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Invited review

Dendrizymes: Expanded ligands for enantioselective catalysis

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Abstract

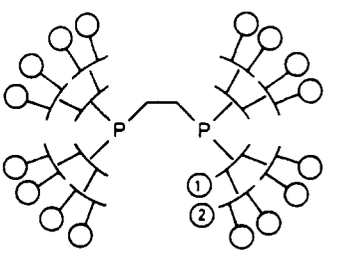
Dendrizymes are a new class of expanded ligands, designed for enantioselective catalysis with transition metal complexes. These expanded ligands consist of a strongly binding chelate core, which is surrounded by space-filling dendrimer substituents, built-up by branching units and optically active groups. In a complex of such a dendrimer ligand a reaction is supposed to take place in the same way as in the pocket of an enzyme.

Keywords: Dendrizymes; Enantioselective catalysis; Expanded ligands; Transition metal complexes

1. Introduction and concept

Most of the optically active chelate phosphines used in enantioselective transition metal catalysts [1,2], such as diop [3,4], prophos [5], chiraphos [6], bppm [7], bppfa [8], norphos [9,10], pyrphos [11] or binap [12], involve a chiral skeleton bearing two diphenylphosphine groups. The chiral information is transferred from the ligand to the catalytically active metal centre via the arrangement of the phenyl rings of the diphenylphosphine groups (axial–equatorial face–edge exposed arrangement). Owing to the limited size of the diphenylphosphine groups, long range effects are not possible with these conventional ligands, although they are extremely effective in a variety of types of reaction [1,2].

The concept of using expanded phosphines represents a new approach to increasing the size of optically active phosphines. The expanded phosphines should contain a PP chelate skeleton, e.g. the $P-CH_2-CH_2-P$ moiety derived from $Cl_2P-CH_2-CH_2-PCl_2$, and several layers attached to the P atoms (Scheme 1). The PP backbone should ensure a strong chelate coordination to the central metal atom of a catalyst. The layers should be made up of non-chiral groups (constructional units) or of chiral groups (functional units) designated 1 and 2 respectively in Scheme 1. When branching elements are used, the next layer will contain twice the number of units of the preceding layer (Scheme 1). By multiple repetition of such layers an expansion will result, giving space-filling dendrimer ligands. The final layer, the "edge" of the molecule, may easily be built up from



Scheme 1.

enantiomerically pure components. In this way, it should be possible to vary the chiral shape of the surroundings of the P atoms of a PP skeleton over a wide range. When the species is coordinated in a catalyst, a modification of the optical induction in enantioselective reactions with respect to small ligands is expected. Because of the space-filling nature of the expanded ligands the chiral information should be forced towards the pocket of the catalyst, in which the enantioselective reaction takes place. For "anchor" ligands or "long-arm" ligands [13–15], without this space-filling property, this is not necessarily the case: In such systems the linear parts of the ligand might dangle away from the reaction centre without interacting with the substrate.

Expansion of molecules by successive addition of layers to a central unit is at the core of the concept of dendritic growth. In dendrimer synthesis the primary goal was for a long time the construction of large molecules. Recently, interest in dendrimer chemistry shifted to functionalities and functions, as outlined in a

