Preparation of Dipyridylmethane Ligands with Pseudo-C_2 Symmetry. Grafting on Polystyrenes via Transformation to Phenolic Derivatives

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Received May 6, 1994[⊗]

Efficient grafting of dipyridylmethane ligands on highly cross-linked as well as gel-type chloromethylated polystyrenes has been achieved using phenolic derivatives of the ligands. In this way, chiral polymer-supported ligands with pseudo-C_2 symmetry were obtained. The synthesis of the ligands and their grafting under mild conditions are described, as well as the preparation of monomeric models. During reduction of 6,6′-(2,2-dimethyl-1-oxopropyl) derivatives with sodium borohydride, the *R,S* isomers were unexpectedly formed with high selectivity.

Introduction

Chiral ligands with nitrogen atoms as donors have in recent years attracted great interest for use in metal-catalyzed asymmetric synthesis.[1] Compared to their phosphorous counterparts, nitrogen-containing ligands exhibit higher stability and are often easier to prepare. A variety of pyridine compounds have been prepared in enantiomerically pure form and successfully applied in asymmetric reactions such as the rhodium-catalyzed hydrosilylation and the addition of diethylzinc to aldehydes.[2,3] The grafting of such ligands on insoluble supports constitutes an attractive technique, ensuring efficient recovery of the often expensive ligands and occasionally resulting in higher selectivity when used in metal-catalyzed reactions.[4] Chiral ligands grafted on solid supports also have certain application, especially column operation such as the chromatographic enantioseparation of organic compounds.[5]

Although methods exist for the grafting of bipyridine on cross-linked polystyrene,[6] we are not aware of any polymer-supported bipyridine with chiral substituents.[7] We have previously prepared 2,2′-dipyridylcarbinols and shown that these ligands can be grafted on chloromethylated polystyrenes under mild conditions.[8] However, the functional yields were not always acceptable, in particular when highly cross-linked resins were used. Thus, under conditions where grafting of the secondary alcohol on the 2% cross-linked gel-type resin SX 2 afforded 42% functional yield, merely 10 and 19% were obtained on SX 12 and macroporous XAD 4, respectively.[8] An analogous tertiary alcohol required considerably more drastic conditions to give acceptable yields even on SX 2.[9]

We were interested in grafting chiral derivatives of compound **1** in order to be able to explore the catalytic properties of polymeric metal complexes of this type of ligands. Due to the low reactivity of tertiary alcohols in the coupling with chloromethylated resins, more efficient methods were required. We have recently demonstrated that the introduction of pendant arms on the ligands is greatly facilitated by transformation into a phenolic derivative.[10] A survey of the methods used in the literature also revealed that phenols readily react with chloromethylated polystyrenes of various kinds, in particular under phase transfer conditions.[11] Analogously, hydroxypyridines[12] and hydroxyquinolines[13] have also been efficiently grafted.

In this paper the preparation of dipyridylmethane derivatives carrying chiral hydroxyalkyl groups and their immobilization on solid supports are described. Bipyridines with these chiral auxiliaries have previously been shown to promote highly enantioselective addition of diethylzinc to aldehydes.[14]

Results and Discussion

A nonchiral dipyridylmethane derivative containing a phenolic function, **2**, was prepared as well as two chiral derivatives with pseudo-C_2 symmetry, **3a** and **3b**, differ-

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1995.

(1) Tomioka, K. *Synthesis* **1990**, 541. Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497.

(2) For some recent examples of chiral pyridine ligands in asymmetric synthesis, see, for example: Nishiyama, H.; Yamaguchi, S.; Park, S.-B.; Itoh, K. *Tetrahedron: Asymmetry* **1993**, *4*, 143.

(3) Chelucci, G. *Gazz. Chim. Ital.* **1992**, *122*, 89.

(4) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. I* **1984**, 2887. Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *J. Chem. Soc., Perkin Trans. I* **1985**, 2615. Itsuno, S.; Wakasugi, T.; Ito, K.; Hirao, A.; Nakahama, A. *Bull. Chem. Soc. Jpn* **1985**, *58*, 1669.

(5) Davankov, V. A.; Navratil, J. D.; Walton, H. F. *Ligand Exchange Chromatography*; CRC Press: Boca Raton, FL, 1988. Moberg, C.; Norin, T.; Rákos, L.; Sjödin, K. *J. Chromatogr.* **1991**, *585*, 309.

(6) Card, R. J.; Neckers, D. C. *Inorg. Chem.* **1978**, *17*, 2345.

(7) A chiral monopyridine has been grafted by an analogous method: Brunner, H.; Brandl, P. *Z. Naturforsch.* **1992**, *47b*, 609.

(8) Elman, B.; Moberg, C. *J. Organomet. Chem.* **1985**, *294*, 117.

(9) Elman, B.; Moberg, C. *Tetrahedron* **1986**, *42*, 223.

(10) Adolfsson, H.; Wärnmark, K.; Moberg, C. *J. Org. Chem.* **1994**, *59*, 2004.

