbaldehyde (*R*)-4

Pyridinium dichromate (1.3 g, 3.5 mmol) was added to a solution of the above alcohol (0.7 g, 2.3 mmol) in anhydrous CH_2Cl_2 (12 mL) and the mixture, allowed to react at 25 °C for 12 h while being vigorously stirred. Diethyl ether (50 mL) and then H_2O (50 mL) were added and the suspension filtered on Celite®. The organic phase was separated, the aqueous phase further extracted with diethyl ether (3 × 20 mL), the collected organic phases dried over Na_2SO_4 and the solvent evaporated at reduced pressure. The remaining bright yellow solid (0.66 g, 94%) was identified as (R_p)-(−)-4-methyl-[2]paracyclo[2](5,8)quinolinophane-2-carbaldehyde (100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 98:2 hexane/isopropanol) as follows: mp 172–173 °C; $[\alpha]_D^{20} = -150.1$ (*c* 0.51, $CHCl_3$); ^{1}H NMR δ 10.20 (s, 1H), 7.74 (s, 1H), 7.00–6.92 (AB system, J_{AB} = 7.2 Hz, 2H), 6.56–6.50 (AB system, J_{AB} = 8.0 Hz, 2H), 5.67 (d, *J* = 7.8 Hz, 1H), 5.41 (d, *J* = 7.8 Hz, 1H), 4.47–4.44 (m, 1H), 3.90 (dd, *J* = 14.0 and 9.1 Hz, 1H), 3.22–3.02 (m, 5H), 2.79 (s, 3H), 2.60 (dt, *J* = 13.0 and 8.7 Hz, 1H); ^{13}C NMR δ 194.7, 150.4, 149.4, 144.2, 141.2, 139.6, 138.0, 137.2, 136.4, 133.0, 132.7, 132.0, 131.2, 128.8, 128.3, 119.2, 37.7, 35.2, 34.5, 31.6, 22.9; IR ($CHCl_3$) ν_{max} 1698 cm^{-1} (C=O). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.51; H, 6.29; N, 4.70. The product was sufficiently pure to be used for the subsequent reactions without further purification.

4.4. (R_p,*R*)-(−)- and (R_p,*S*)-(+)-(4-Methyl-[2]paracyclo[2](5,8)quinolinophan-2-yl)phenylmethanol (R_p,*R*)-5 and (R_p,*S*)-5

Phenylmagnesium bromide (16 mL, 0.5 M in THF, 8.0 mmol) was added to a solution of the aldehyde (*R*)-**4** (0.60 g, 2.0 mmol) in anhydrous THF (5 mL), and the mixture allowed to react at 25 °C for 1 min before being poured into a satd aqueous NH_4Cl (25 mL). After the usual work-up (see above), chromatography of the crude on SiO_2 (100 g, eluent 8:2 v/v petroleum ether/diethyl ether) allowed two white crystal products to be separated. The first eluted one (0.17 g, 23%) was identified as (R_p,*R*)-(−)-(4-methyl-[2]paracyclo[2](5,8)-quinolinophan-2-yl)phenylcarbinol on the basis of the following spectroscopic and analytical properties and on the basis of the observed NOE between the aromatic protons overlying the heterocyclic ring and the ortho protons of the phenyl group bonded to the stereogenic carbon.

(R_p,*R*)-**5** (100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 98:2 hexane/isopropanol): mp 171–172 °C; $[\alpha]_D^{29} = -250$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.59 (d, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 6.94–6.82 (AB system, J_{AB} = 7.3 Hz, 2H), 6.88 (s, 1H), 6.50–6.44 (AB system d, J_{AB} = 7.9 and 1.6 Hz, 2H), 6.28 (broad s, 1H), 5.78 (s, 1H), 5.63 (dd, *J* = 7.9 and 1.3 Hz, 1H), 5.26 (dd, *J* = 7.9 and 1.5 Hz, 1H), 4.34 (m, 1H), 3.81 (dd, *J* = 13.8 and 9.0 Hz, 1H), 3.29–3.05 (m, 4H), 3.00 (dt, *J* = 13.8 and 8.2 Hz, 1H), 2.54 (s, 3H), 2.45 (dt, *J* = 12.8 and 9.0 Hz, 1H); ^{13}C NMR δ 157.2, 147.7, 144.6, 143.6, 139.2, 138.8, 137.8, 137.3, 133.9, 133.0, 132.5, 131.4, 129.5, 128.7, 128.3, 128.0, 127.9, 127.2, 120.9, 74.5, 37.6, 35.1, 34.4, 31.9, 22.9; IR ($CHCl_3$) ν_{max}