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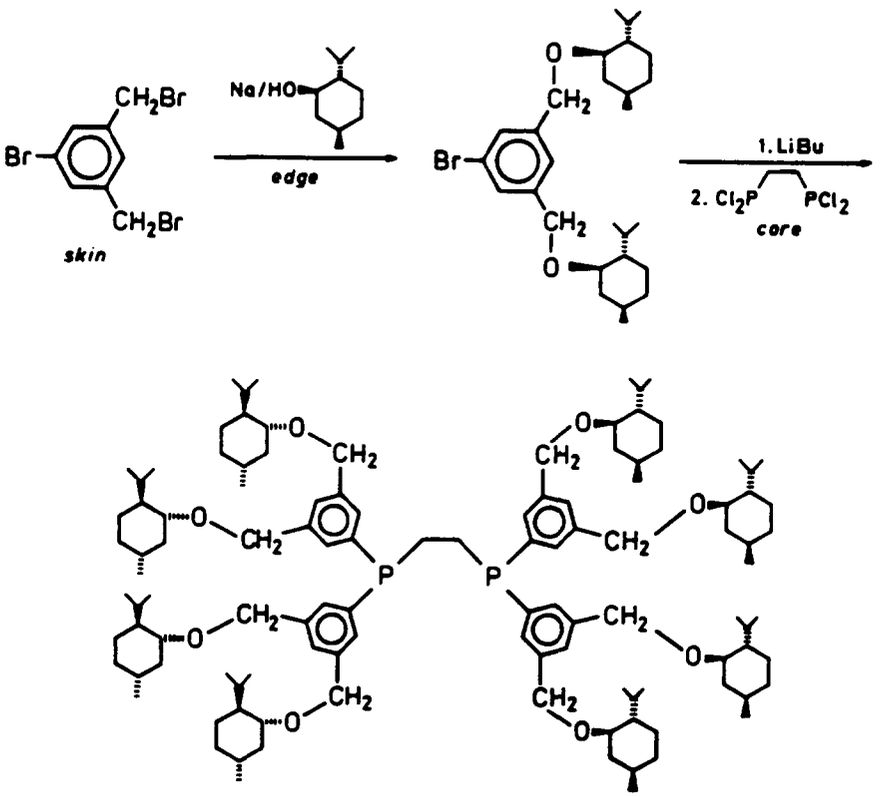
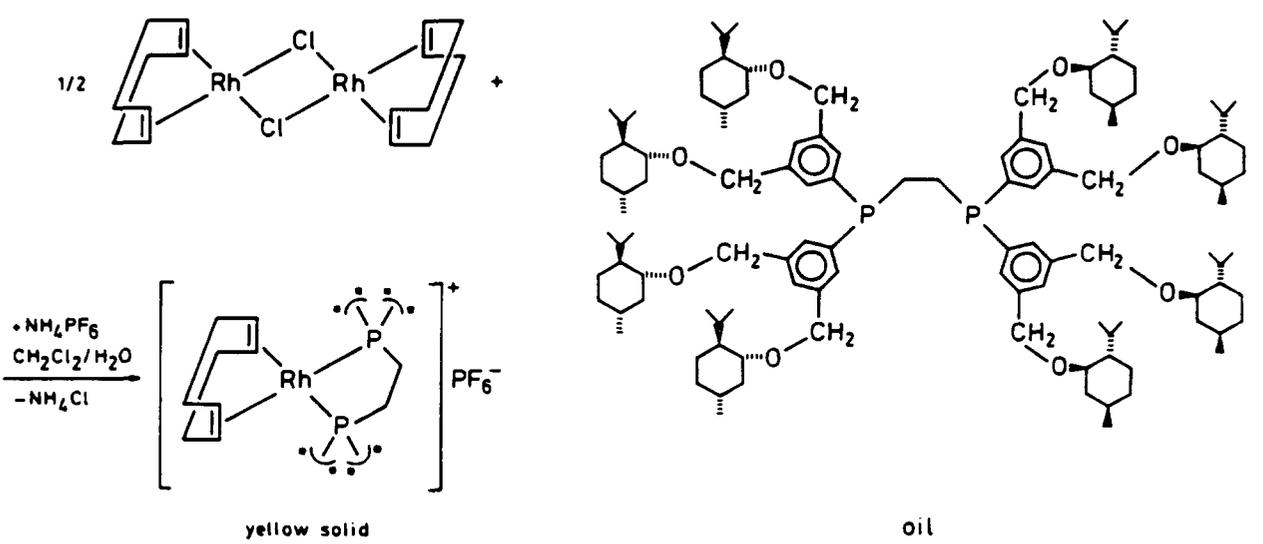


Scheme 2.

recent review by Vögtle and coworkers [16]. Most of the new dendrimers include a multitude of functionalities to obtain multiple effects, e.g. in redox systems [17] and light-harvesting systems [18]. The present approach is different. The functionality should be present in the dendrimer only once, in the center. It is at this site that a metal atom must catalyze a specific reaction. Together with the dendritic structure, such a set-up resembles the prosthetic group of an enzyme, and so we suggest the name dendrizymes for these systems. There are so many "zymes" around these days, such as enzymes and chemzymes, abzymes and ribozymes, why not dendrizymes?