(11) N'Guyen, T. D.; Boileau, S. *Tetrahedron Lett.* **1979**, 2651. Nishikubo, T.; Iizava, T.; Kobayashi, K.; Okawara, M. *Makromol. Chem. Rapid Commun.* **1980**, *1*, 765. Nishikubo, T.; Iizawa, T.; Kobayashi, K.; Masuda, Y.; Okawara, M. *Macromolecules* **1983**, *16*, 722. Iizawa, T.; Nishikubo, T.; Masuda, Y.; Okawara, M. *Macromolecules* **1984**, *17*, 992. Fréchet, J. M. J. *Polym. Sci. Techn.* **1984**, *24*, 1. Itsuno, S.; Wakasugi, T.; Ito, K. *Polym. Bull.* **1988**, *20*, 435. Uno, H.; Takata, K.; Mizutani, Y. *React. Polym.* **1991**, *15*, 121.

(12) (a) Chessa, G.; Marangoni, G.; Pitteri, B. *React. Polym.* **1990**, *12*, 219. (b) Chessa, G.; Marangoni, G.; Pitteri, B.; Visentin, F. *React. Polym.* **1992**, *18*, 7.

(13) Moberg, C.; Weber, M.; Högberg, K.; Muhammed, M.; Nilsson, A.-C. *React. Polym.* **1990**, *12*, 31.

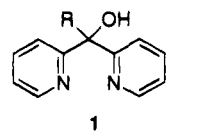
(14) Chelucci, G.; Soccolini, F. *Tetrahedron: Asymmetry* **1992**, *3*, 1235. Falorni, M.; Giacomelli, G. *Gazz. Chim. Ital.* **1992**, *122*, 339. Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191.

0022-3263/95/1960-1755$09.00/0

Table 1. Some Properties of the Polymers Used and Amount of Chloromethyl Groups in Polymers 4

polymer	type	particle size	amount of CH_2Cl groups (mmol/g)	
DVB	macroporous	ca. 15 μm	1.7	**4a**
Dynospheres	macroporous	10.3 μm (monodisperse)	1.8	**4b**
Bonopore	macroporous	ca. 100 μm	4.0	**4c**
SX-1	gel-type		4.9	**4d**

ing only in the nature of the alkyl group of the chiral substituent.



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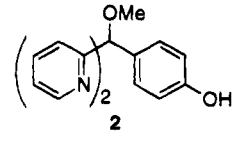

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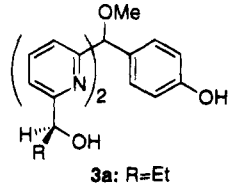
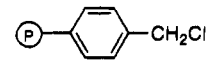


3a: R=Et
3b: R=*t*-Bu



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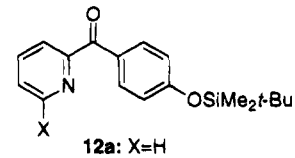
Four styrene–divinylbenzene polymers were selected for use as supports for grafting the pyridine ligands. These consisted of two highly cross-linked macroporous divinylbenzene resins with bead size of ca. 100 and 15 μm, respectively (referred to as Bonopore and DVB), a monodisperse resin with particle size 10.3 μm (Dynospheres), and a 1% cross-linked gel-type polymer (SX 1). These resins were chloromethylated[15] to yield polymers (**4**) with different amounts of chloromethyl groups, as shown in Table 1.

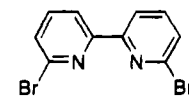
Preparation of Ligands. Ligand **2** was prepared via two different procedures. In the first procedure, di(2-pyridyl) ketone (**5**) was reacted with [4-(*tert*-butyldimethylsilyl)oxy)phenyl]magnesium bromide (**6**) to afford compound **7**, which in turn was methylated to give ether **8** along with a small amount of dimethylated compound **9** (Scheme 1). The desired product **2** was obtained by deprotection of the phenolic group in an overall yield (from **5**) of 62%.

In the second procedure, 2-lithiopyridine (**10**) was reacted with ethyl 4-(*tert*-butyldimethylsilyl)oxy)benzoate (**11**) to yield compound **7**,[16] which was subsequently transformed into ligand **2** as described above (Scheme 1). This method for the preparation of **2** resulted in a somewhat lower overall yield (41%) than that described above. During condensation, two minor products were obtained, identified by ^{1}H NMR spectroscopy as intermediate **12a** and coupling product **13**.

For the preparation of analogues bearing chiral groups in the 6-position of the pyridine nuclei, some different strategies were exploited. Thus, the bis-*N*-oxide of compound **8** (85% obtained using *m*-chloroperbenzoic acid) was treated with *N,N*-dimethylcarbamoyl chloride and trimethylsilyl cyanide to give a dinitrile (**14**, 85%), which was subsequently treated with ethylmagnesium



12a: X=H
12b: X=Br
12c: X=CH(OMe)Et
12d: X=CH(OMe)*t*-Bu



13

bromide to yield diketone **15** (63%, Scheme 2). Reduction of the keto groups using (−)-(*S*)-chlorodiisopinocampheylborane [(−)-Ipc_2BCl][17] afforded, after acidic workup, deprotected homochiral bisalcohol **3a** (94% yield). The alcohol, obtained as the major product from the reduction, was thought to have the *S,S* configuration, since this is the expected absolute configuration considering the mechanism of the reaction.[17] Further support for this assumption comes from the reduction of 6-bromo-2-acetylpyridine using the same reagent, which gave an alcohol with *S* absolute configuration.[18]