3684, 3339 (broad), 3015, 2931–2852, 1591, 1413, 969, 704 cm^{-1}. Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45; H, 6.64; N, 3.69. Found: C, 85.32; H, 6.71; N, 3.57. The second eluted product (0.22 g, 30%) was assigned the structure of (R_p,*S*)-(+)-(4-methyl-[2]paracyclo-[2](5,8)-quinolinophan-2-yl)phenylcarbinol on the basis of its spectral and analytical characteristics and by the absence of any NOE between the protons of the phenyl group and the aromatic protons overlying the heterocyclic ring. (R_p,*S*)-**5** (100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 98:2 hexane/isopropanol): mp 98–99 °C; $[\alpha]_D^{29} = +225$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.39 (d, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.26 (m, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.87 (s, 1H), 6.83 (d, *J* = 7.3 Hz, 1H), 6.49 (tight AB system J_{AB} = 8.5 Hz, 2H), 6.26 (broad s, 1H), 5.89 (s, 1H), 5.74 (d, *J* = 7.8 Hz, 1H), 5.48 (d, *J* = 7.6 Hz, 1H), 4.37–4.31 (m, 1H), 3.83 (dd, *J* = 14.0 and 9.3 Hz, 1H), 3.19–2.98 (m, 5H), 2.62 (s, 3H), 2.56 (dt, *J* = 13.0 and 9.1 Hz, 1H); ^{13}C NMR δ 156.7, 147.7, 144.6, 143.4, 139.3, 138.9, 137.7, 137.2, 133.9, 132.9, 132.5, 131.3, 129.4, 128.5, 128.3, 128.3, 127.8, 127.8, 127.3, 120.6, 74.8, 37.6, 35.2, 34.4, 32.0, 22.8; IR ($CHCl_3$) ν_{max} 3684, 3339 (broad), 3015, 2931–2852, 1591, 1413, 969, 704 cm^{-1}. Elem. Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45; H, 6.64; N, 3.69. Found: C, 85.39; H, 6.55; N, 3.56.

4.5. (R_p,*R*)-(−)- and (R_p,*S*)-(+)-(4-Methyl-[2]paracyclo-[2](5,8)quinolinophan-2-yl)(naphth-1-yl)methanol, (R_p,*R*)-6 and (R_p,*S*)-6

They were obtained in the same way as the above phenylcarbinols except that 1-naphthylmagnesium bromide was used as the Grignard reagent. The first eluted product (0.14 g, 16%) was identified as (R_p,*R*)-(−)-(4-methyl-[2]paracyclo[2](5,8)quinolinophan-2-yl)(naphth-1-yl)carbinol on the basis of the following spectroscopic and analytical characteristics and on the basis of the observed NOE between the aromatic protons overlying the heterocyclic ring and the β- and *peri* protons of the naphthyl group. (R_p,*R*)-**6** (100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 98:2 hexane/isopropanol): mp 161–163 °C; $[\alpha]_D^{29} = -315$ (*c* 0.50, $CHCl_3$); ^{1}H NMR δ 8.48 (m, 1H), 7.91 (m, 2H), 7.70 (dd, *J* = 7.1 and 1.0 Hz, 1H), 7.57–7.47 (m, 3H), 6.96–6.80 (AB system, J_{AB} = 7.3 Hz, 2H), 6.80 (s, 1H), 6.56–6.50 (AB system, J_{AB} = 7.9 Hz, ^4J = 1.7 Hz, 2H), 6.38 (s, 1H), 6.37 (broad s, 1H), 5.92 (dd, *J* = 7.8 and 1.6 Hz, 1H), 5.30 (dd, *J* = 7.8 and 1.6 Hz, 1H), 4.48–4.40 (m, 1H), 3.79 (dd, *J* = 13.7 and 9.0 Hz, 1H), 3.29–2.97 (m, 5H), 2.54 (s, 3H), 2.45 (dt, *J* = 12.8 and 9.0 Hz, 1H); ^{13}C NMR δ 157.3, 148.2, 144.5, 139.5, 138.7, 138.2, 138.0, 137.3, 134.4, 134.0, 133.1, 132.4, 131.6, 131.3, 129.3, 129.0, 128.9, 128.8, 128.8, 126.9, 126.1, 125.7, 125.4, 124.7, 120.6, 73.5, 37.7, 35.2, 34.6, 31.5, 23.0; IR ($CHCl_3$) ν_{max} 3340 (broad), 3049, 3021, 2931–2856, 1590, 1507, 1228, 965 cm^{-1}. Anal. Calcd for $C_{31}H_{27}NO$: C, 86.68; H, 6.34; N, 3.26. Found: C, 86.39; H, 6.41; N, 3.21.