2. First syntheses: products with unusual properties

The synthesis of a two-layer phosphine is shown in Scheme 2. Starting material is the commercially avail-



Scheme 3.

able compound 1-bromo-3,5-dimethylbenzene, the bromination of which with *N*-bromosuccinimide by the Wohl–Ziegler procedure gives 1-bromo-3,5-di(bromomethyl)benzene. In the next step the bromo substituents at the benzylic positions are subjected to a Williamson ether synthesis by reaction with the Na derivative of the optically active alcohol (−)-menthol. A halogen–metal exchange between *n*-butyllithium with the aryl bromide gives an organolithium species, which reacts with bis(dichlorophosphino)ethane to give the two-layer phosphine, as shown in Scheme 2 [19].

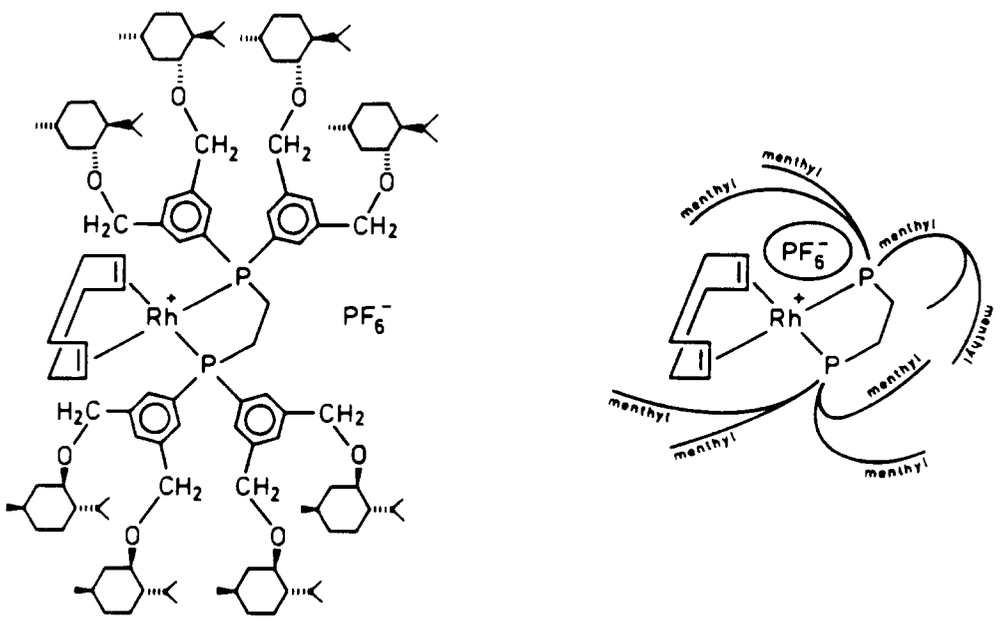
The two-layer phosphine consists of an inner layer of four 3,5-disubstituted arenes and an outer layer of eight menthyl groups. The substituents at the phosphorus atoms have a maximum radius of about 12 Å. In contrast, the optically active diphenylphosphino ligands end at a distance of about 6 Å from the phosphorus atom. With these conventional ligands, chirality transfer over longer distances is not possible.

The two-layer phosphine of Scheme 2 turned out to be an oil; all attempts to crystallize it failed. As the expanded phosphine is intended to go as a ligand into Rh(I) catalysts anyway, we tried to incorporate the oily species into a Rh complex in the hope that the complex would be a solid. For this purpose we chose $[Rh(cod)Cl]_2$ the reaction of which with the two-layer phosphine in dichloromethane–water containing NH_4PF_6 (according to the procedure described by Schrock and Osborn [20]) could be expected to give the complex $[Rh(cod)PP]PF_6$, where PP denotes the two-layer phosphine (Scheme 3). After evaporation of the dichloromethane a yellow solid was indeed obtained, and so the problem of converting the oily cocatalyst into a solid pre-catalyst was solved.