Alternative methods were used for the preparation of a chiral derivative containing chiral substituents with *tert*-butyl groups. The first method consisted of initial reaction of 2-bromo-6-lithiopyridine (**16**), obtained from 2,6-dibromopyridine,[19] with ethyl (4-(*tert*-butyldimethylsilyl)oxy)benzoate (**11**) to afford dipyridylmethane derivative **17** (71%) along with compounds **12b** and **13**. Methylation of the tertiary alcohol gave **18** (83% yield) together with a small amount of the dimethylated compound **19** (Scheme 3). The dibromide was treated with butyllithium followed by *2,2*-dimethylpropionitrile to give diketone **20** (83%), which was reduced, analogous to **15**, to yield alcohol **3b**. The absolute configuration of the major product is unknown. The workup procedures suggested for the reduction resulted in extensive loss of product,[17,20] as did also chromatography on silica gel.

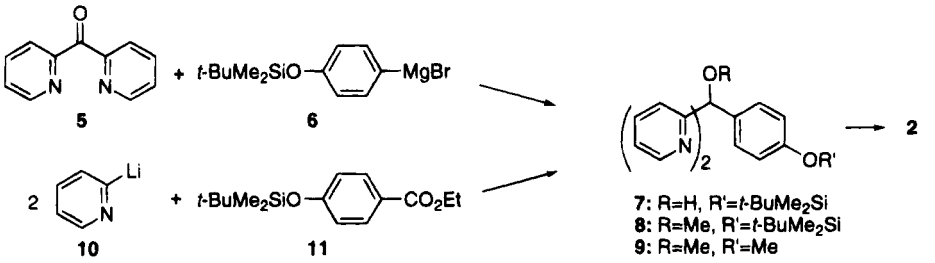
Compound **17** could also be prepared by reaction of bis-(6-bromo-2-pyridyl) ketone (**21**) with [4-(*tert*-butyldimethylsilyl)oxy)phenyl]lithium (**22**), obtained from reaction of the corresponding bromide with butyllithium, although in lower yield (44%).

The diastereoselectivity in the reduction of the ketones **15** and **20** was deduced by analysis of the ^{1}H NMR spectra of the products. The alcohols proved inconvenient for this purpose since the chemical shifts varied with the concentration of the solutions, probaly due to intermolecular hydrogen bonding. Therefore, **3a** and **3b** were methylated prior to analysis, to yield **23a** and **23b**, respectively. The ^{1}H NMR spectra of the tetraethers obtained were in agreement with those expected, with different chemical shifts for all protons of the two diastereotopic 6-(1-hydroxyalkyl)pyridine groups and an AA'BB' pattern for the remaining aromatic group.

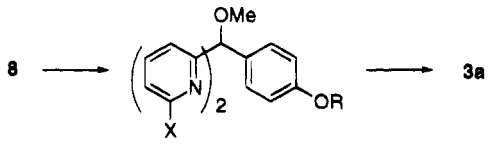
A total of four different stereoisomers, two homochiral and two pseudochiral[21] meso isomers, may form in the reaction. In the reduction of 2-acetylpyridines using (−)-Ipc_2BCl, the *S* and *R* alcohols are formed in ratios of approximately 95:5.[18] Assuming the same magnitude of stereoselection for the reduction of the first keto group

(15) Warshawsky, A.; Deshe, A.; Gutman, R. *Br. Polym. J.* **1984**, *16*, 234.
(16) Jameson, D. L.; Hilgen, S. E.; Hummel, C. E.; Pichla, S. L. *Tetrahedron Lett.* **1989**, *30*, 1609.
(17) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539.
(18) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169.
(19) Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 2379.
(20) Parks, J. E.; Wagner, B. E.; Holm, R. H. *J. Organomet. Chem.* **1973**, *56*, 53.
(21) Prelog, V.; Helmchen, G. *Helv. Chim. Acta* **1972**, *55*, 2581.

Scheme 1



Scheme 2



of **15**, the *SS*, *RrS*, *RsS*, and *RR* isomers are expected to be formed in a ratio of 90.25:4.75:4.75:0.25, provided that the two groups react independently. (It should be noted that a very small amount of the unfavored enantiomer is expected.) In order to verify that the meso compounds were not present, it was desirable to have access to all possible isomers. Therefore, ketones **15** and **20** were both reduced using sodium borohydride instead of the asymmetric reagent and the products obtained methylated. In the mixture obtained by reduction of **15**, the homochiral compounds were identified by ^{1}H NMR spectroscopy by comparison with the spectrum of the isomer obtained by asymmetric reduction. In addition, two compounds, which due to their simpler spectra with pairwise identical 6-(1-hydroxyalkyl)pyridine groups were thought to be the pseudochiral *RrS* and *RsS* isomers, were identified. From a statistical distribution, a 1:1:1:1 ratio of the four isomers (by NMR as an apparent 2:1:1 ratio in the absence of asymmetric shift reagent) was expected. The two meso compounds were, indeed, formed in equal amounts but in slight excess (13%) over the homochiral isomers (a 43.5:28.2:28.3 ratio was observed by ^{1}H NMR spectroscopy).