The second eluted product (0.34 g, 40%) was identified as (R_p,*S*)-(+)-(4-methyl-[2]paracyclo[2](5,8)quinolinophan-2-yl)(naphth-1-yl)carbinol by its spectral and analytical properties and by the absence of any NOE between the naphthyl protons and the aromatic protons of cyclophane moiety. (R_p,*S*)-**6** (100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 98:2 hexane/isopropanol): mp 157–159 °C; $[\alpha]_D^{29} = +245$ (*c* 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (m, 1H), 7.89–7.82 (m, 2H), 7.49–7.42 (m, 4H), 7.00–6.86 (AB system, J_{AB} = 7.3 Hz, 2H), 6.86 (s, 1H), 6.60 (s, 1H), 6.51 (AB system, J_{AB} = 8.4 Hz, 2H), 6.30 (broad s, 1H), 5.77 (d, *J* = 7.5 Hz, 1H), 5.51 (d, *J* = 7.5 Hz, 1H), 4.44–4.38 (m, 1H), 3.84 (dd, *J* = 13.9 and 9.2 Hz, 1H), 3.20–2.99 (m, 5H), 2.60–2.53 (m, 1H), 2.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.2, 147.8, 144.7, 139.4, 139.0, 138.4, 137.8, 137.3, 134.2, 133.9, 133.0, 132.5, 131.5, 131.3, 129.5, 128.8, 128.7, 128.3, 127.9, 126.7, 126.2, 125.6, 125.3, 124.5, 120.4, 73.5, 37.6, 35.2, 34.4, 32.0, 22.8; IR ($CHCl_3$) ν_{max} 3335 (broad), 3011, 2932–2856, 1591, 1507, 1435, 965 cm^{-1}. Anal. Calcd for $C_{31}H_{27}NO$: C, 86.68; H, 6.34; N, 3.26. Found: C, 86.51; H, 6.44; N, 3.17.

4.6. (R_p,*S*)-(+)- and (R_p,*R*)-(−)-2-Methyl-1-(4-methyl-[2]paracyclo[2](5,8)quinolinophan-2-yl)propanol (R_p,*S*)-7 and (R_p,*R*)-7