Purification of complexes such as $[Rh(cod)PP]PF_6$ involves washing with toluene or light petroleum, which removes purely organic material from the Rh(I) salts. Surprisingly, the complex $[Rh(cod)PP]PF_6$ dissolves not only in toluene but also in pentane or hexane. The parent compound $[Rh(cod)PP]PF_6$, in which PP is diphos (bis(diphenylphosphino)ethane), does not dissolve under these conditions. Thus the solubility is introduced by the expansion of the phosphine ligand.

Scheme 4 shows a tentative explanation of the strange solubility behavior. If it is assumed that the Rh(I) cation and the PF_6 anion form an ion pair and the long arms of the expanded phosphine close around it, orienting their hydrophobic menthyl groups to the outside, then a kind of "cell membrane" could be formed. Internally, the ion pair could be stabilized by ether dipoles, which are abundantly available. Although it is an ion pair in the interior, such a ball containing only menthyl groups on the outside could be soluble even in aliphatic hydrocarbons.

Support for this explanation comes from the following facts. The solubility in pentane is observed not only for the PF_6 salts but also for the CF_3SO_3 salts, not only for compounds with eight menthyl groups but also for those with eight bornyl groups, and not only for 3,5-disubstituted compounds but also for 2,4- and 2,5-disubstituted compounds. However, such solubility is not shown by the complexes $[Rh(cod)PP]PF_6$ containing unbranched PP ligands. Compounds having only four menthyl or four bornyl groups in the 2-, 3- and 4-positions of the arene in the first layer are insoluble in pentane, obviously because the hydrophobic menthyl or bornyl "surface" is no longer closed.



Scheme 4.

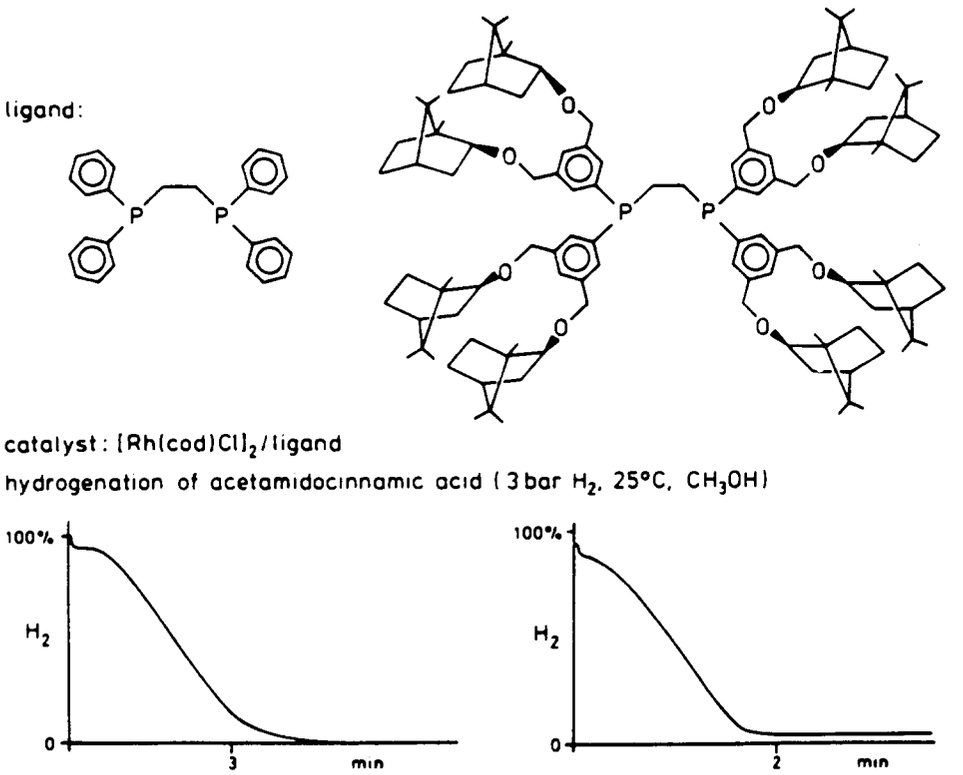


Fig. 1. Hydrogenation of acetamidocinnamic acid (H_2 at 3 bar; 25°C; CH_3OH) with in-situ catalysts $[Rh(cod)Cl]_2$–ligand. The percentage consumption of hydrogen is shown as a function of time.