From the analogous reduction of compound **20**, a completely different distribution of isomers was obtained. To our surprise, the two meso isomers (formed in approximately equal amounts) were in this case formed in a 60% excess over the homochiral isomers, according to ^{1}H NMR spectroscopy. To ascertain that the products obtained really were isomers, racemic 2-lithio-6-(1-methoxyethyl)pyridine (**24a**) and 2-lithio-6-(1-methoxy-2,2-dimethylpropyl)pyridine (**24b**) were both reacted with ester **11**, which resulted, according to ^{1}H NMR spectroscopy, in a mixture of isomers **25a** and **25b**, respectively (Scheme 4). From the first reaction, the monocondensation product **12c** was also obtained. Deprotection and methylation of **25a** yielded a mixture of isomers **23a**, which proved to consist of the expected 1:1 mixture of homochiral and meso compounds, but in this case one of the meso isomers was obtained in a slight excess (12% by ^{1}H NMR spectroscopy) over the other. The same treatment of compound **25b** resulted in about equal amounts of homochiral and pseudochiral isomers, with the latter in a ca. 3:1 ratio. When ethyl ester **11** was exchanged for its methyl ester, around 35% excess of pseudochiral over homochiral isomers was observed, probably since the coupling reaction took place at lower temperature. This is supported by the observation of a coupling product, a bipyridine derivative (**13**), from the reaction involving the ethyl ester, which is expected to be formed at higher temperature. This also resulted in a lower chemical yield (47% compared to 80%).

It can thus be concluded that the product obtained by reduction of the first keto function of **20** using sodium borohydride (with equal probability having *R* or *S* absolute configuration) results in a complex that affords highly stereoselective reduction of the second function, with opposite absolute configuration, most probably via intramolecular complexation. Inspection of molecular models reveals that in an intramolecular complex, hydride attack at the second carbonyl function from the side resulting in formation of a center of absolute configuration different from that of the first formed center should, indeed, be favored. It should be noted that the 80:20 ratio of pseudochiral and homochiral isomers formed in the reduction of **20** (1,9-induction) is considerably higher than the meso:d,l ratio observed in the reduction of 1,5-ketones by $LiAlH_4$ but instead comparable to those observed when the keto groups are more closely situated.[22]

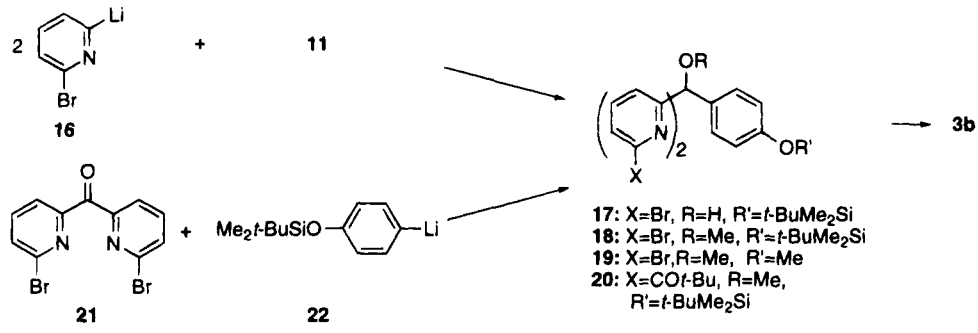
With all four isomers of **23a** and **23b** in hand, it could be concluded that the asymmetric reduction of ketones **15** and **20** occurred with high stereoselectivity, since signals from the meso isomers could not be detected in the ^{1}H NMR spectra of the products. This shows that the chiral reagent formed after reduction of the first keto group (containing two stereogenic centers with approximately 95% *SS* and 5% *RS* absolute configuration) exhibits a higher stereoselection than (−)-Ipc_2BCl, resulting in less than the expected 9.5% of meso isomers. It is interesting to note that in the reduction using $NaBH_4$ the absolute configuration of the second stereogenic center is opposite to that of the one initially formed in the major isomer, whereas the isomer with same absolute confiruation at both stereogenic centers is favored when Ipc_2BCl is employed.

Attempts to determine the amount of the minor enantiomer (*RR*) using a chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium-(III) or HPLC (chiral columns CHIRALCEL OD and AGD, see Experimental Section) were unfortunately unsuccessful. With 95% *S* absolute configuration in the first step, the maximum amount of the isomer with *RR* configuration that can possibly be fomred is, though, 5%.

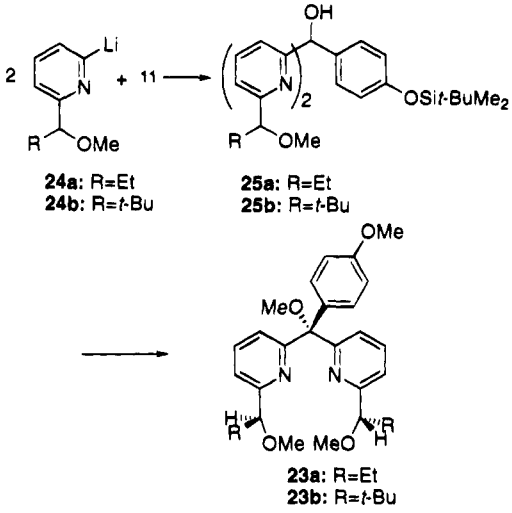
The stereoselectivity observed in the reduction of the bispyridyl derivatives is thus considerably higher than that observed in the corresponding reaction of monopyridine units.[18] The same phenomenon was also observed in the asymmetric reduction of the corresponding tripy-

(22) Maier, G.; Roth, C.; Schmitt, R. K. *Chem. Ber.* **1985**, *118*, 704.