The products were prepared from aldehyde (*R*)-**4** (0.91 g, 3.0 mmol) as described above using isopropylmagnesium bromide as the alkylating reagent. Chromatography of the crude product on silica gel (eluent, 7:3 petroleum ether/ethyl acetate) allowed the reduction product 2-hydroxymethyl-4-methyl-[2]paracyclo-[2](5,8)-quinolinophane (0.51 g, 56%) to be separated from the diastereomeric mixture of the addition products. The two diastereomeric adducts (0.24 g, 23%) were separated by preparative HPLC on a 50 cm × 10mm WATER Delta-pak, prepPak C18 column by eluting with 7:3 MeCN/H_2O mixture. The first eluted product (0.1 g, 9%) was assigned the structure of (R_p,*S*)-(+)-2-methyl-1-(4-methyl-[2]paracyclo[2](5,8)quinolino-phan-2-yl)propanol according to the following spectroscopic and analytical properties. (R_p,*S*)-**7** (100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 99:1 hexane/isopropanol): mp 182–184 °C (from MeCN); $[\alpha]_D^{27} = +16$ (*c* 0.50, $CHCl_3$); ^{1}H NMR δ 7.01 (s, 1H), 6.91–6.89 (AB system, J_{AB} = 7.2 Hz, 2H), 6.46 (s, 2H), 5.71 (d, *J* = 7.8 Hz, 1H), 5.44 (d, *J* = 7.8 Hz, 1H), 5.14 (broad s, 1H), 4.75 (d, *J* = 3.4 Hz, 1H), 4.24 (m, 1H), 3.85 (dd, *J* = 13.9 and 9.3 Hz, 1H), 3.16 (dd, *J* = 12.8 and 10.1 Hz, 1H), 3.11–2.88 (m, 4H), 2.72 (s, 3H), 2.56 (dt, *J* = 13.0 and 9.1 Hz, 1H), 2.12 (m, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR δ 157.6, 148.0, 144.1, 139.4, 139.0, 137.7, 137.2, 133.7, 132.7, 132.5, 131.2, 129.2, 128.2, 127.8, 120.3, 76.4, 37.7, 35.3, 34.7, 34.4, 32.0, 23.0, 19.9, 15.4; IR ($CHCl_3$) ν_{max} 3374 (broad), 3022, 2967–2856, 1593, 1434, 1226, 1018 cm^{-1}. Anal. Calcd for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.28; H, 7.77; N, 4.10.

The second eluted product (72 mg, 7%) was identified as (R_p,*R*)-(−)-2-methyl-1-(4-methyl-[2]paracyclo[2](5,8)quinolinophan-2-yl)propanol on the basis of the following spectroscopic and analytical properties and by the positive NOE between the protons of the isopropyl group

and the aromatic protons of the cyclophane moiety. (R_p,R)-**7** (100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 99:1 hexane/isopropanol): mp 118–120 °C (from MeCN); $[\alpha]_D^{29} = -19$ (*c* 0.50, $CHCl_3$); ^{1}H NMR δ 7.00 (s, 1H), 6.90–6.80 (AB system, J_{AB} = 7.2 Hz, 2H), 6.52 (s, 2H), 5.77–5.44 (AB system, J_{AB} = 7.9 Hz, 2H), 5.28 (broad s, 1H), 4.64 (d, *J* = 3.8 Hz, 1H), 4.32–4.24 (m, 1H), 3.87 (dd, *J* = 14.0 and 9.1 Hz, 1H), 3.17 (dd, *J* = 13.0 and 9.7 Hz, 1H), 3.13–2.95 (m, 4H), 2.73 (s, 3H), 2.58 (dt, *J* = 13.0 and 9.0 Hz, 1H), 2.36–2.24 (m, 1H), 1.25 (d, *J* = N6.9 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 157.7, 148.3, 143.8, 139.5, 138.7, 138.0, 137.2, 133.8, 132.9, 132.5, 131.3, 129.3, 128.7, 128.5, 120.4, 76.1, 37.8, 35.4, 34.8, 34.5, 31.5, 23.1, 20.0, 16.1; IR ($CHCl_3$) ν_{max} 3355 (broad), 3036, 3008, 2967–2836, 1593, 1434, 1017 cm^{-1}. Elem. Anal. Calcd for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.62; H, 7.95; N, 4.18.

4.7. (R_p,S)-(+)- and (R_p,R)-(−)-2,2-dimethyl-1-(4-methyl-[2]paracyclo[2](5,8)quinolinophan-2-yl)propanol (R_p,S)-8 and (R_p,R)-8