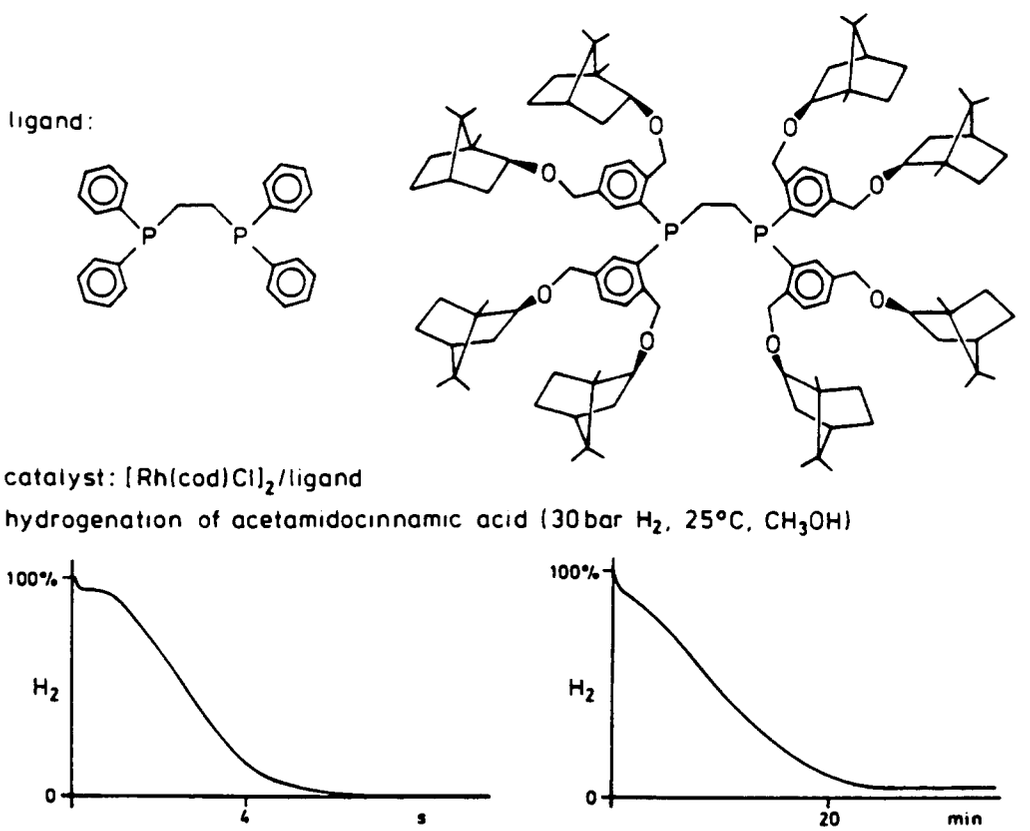


Fig. 2. Hydrogenation of acetamidocinnamic acid (H_2 of 30 bar; 25°C; CH_3OH) with in-situ catalysts $[Rh(cod)Cl]_2$–ligand. The percentage consumption of hydrogen is shown as a function of time.

It was mentioned above that the two-layer phosphine of Scheme 2 containing eight menthyl groups on the outside is an oil. Other menthyl compounds with other substitution patterns in the arene layer, and also expanded ligands derived from (−)-aminomethylpinane on the outside, are also oils. In contrast, all the expanded ligands derived from (−)-borneol turned out to be solids. For example the borneoxy derivative shown in Fig. 1 (see below) has a melting point of 73–76°C [19].