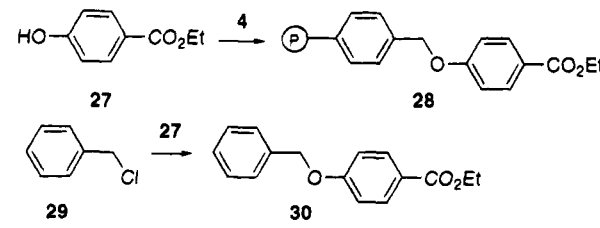
Scheme 3



Scheme 4

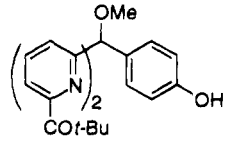


Scheme 5



ridylmethane derivative.[23] Therefore, preparation of nonchiral bispyridine derivatives, such as **14** or **17**, which are subsequently subjected to chiral modification, is preferred over initial preparation of monopyridine compounds **24** via asymmetric reduction when high stereoselectivity is desired. The disadvantage with this method is that the bisalcohols obtained by asymmetric reduction, in particular **3b**, proved difficult to isolate in high yield.

To circumvent this problem, an alternative method was chosen to obtain the polymeric ligands, involving grafting of the deprotected diketone **20** (**26**) prior to reduction (see below). It has been previously demonstrated that the reduction of keto groups on polystyrene-bound substituents using *B*-chlorodiisopinocampheylborane results in high stereoselectivity.[24]



Preparation of Polymer-Supported Ligands. To evaluate the reactivity of the chloromethylated polystyrenes **4a**–**d** toward phenolic compounds, we first decided to study their reactions with ethyl 4-hydroxybenzoate (**27**) to yield resins **28** (Scheme 5). Of the reaction conditions tried (NaH/THF, K_2CO_3, NaH or KH/DMF, NaH/15-crown-5/THF), the most satisfactory results were obtained using DMF as solvent at room temperature in the presence of sodium hydride or potassium carbonate. The use of cesium carbonate did not improve the results.[12a]

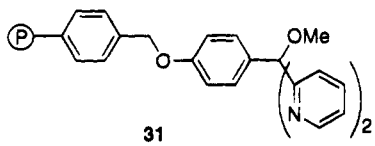
The polymers obtained (**28**) were characterized by infrared spectroscopy. The spectra were compared to that of ethyl 4-(benzyloxy)benzoate (**30**), obtained from ester **27** and benzyl chloride. The amount of grafting was estimated by the increase in weight and found to be 0.65, 0.5, 0.7, and 2 mmol of ligand/g of polymer for **28 a**–**d**, respectively (corresponding to functional yields of 60, 45, 30, and 65%, respectively). For the three macroporous resins, the amount of grafting was thus similar and therefore independent of the initial amount of chloromethyl groups. This probably indicates that a large number of the functional groups on more highly substituted resins are inaccessible to the large reagents.

With these results in hand, ligand **2** was reacted with the chloromethylated polymers **4a**–**d** under the same conditions as described for ethyl 4-hydroxybenzoate, affording polymers **31a**–**d** containing 0.61, 0.56, 0.65, and 1.84 mmol of ligand/g polymer, respectively, based on data from elemental analyses. This corresponds to functional yields of 79, 73, 33, 81%, respectively. It should be noted that polymer SX-1 proved to be more reactive than the other polymers, since it reacted in THF in the presence of 18 crown-6-*N*-ether and potassium hydride at room temperature, whereas under these conditions highly cross-linked polymers **4a**–**c** were unreactive.

The chiral ligand **3a** was grafted on polymer **4b** using potassium carbonate in DMF under the same conditions as those used for the polymers described above, to give a polymer (**32a**) containing 0.12 mmol of ligand/g, corresponding to a functional yield of 8%. Polymer-supported **32b** was most conveniently obtained by grafting ketone **26**, which gave polymer **33** in DMF with sodium hydride as base, followed by asymmetric reduction.

Conclusion. It has been demonstrated that chiral dipyridylmethane derivatives can be obtained with high

(23) Adolfsson, H.; Wärnmark, K.; Moberg, C. *J. Chem. Soc., Chem. Commun.* **1992**, 1054.
(24) Antonsson, T.; Jacobsson, U.; Moberg, C.; Rákos, L. *J. Org. Chem.* **1989**, *54*, 1191.



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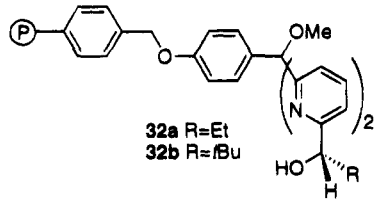
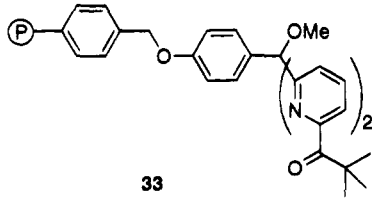


32a R=Et
32b R=tBu



33

stereoselectivity. Polymer-supported ligands were obtained by reaction sequences where the reaction with the polymer constituted the last or next to last step, thereby avoiding undesired side reactions leading to contamination of the polymers. This new methodology, using phenolic derivatives of the ligands, should be applicable to a variety of other ligands.