The products were prepared from the (R_p)-aldehyde (1.0 g, 3.3 mmol) and 1 M *tert*-butylmagnesium chloride (1.0 M in THF, 3.5 mL, 3.5 mmol) in THF (5.0 mL). After the usual work-up, the crude product was dissolved in pyridine (5 mL), benzoyl chloride (1.5 equiv) added and the mixture made to react at 60 °C for 2 h. Most of the pyridine was evaporated at reduced pressure. The residue was taken up with diethyl ether (20 mL) and the ethereal solution was washed with satd aqueous $NaHCO_3$ and dried with Na_2SO_4. After solvent evaporation, chromatography of the residue on SiO_2 (eluent, 95:5 petroleum ether/diethyl ether) allowed a diastereomeric mixture of benzoates to be obtained, which were separated by preparative HPLC (50 cm × 10 mm Water Delta-pak, prepPak C18 column, eluent 84:16 v/v MeCN/H_2O mixture). The first eluted product (0.12 g) was dissolved in THF (5 mL), 40% aq tetrabutylammonium hydroxide (0.5 mL) then added and the mixture allowed to react at 60 °C for 30 min before H_2O (30 mL) was added. The mixture was extracted with diethyl ether (2 × 20 mL) and the collected organic phases dried over Na_2SO_4. After solvent evaporation, the remaining crude product was purified by chromatography on SiO_2 (eluent 9:1 petroleum ether/diethyl ether) with 82 mg (95%) of a white crystalline solid collected and identified as (R_p,S)-(+)-2,2-dimethyl-1-(4-methyl-[2]paracyclo[2](5,8)quinolinophan-2-yl)propanol on the basis of the following spectroscopic and analytical characteristics.

(R_p,S)-**8** (23% from (R_p)-**4**, 100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 99:1 hexane/isopropanol): mp 128–130 °C; $[\alpha]_D^{25} = +27$ (*c* 0.50 $CHCl_3$); ^{1}H NMR δ 7.02 (s, 1H), 6.92–6.81 (AB system, J_{AB} = 7.2 Hz, 2H), 6.47 (s, 2H), 5.74 (d, *J* = 7.7 Hz, 1H), 5.46 (d, *J* = 7.7 Hz, 1H), 5.10 (broad s, 1H), 4.49 (s, 1H), 4.23 (m, 1H), 3.87 (dd, *J* = 14.1 and 9.3 Hz, 1H), 3.17 (dd, *J* = 12.8 and 9.6 Hz, 1H), 3.15–2.80 (m, 4H), 2.74 (s, 3H), 2.57 (dt, *J* = 12.9 and 9.2 Hz, 1H), 0.95 (s, 9H); ^{13}C NMR δ 156.8, 148.2, 142.8, 139.3, 139.2, 137.7, 137.1, 133.7, 132.5, 132.4, 131.2, 129.1, 128.2, 127.8, 122.7, 80.0, 37.7, 36.1, 35.3, 34.4, 31.9, 26.1, 23.0; IR ($CHCl_3$) ν_{max} 3693, 3397 (broad), 3027, 2959–2870, 1591, 1434, 1221, 1066, 867 cm^{-1}. Anal. Calcd for $C_{25}H_{29}NO$: C, 83.52; H, 8.13; N, 3.90. Found: C, 83.37; H, 7.99; N, 3.81. The (*S*)-configuration of the stereogenic carbon was ascertained by the absence of any NOE between the protons of the *tert*-butyl group and the aromatic protons of the cyclophane moiety.

In the same way, the hydrolysis of the second eluted benzoate provided a pure product that was identified as (R_p,R)-(−)-2,2-dimethyl-1-(4-methyl-[2]paracyclo-[2]-(5,8)quinolinophan-2-yl)propanol on the basis of its spectroscopic and analytical characteristics and of the observed NOE between the aromatic protons overlooking the heterocyclic ring and those of the *tert*-butyl group.

(R_p,R)-**8** (19% from (R_p)-**4**, 100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 99:1 hexane/isopropanol): mp 72–75 °C; $[\alpha]_D^{25} = -50$ (*c* 0.50, $CHCl_3$); ^{1}H NMR δ 7.00 (s, 1H), 6.89–6.78 (AB system, J_{AB} = 7.2 Hz, 2H), 6.56 (AB system, J_{AB} = 8.7 Hz, 2H), 5.82 (d, *J* = 7.8 Hz, 1H), 5.49 (d, *J* = 7.8 Hz, 1H), 5.04 (s, 1H), 4.42 (s, 1H), 4.3 (m, 1H), 3.87 (dd, *J* = 13.7 and 9.1 Hz, 1H), 3.18 (dd, *J* = 12.5 and 9.8 Hz, 1H), 3.11–2.98 (m, 4H), 2.72 (s, 3H), 2.64 (dt, *J* = 12.7 and 9.0 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR δ 156.8, 148.2, 142.8, 139.3, 139.2, 137.7, 137.1, 133.7, 132.5, 132.4, 131.2, 129.1, 128.2, 127.8, 122.7, 80.0, 37.7, 36.1, 35.3, 34.4, 31.9, 26.1, 23.0; IR ($CHCl_3$) ν_{max} 3673, 3380 (broad), 3064, 2962–2869, 1590, 1434, 1232, 1069 cm^{-1}. Anal. Calcd for $C_{25}H_{29}NO$: C, 83.52; H, 8.13; N, 3.90. Found: C, 83.27; H, 8.20; N, 3.61.