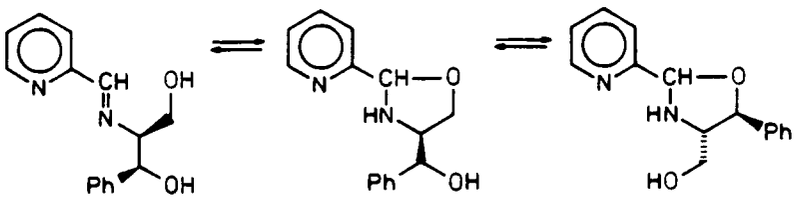
3. Rate and enantioselectivity of catalytic reactions

As stated above, the "surface" of menthyl groups conveys unexpected solubility properties to complexes of the type $[Rh(cod)PP]PF_6$. On the contrary this "cell membrane" of menthyl groups could be detrimental to catalysis if it prevented fast approach of the substrates to the transition metal at the center. Therefore a detailed kinetic study of the rate of a model catalysis was carried out with catalysts containing expanded ligands and the corresponding parent species [21].

As the model catalystic reaction we chose the hydrogenation of acetamidocinnamic acid in methanol at room temperature, which gives *N*-acetylphenylalanine. In-situ catalysts derived from the procatalyst $[Rh(cod)Cl]_2$ were used, and as the cocatalyst the respective parent or expanded ligand was added. The study showed that the rate of the catalytic hydrogenation was strongly dependent on the substitution pattern of the expanded ligand. Figs. 1 and 2 depict two extremes.

In Fig. 1 the cocatalysts are diphos and its expanded version containing eight borneoxy substituents in the benzylic positions of the 3,5-disubstituted arenes. These hydrogenations were carried out under 3 bar H_2 pressure. The percentage uptake of hydrogen as a function of time is shown at bottom left of Fig. 1 for diphos as the cocatalyst and at bottom right for its 3,5-expanded derivative. With diphos, hydrogen uptake is complete after a little more than 3 min, whereas for the expanded ligand it is already complete after a little less than 2 min. Thus in the hydrogenation of acetamidocinnamic acid with Rh catalysts the reaction is faster with the expanded phosphine than with the parent compound. For other substitution patterns, however, this may not be the case, as can be seen from Fig. 2.

The reaction involving use of the expanded ligand containing eight borneoxy substituents at the benzylic positions of the 2,5-disubstituted arenes is much slower



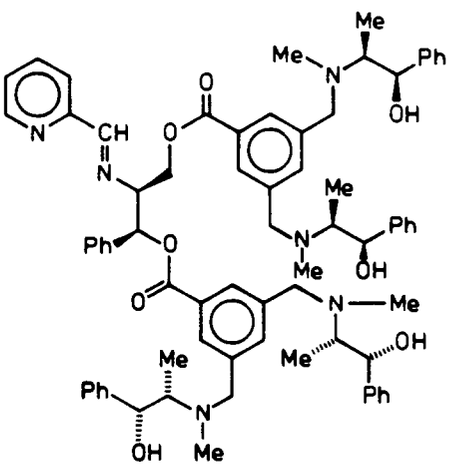


Fig. 3. Enantioselective cyclopropanation of styrene with ethyl diazoacetate catalyzed by in-situ catalysts $Cu(CF_3SO_3)$–expanded pyridinealdimines. The products were *cis*- and *trans*-ethyl 2-phenylcyclopropanecarboxylate.

than that involving the parent ligand, diphos. For diphos as cocatalyst the hydrogenation of acetamidocinnamic acid at 30 bar H_2 pressure is complete after a little more than 4 s, whereas for the expanded ligand it requires more than 20 min. This represents a retardation by a factor of about 300, and this effect is mainly due to the *ortho* substituents of the expanded ligand in Fig. 2. Similar retardations were also found for other expanded ligands with *ortho* substituents [21]. Thus the activity of catalysts containing expanded ligands depends on the substitution pattern. There are substitution patterns, such as the 3,5-disubstitution of the expanded ligand in Fig. 1, for which no retardation is seen and expansion definitely does not inhibit the catalytic activity.