Experimental Section

General. The following compounds were prepared by literature methods: chloromethylated polystyrenes **4a–d**,[15] bis(6-bromo-2-pyridyl) ketone,[20] 2-bromo-6-(1-methoxyethyl)-pyridine,[18] and 2-bromo-6-(1-methoxy-2,2-dimethylpropyl)pyridine.[18] Commercially available reagents were used unless otherwise stated. THF was distilled from Na/benzophenone ketyl, Et_2O from $LiAlH_4$, and DMF over CaH_2 before use. ^1H NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard at 250 or 400 MHz.

4-((*tert*-Butyldimethylsilyl)oxy)-1-bromobenzene. To a solution of 4-hydroxybromobenzene (2 g, 11.56 mmol) and *tert*-butyldimethylsilyl chloride (2.1 g, 13.87 mmol) in dry THF (20 mL) was added triethylamine (1.4 g, 13.87 mmol) via a syringe. The white suspension formed was stirred for 12 h at rt. Water (40 mL) was added, and the aqueous phase was extracted with Et_2O (2 × 40 mL). The organic layers were dried ($MgSO_4$), and the solvent was evaporated under vacuum to yield 2.32 g (70%) of the desired product as a colorless oil: ^1H NMR (250 MHz) δ 7.28 (d, J = 8.9 Hz, 2H), 6.68 (d, J = 8.9 Hz, 2H), 0.95 (s, 9 H), 0.15 (s, 6H).

Ethyl 4-((*tert*-Butyldimethylsilyl)oxy)benzoate (11). To a solution of ethyl 4-hydroxybenzoate (1.66 g, 10 mmol) in dry THF (30 mL) were added triethylamine (1.4 mL, 10 mmol) and *tert*-butyldimethylsilyl chloride (1.50 g, 10 mmol). The reaction mixture was stirred for 2 days at rt. THF was evaporated under vacuum, and the resulting residue was dissolved in CH_2Cl_2 (50 mL). The organic phase was washed twice with 10% aqueous Na_2CO_3 (40 mL) and the solvent evaporated under vacuum, affording 2.46 g (87%) of the desired product as a colorless oil: IR ($CHCl_3$) 1718 cm^{-1}; ^1H NMR (250 MHz) δ 7.94 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 4.34 (q, 2H, J = 7.5 Hz), 1.37 (t, 3H, J = 7.5 Hz), 0.98 (s, 9H), 0.22 (s, 6H).

Di(2-pyridyl)[4-((*tert*-butyldimethylsilyl)oxy)phenyl]-methanol (7). Procedure A. To a suspension of magnesium (253 mg, 10.41 mmol) in THF (40 mL) were added 1,2-dibromoethane (ca. 550 μL, 5 mmol) to activate the metal and 4-(*tert*-butyldimethylsilyl)oxy)-1-bromobenzene (1.4 g, 4.87 mmol) diluted with THF (20 mL). The resulting mixture was stirred for 15 min under N_2. Di(2-pyridyl) ketone (**5**, 0.96 g, 5.22 mmol) in THF (20 mL) was added to the Grignard reagent. The dark red solution was stirred for 12 h at rt under N_2. The reaction was hydrolyzed with saturated aqueous NH_4Cl (50 mL). THF was evaporated under vacuum, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). Drying ($MgSO_4$) and evaporation of the solvent gave a crude product which after chromatography on silica gel (eluent EtOAc/hexane 1/1) yielded 1.53 g (75%) of compound **7**: mp 120 °C (hexane); ^1H NMR (250 MHz) δ 8.53 (ddd, 2H, J = 4.9, 1.8 and 1 Hz), 7.77 (dt, 2H, J = 7.5 and 1.0 Hz), 7.71 (td, 2H, J = 7.5 and 1.8 Hz), 7.21 (ddd, 2H, J = 7.5 Hz, 4.9 and 1.0 Hz), 7.11 (d, 2H, J = 8.8 Hz), 6.80 (s, 1H), 6.74 (d, 2H, J = 8.8 Hz), 0.96 (s, 9H), 0.16 (s, 6H). Anal. Calcd for $C_{23}H_{28}N_2O_2Si$: C, 70.37; H, 7.19; N, 7.14. Found: C, 70.37; H, 7.40; N, 6.97.