4.8. (R_p)-(−)-2-Methoxycarbonyl-4-methyl-[2]paracyclo[2](5,8)quinolinophane (*R*)-10

Aqueous hydrogen peroxide (35%, 0.21 mL, 2.5 mmol) was slowly added to a solution of the aldehyde (*R*)-**4** (0.25 g, 0.83 mmol) in formic acid (1 mL), at 0 °C. The initial red colour changed to yellow ochre, while the mixture was kept at 4 °C overnight. The mixture was extracted with $CHCl_3$ and the aqueous phase was acidified until pH 5–6, before being extracted again with $CHCl_3$ (3 × 25 mL). The collected organic phases were dried over Na_2SO_4 and the solvent evaporated at reduced pressure. A portion (100 mg) of the remaining yellow solid (250 mg) was chromatographed on SiO_2 (eluent, ethyl acetate) to give a white crystal product identified as (*R*)-(−)-4-methyl-[2]paracyclo[2](5,8)quinolinophanecarboxylic acid (*R*)-**9** (100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 97:3 hexane/isopropanol) by the following spectroscopic and analytical data: mp 137–138 °C (from diethyl ether); $[\alpha]_D^{25} = -27.6$ (*c* 0.10, $CHCl_3$); ^{1}H NMR δ 8.03 (s, 1H), 7.06–6.96 (AB system, J_{AB} = 7.5 Hz, 2H), 6.54 (s, 2H), 5.66 (d, *J* = 7.7 Hz, 1H), 5.44 (d, *J* = 7.6 Hz, 1H), 4.28–4.16 (m, 1H), 3.94 (dd, *J* = 14.2 and 10.2 Hz, 1H), 3.26–3.04 (m, 5H), 2.86 (s, 3H), 2.70–2.57 (m,1H). IR ($CHCl_3$) ν_{max} 3690, 1723 cm^{-1} (C═O);

Elem. Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.29; H, 6.13; N, 4.46. The crude product (150 mg) was dissolved in diethyl ether (5 mL) and a freshly prepared solution of diazomethane in diethyl ether was added dropwise until a pale yellow solution was obtained. The solvent was cautiously evaporated at reduced pressure and the remaining crude purified by chromatography on SiO_2 (eluent, petroleum ether/diethyl ether 6:4 v/v). The collected white solid (135 mg, 82% with respect to the starting aldehyde) was identified as (R_p)-(−)-2-methoxycarbonyl-4-methyl-[2]paracyclo-[2](5,8)quinolinophane as follows: mp 161–162 °C; $[\alpha]_D^{20} = -22.6$ (*c* 0.67, $CHCl_3$); ^{1}H NMR δ 7.90 (s, 1H), 6.96–6.87 (AB system, J_{AB} = 7.2 Hz, 2H), 6.54–6.49 (AB system, d J_{AB} = 7.9 and 1.5 Hz, 2H), 5.70 (dd, J = 7.7 and 1.1 Hz, 1H), 5.42 (dd, J = 7.7 and 1.5 Hz, 1H), 4.42–4.36 (m, 1H), 4.08 (s, 3H), 3.88 (dd, J = 14.1 and 9.0, 1H), 3.21–3.00 (m, 5H), 2.78 (s, 3H), 2.58 (dt, J = 13.0 and 9.0 Hz, 1H); ^{13}C NMR δ 166.6, 150.1, 144.4, 144.0, 141.0, 139.7, 137.9, 136.8, 135.8, 132.9, 132.5, 131.3, 131.1, 128.7, 128.5, 123.1, 52.8, 37.7, 35.2, 34.5, 31.8, 22.9; IR ($CHCl_3$) 1718 cm^{-1} (C=O). Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.26. Found: C, 79.82; H, 6.24; N, 4.19.