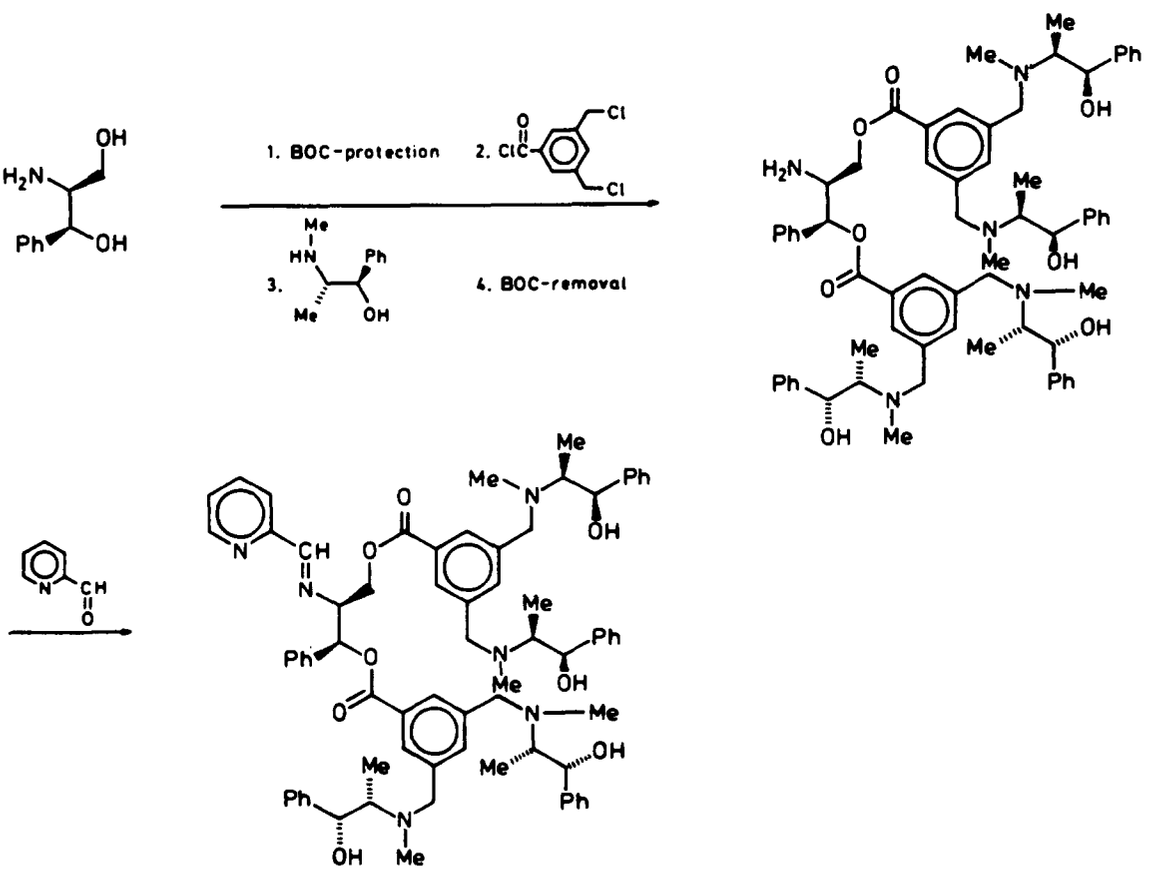
The enantioselectivities of reactions involving the new optically active expanded ligands were also studied. For this purpose the following reactions were used: (i) hydrogenation of acetamidocinnamic acid, (ii) hydrosilylation of acetophenone with diphenylsilane and (iii) cyclopropanation of styrene with ethyl diazoacetate. The enantioselectivities were usually extremely low [22–25], perhaps owing to the high flexibility of the substituents in most of the ligands prepared to date, but it can be seen from Fig. 3 that expansion can be helpful in improving the enantioselectivity in a particular case.

In the enantioselective cyclopropanation of styrene with ethyl diazoacetate to give ethyl 2-phenylcyclopropanecarboxylate, $Cu^{(I)}$ triflate modified by optically active pyridinealdimines was used as the catalyst. At the top of Fig. 3 are shown results for a pyridinealdimine derived from (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol in equilibrium with several cyclic aminoacetals. Optical induction was almost zero, being 2% ee (1*R*,2*S*) for the *cis* isomer and 1% ee (1*R*,2*R*) for the *trans* isomer of ethyl 2-phenylcyclopropanecarboxylate. At the bottom of Fig. 3 is shown an expanded ligand containing additional layers of a 3,5-disubstituted arene and terminal substituents derived from (1*R*,2*S*)-ephedrine, use of which under the same react conditions resulted in an enantioselectivity of 10% ee (1*S*,2*R*) for the *cis* isomer, and 8% ee (1*S*,2*S*) for the *trans* isomer, revealing that an increase in the size of the ligand can improve the enantioselectivity [24].