Procedure B. To a solution of 2-bromopyridine (680 μL, 7.13 mmol) in dry THF (40 mL) cooled to −78 °C was added under N_2 a solution of butyllithium in hexane (2.88 mL, 2.5 M, 7.13 mmol). The solution turned from yellow to orange. After the solution was stirred at this temperature for 10 min, compound **11** (1 g, 3.57 mmol) was added and the solution stirred at −78 °C for 2 h. The solution became slightly brown. The solution was allowed to reach rt, after which time it became dark blue. After treatment with saturated aqueous NH_4Cl (40 mL), THF was evaporated and the resulting aqueous layer extracted with CH_2Cl_2 (2 × 40 mL). After drying ($MgSO_4$) and evaporation of the solvent, the crude product was chromatographed on silica gel (eluent EtOAc/hexane 3/7), affording 675 mg (50%) of compound **7** and 253 mg of **12a**. Compound **12a**: ^1H NMR (250 MHz) δ 8.68 (ddd, 1H, J = 4.9, 1.8 and 1 Hz), 8.05 (d, 2H, J = 8.8 Hz), 7.96 (dt, 1H, J = 7.7 and 1.0 Hz), 7.65 (td, 1H, J = 7.7 and 1.8 Hz), 7.43 (ddd, 1H, J = 7.7, 4.9 and 1.4 Hz), 6.89 (d, 2H, J = 8.8 Hz), 0.97 (s, 9H), 0.23 (s, 6H). Anal. Calcd for $C_{18}H_{23}NO_2Si$: C, 68.97; H, 7.40; N, 4.47. Found: C, 68.73; H, 7.50; N, 4.47.

Di(2-pyridyl)methoxy[4-((*tert*-butyldimethylsilyl)oxy)-phenyl]methane (8). A suspension of sodium hydride (as an 80% suspension in oil, 90 mg, 3 mmol) and alcohol **7** (1 g, 2.55 mmol) in THF (20 mL) was stirred at rt for 30 min. Methyl iodide (187 μL, 3 mmol) was added and the resulting solution stirred for 12 h at rt. The solution was hydrolyzed with 10% aqueous $NaHCO_3$ (10 mL), and THF was evaporated under vacuum. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). After drying ($MgSO_4$) and evaporation of the solvent, the resulting product was chromatographed on neutral aluminum oxide (eluent EtOAc/hexane 4/6), affording 870 mg (84%) of the desired product **8** and 100 mg of **9** as byproduct. Compound **8**: mp 151 °C; ^1H NMR (400 MHz) δ 8.58 (ddd, 2H, J = 4.9, 1.8 Hz and 1 Hz), 7.68 (dt, 2H, J = 7.9 and 1.4 Hz), 7.63 (td, 2H, J = 7.9 and 1.8 Hz), 7.29 (d, 2H, J = 8.8 Hz), 7.10 (ddd, 2H, J = 7.9, 4.9 and 1.4 Hz), 6.78 (d, 2H, J = 8.8 Hz), 3.16 (s, 3H), 0.96 (s, 9H), 0.18 (s, 6H). Compound **9**: ^1H NMR (250 MHz) δ 8.59 (ddd, 2H, J = 4.9, 1.8 and 1 Hz), 7.69–7.60 (m, 4H), 6.99 (d, 2H, J = 8.9 Hz), 7.13 (ddd, 2H, J = 7.6, 4.9 and 1 Hz), 6.85 (d, 2H, J = 8.9 Hz), 3.78 (s, 3H), 3.18 (s, 3H).

Di(2-pyridyl)methoxy(4-hydroxyphenyl)methane (2). A solution of **8** (180 mg, 0.443 mmol) in 1 M H_2SO_4 (5 mL) was stirred at rt for 12 h. The solution was extracted with CH_2Cl_2 (3 × 30 mL). The aqueous phase was neutralized with 10% aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated, affording 127 mg (98%) of the desired product **2** as a white solid: mp 174 °C; ^1H NMR (250 MHz) δ 8.55 (ddd, 2H, J = 4.6, 1.8 and 1 Hz), 7.75 (dt, 2H, J = 7.7 and 1.3 Hz), 7.67 (td, 2H, J = 7.7 and 1.8 Hz), 7.16 (d, 2H, J = 8.8 Hz), 7.14 (ddd, 2H, J = 7.7, 4.6 and 1.3 Hz), 6.6 (d, 2H, J = 8.8 Hz), 3.15 (s, 3H). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.74; H, 5.40; N, 9.28.

Bis(1-Oxo-2-pyridyl)methoxy[4-((*tert*-butyldimethylsilyl)oxy)phenyl]methane. A solution of product **8** (1.25 g, 3.1 mmol) and *m*-chloroperbenzoic acid (80%, 2.64 g, 12.24 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 12 h under N_2. After the addition of additional CH_2Cl_2 (50 mL), NH_3 (g) was bubbled into the solution for 3 min and the ammonium salt formed was removed by filtration. Evaporation of the solvent

afforded 1.15 g (85%) of a white solid. ^{1}H NMR (250 MHz) δ 8.05 (br d, 2H, J = 6.3 Hz), 7.86 (d, 2H, J = 8.9 Hz), 7.67–7.59 (br m, 2H), 7.25 (td, 2H, J = 7.7 and 1.4 Hz), 7.11 (app br t, 2H, J = 7.0 Hz), 6.81 (d, 2H, J = 8.9 Hz), 3.24 (s, 3H), 0.96 (s, 9H), 0.19 (s, 6H).