4.9. (R_p)-(−)-Diphenyl(4-methyl-[2]paracyclo[2](5,8)-quinolinophan-2-yl)methanol (R_p)-11

Phenylmagnesium bromide (1.0 mL, 1.0 M in THF, 1.0 mmol) was added to a solution of the above ester (0.13 g, 0.40 mmol) in anhydrous THF (10 mL) at 25 °C under a nitrogen atmosphere. The mixture was made to react for 3 h and then water (25 mL) was added. After the usual work-up, chromatography of the crude product on SiO_2 (eluent, petroleum ether/diethyl ether 8:2) allowed a white crystalline solid to be collected, which was identified as (*R*)-(−)-diphenyl(4-methyl-[2]paracyclo[2](5,8)quinolinophan-2-yl)carbinol (153 mg, 84%, 100% ee by HPLC analysis, 0.46 × 25 cm CHIRACEL ODH column, 98:2 hexane/isopropanol) on the basis of the following spectral and analytical data: mp 211–212 °C (diethyl ether); $[\alpha]_D^{27} = -24.0$ (*c* 0.46, $CHCl_3$); ^{1}H NMR δ 7.6 (m, 2H), 7.4 (m, 2H), 7.32–7.25 (m, 7H), 7.00 (s, 1H), 6.95–6.85 (AB system, J_{AB} = 7.3 Hz, 2H), 6.46 (s, 2H), 5.48–5.34 (AB system, J_{AB} = 7.8 Hz, 2H), 4.29–4.23 (m, 1H), 3.85 (dd, J = 13.9 and 9.0, 1H), 3.16 (dd, J = 13.0 and 9.6 Hz, 1H), 3.10–2.94 (m, 4H), 2.66 (s, 3H), 2.52 (dt, J = 13.0 and 9.0 Hz, 1H); ^{13}C NMR δ 159.3, 147.3, 146.4, 146.3, 144.1, 139.3, 138.9, 137.7, 137.2, 134.2, 133.1, 132.5, 131.3, 129.2, 128.4, 128.2, 128.1, 128.0, 127.9, 127.3, 127.3, 122.3, 80.6, 37.7, 35.2, 34.3, 31.9, 23.1; IR ($CHCl_3$) 3313 cm^{-1} (broad, OH). Anal. Calcd for $C_{33}H_{29}NO$: C, 87.00; H, 6.42; N, 3.07. Trovato: C, 87.15; H, 6.47; N, 2.98.

4.10. General procedure for the stereoselective addition of diethylzinc to aldehydes

Diethylzinc (3.3 mL, 0.1 M in toluene, 3.3 mmol) was added by a syringe to a solution of (***S***)-(−)-**1** (20 mg, 0.066 mmol) in dry toluene (3 mL) under nitrogen at 20 °C and the mixture allowed to react for 20 min. The aldehyde (0.66 mmol) was added and the mixture was made to react at 0 °C for the time reported in the tables. Saturated aqueous NH_4Cl was added (10 mL) and the mixture extracted with diethyl ether (3 × 20 mL). The collected organic phases were washed with water, dried over Na_2SO_4 and analyzed by GLC, after suitable dilution, under the same conditions as those reported in the literature.[36] Ministero dell'Istruzione, Università e Ricerca (MIUR) and to the University of Perugia (COFIN 2004, contract no. 2004033322) for financial support.