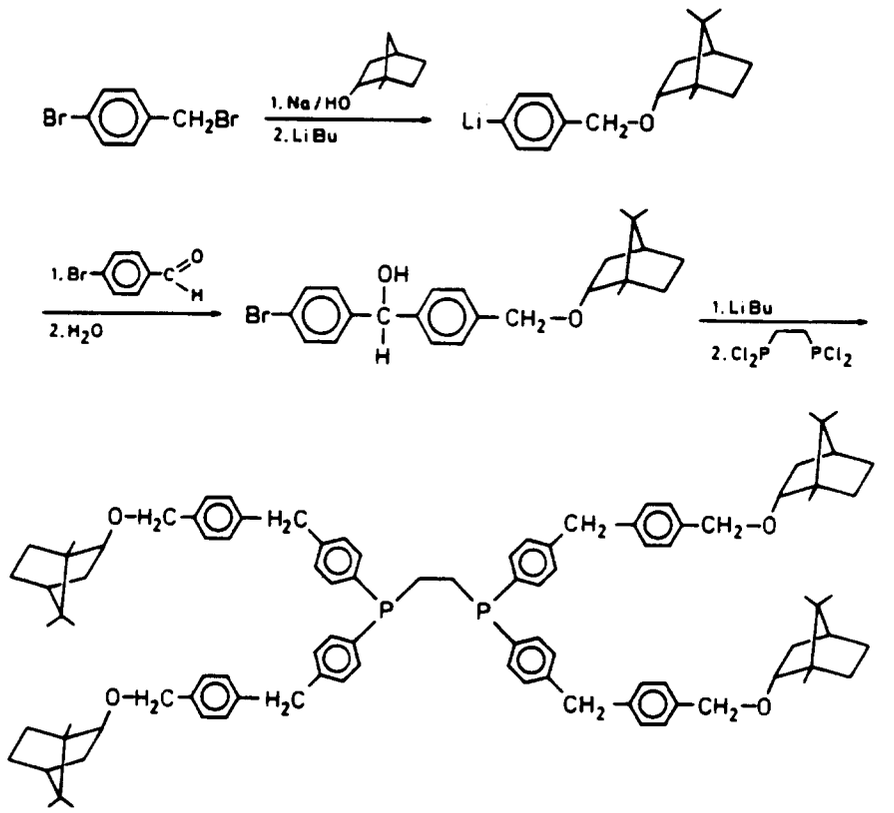
4. Additional syntheses

Several additional syntheses of expanded ligands have been carried out for both phosphorus ligands and nitrogen ligands. Two examples will show the strategies involved.

Scheme 5 shows the synthesis of the pyridinealdimine ligand used in the Cu-catalyzed cyclopropanation reaction depicted in Fig. 3. The starting material is the



Scheme 5.



Scheme 6.

commercially available optically active aminoalcohol (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol. The synthesis involves initial BOC protection of the amino group, followed by reaction of the alcoholic groups with the acid chloride of 3,5-bis(chloromethyl)benzoic acid and reaction of the product with (1*R*,2*S*)-ephedrine. Removal of the BOC gives the primary amine, shown on the right-hand side, which in the final step forms a Schiff base with pyridinealdehyde to give the expanded pyridinealdimine (Scheme 5, bottom) [24].

Scheme 6 shows the synthesis of a three-layer chelate phosphine which contains no branching units. 1-Bromo-4-bromomethylbenzene is first converted into the borneoxy ether at the benzylic position and then into the organolithium derivative, which is then treated with 4-bromobenzaldehyde to give a diarylcarbinol after hydrolysis.

Use of excess of butyllithium converts the diarylcarbinol function into a diphenylmethane moiety and, simultaneously, a halogen–metal exchange takes place. Finally, reaction with $Cl_2P–CH_2–CH_2–PCl_2$ gives the linear three-layer phosphine [25].

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