References

1. Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886.
2. Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.
3. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856.
4. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69.
5. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823–2824.
6. Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841–842.
7. Li, M.; Zhu, X.-Z.; Yuan, K.; Cao, B.-X.; Hou, X.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 219–222.
8. Bolm, C.; Hermanns, N.; Kesselgruber, M.; Hildebrand, J. P. *J. Organomet. Chem.* **2001**, *624*, 157–161.
9. Bolm, C.; Muñiz-Fernández, K.; Seger, A.; Raabe, G.; Günther, K. *J. Org. Chem.* **1998**, *63*, 7860–7867.
10. Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444–445.
11. Nicolosi, G.; Patti, A.; Morrone, R.; Piattelli, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1639–1642.
12. Deng, W.-P.; Hou, X.-L.; Dai, L.-X. *Tetrahedron: Asymmetry* **1999**, *10*, 4689–4693.
13. Malézieux, B.; Andrés, R.; Gruselle, M.; Rager, M.-N.; Thorimbert, S. *Tetrahedron: Asymmetry* **1999**, *10*, 3253–3257.
14. Malfait, S.; Pélinski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2595–2610.
15. Uemura, M.; Miyake, R.; Nakayama, K.; Shiro, M.; Hayashi, Y. *J. Org. Chem.* **1993**, *58*, 1238–1244.
16. Watanabe, M.; Araki, S.; Butsugan, Y.; Uemura, M. *J. Org. Chem.* **1991**, *56*, 2218–2224.
17. Bräse, S.; Dahmen, S.; Höfener, S.; Lauterwasser, F.; Kreis, M.; Ziegert, R. E. *Synlett* **2004**, 2647–2669.
18. Wu, X.-W.; Zhang, T.-Z.; Yuan, K.; Hou, X.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 2357–2365.
19. Höfener, S.; Lauterwasser, F.; Bräse, S. *Adv. Synth. Catal.* **2004**, *346*, 755–759.
20. Danilova, T. I.; Rozenberg, V. I.; Starikova, Z. A.; Bräse, S. *Tetrahedron: Asymmetry* **2004**, *15*, 223–229.
21. Danilova, T. I.; Rozenberg, V. I.; Sergeeva, E. V.; Starikova, Z. A.; Bräse, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2013–2019.
22. Danilova, T. I.; Rozenberg, V. I.; Vorontsov, E. V.; Starikova, Z. A.; Hopf, H. *Tetrahedron: Asymmetry* **2003**, *14*, 1375–1383.
23. Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940–5941.
24. Dahmen, S.; Bräse, S. *Chem. Commun.* **2002**, 26–27.
25. Wu, X.-W.; Hou, X.-L.; Dai, L.-X.; Tao, J.; Cao, B.-X.; Sun, J. *Tetrahedron: Asymmetry* **2001**, *10*, 529–532.
26. Rozenberg, V. I.; Antonov, D. Y.; Zhuravsky, R. P.; Vorontsov, E. V.; Khrustalev, V. N.; Ikonnikov, N. S.;

Belokon, Y. N. *Tetrahedron: Asymmetry* **2000**, *11*, 2683–2693.
27. Ruzziconi, R.; Piermatti, O.; Ricci, G.; Vinci, D. *Synlett* **2002**, 747–750.
28. Cipiciani, A.; Fringuelli, F.; Mancini, V.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. *J. Org. Chem.* **1997**, *62*, 3744–3747.
29. Ricci, G.; Ruzziconi, R.; Giorgio, E. *J. Org. Chem.* **2005**, *70*, 1011–1018.
30. Ricci, A.; Taddei, M. *Synthesis* **1986**, 633–635.
31. Cipiciani, A.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. *J. Org. Chem.* **2002**, *67*, 2665–2670.
32. Fringuelli, F.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. *Chem. Lett.* **2000**, 38–39.
33. Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036.
34. Brandt, P.; Hedberg, C.; Lawoon, K.; Pinho, P.; Andersson, P. G. *Chem. Eur. J.* **1999**, *5*, 1692–1699.
35. Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998–9006.
36. Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327–6335.
37. Chelucci, G.; Soccolini, F. *Tetrahedron: Asymmetry* **1992**, *3*, 1235–1238.
38. Ishizaki, M.; Fujita, K.-i.; Shimamoto, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 411–424.
39. Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205–207.
40. Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309–6318.
41. Waters, J. F.; Sutter, J. K.; Meador, M. A. B.; Baldwin, L. J.; Meador, M. A. *J. Polym. Sci., Part A: Polym. Chem.* **1991**, *29*, 1917–1924.
42. Falk, H.; Reich-Rohrwig, P.; Schlögl, K. *Tetrahedron* **1970**, *26*, 511–527.