Bis(6-cyano-2-pyridyl)methoxy[4-((*tert*-butyldimethylsilyl)oxy)phenyl]methane (14). To a solution of the above *N*-oxide (1.3 g, 2.96 mmol) in CH_2Cl_2 (40 mL), *N*,*N*-dimethylcarbamoyl chloride (0.54 mL, 5.90 mmol) and trimethylsilyl cyanide (0.79 mL, 5.90 mmol) were added. After 12 h stirring at rt, a further 5.9 mmol of dimethylcarbamoyl chloride and trimethylsilyl cyanide were added. After 18 h stirring at reflux, the reaction mixture was cooled to rt, before adding more dimethylcarbamoyl chloride (0.54 mL, 5.90 mmol) and trimethylsilyl cyanide (0.79 mL, 5.90 mmol). The reaction was monitored by TLC (SiO_2, eluent EtOAc/hexane 1.5/8.5). The reaction mixture was cooled to rt before adding 10% aqueous Na_2CO_3 (50 mL). After phase separation, the aqueous layer was extracted with CH_2Cl_2 (40 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated under vacuum, affording 2 g of a red oil, which after chromatography on silica gel (eluent EtOAc/hexane 1.5/8.5) gave 1.15 g (85%) of dinitrile **14** as a white solid: mp 165 °C dec; IR (KBr) 2230 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.94 (dd, 2H, J = 7.5 and 1.2 Hz), 7.83 (t, 2H, J = 7.5 Hz), 7.60 (dd, 2H, J = 7.5 and 1.2 Hz), 7.20 (d, 2H, J = 8.75 Hz), 6.80 (d, 2H, J = 8.75), 3.18 (s, 3H), 0.97 (s, 9H), 0.21 (s, 6H).

Bis[6-(1-oxopropyl)-2-pyridyl]methoxy[4-((*tert*-butyldimethylsilyl)oxy)phenyl]methane (15). To a suspension of magnesium (182 mg, 7.49 mmol) in benzene/Et_2O 1/1 (20 mL) was added dropwise bromoethane (565 μL, 7.49 mmol) under N_2. The solution was stirred at rt until complete consumption of magnesium. A solution of compound **14** (1.14 g, 2.5 mmol) in benzene (20 mL) was added at rt over a period of 10 min. During this addition, a white precipitate was formed and the suspension turned red within a few minutes. The resulting suspension was stirred for 1.5 h, before addition of saturated aqueous NH_4Cl (50 mL). The organic solvents were evaporated under vacuum, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). After drying ($MgSO_4$) and evaporation of the solvent, the crude product obtained as a brown thick oil was chromatographed on silica gel (eluent EtOAc/hexane 2.5/7.5) to give 815 mg (63%) of the desired product **15**: IR ($CHCl_3$) 1700 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.91–7.77 (m, 6H), 7.37 (d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.8 Hz), 3.24 (s, 3H), 2.92 (q, 4H, J = 7.3 Hz), 1.05 (t, 6H, J = 7.3 Hz), 0.97 (s, 9H), 0.20 (s, 6H).

Bis(6-bromo-2-pyridyl)[4-((*tert*-butyldimethylsilyl)oxy)phenyl]methanol (17). Procedure A. To a solution of 4-(*tert*-butyldimethylsilyl)oxy)-1-bromobenzene (420 mg, 1.46 mmol) in dry THF (15 mL) cooled at −78 °C was added a solution of butyllithium in hexane (640 μL, 2.5 M, 1.60 mmol). The clear yellow solution was stirred for 30 min at this temperature before bis(6-bromo-2-pyridyl) ketone (**21**, 500 mg, 1.46 mmol) was added. The dark green solution was stirred for 2 h at −78 °C. During this period the solution became orange. The solution was warmed to rt and stirred for a futher 1 h at rt. After treatment with saturated aqueous NH_4Cl (15 mL) and phase separation, the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated under vacuum, affording 839 mg of crude product as a yellow oil. Flash chromatography on silica gel with EtOAc/hexane 0.5/9.5 as eluent yielded 352 mg (44%) of **17** as a colorless oil: ^{1}H NMR (250 MHz) δ 7.79 (dd, 2H, J = 7.7 and 0.5 Hz), 7.54 (t, 2H, J = 7.7 Hz), 7.36 (dd, 2H, J = 7.7 and 0.5 Hz), 7.17 (d, 2H, J = 8.7 Hz), 6.77 (d, 2H, J = 8.7 Hz), 6.24 (s, 1H), 0.97 (s, 9H), 0.18 (s, 6H). Anal. Calcd for $C_{23}H_{26}N_2O_2Br_2Si$: C, 50.19; H, 4.76; N, 5.09. Found: C, 50.33; H, 4.62; N, 4.96.

Procedure B. A suspension of 2,6-dibromopyridine (1.73 g, 7.30 mmol) in Et_2O (20 mL) was treated with butyllithium (3.20 mL, 2.5 M, 8.0 mmol) over a period of 10 min, under N_2 at −78 °C. After the solution was stirred for 30 min at this temperature, the clear yellow solution obtained was treated with ester **11** (1.02 g, 3.66 mmol) and stirred for 1 h at −78 °C. The orange solution was allowed to warm to rt over a period of 30 min and then stirred for 1 h. The dark blue solution was hydrolyzed with saturated aqueous NH_4Cl (20 mL), giving a yellow solution. After phase separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated to give the crude product as a yellow oil. After chromatography on silica gel (eluent EtOAc/hexane 1/9), 1.4 g (71%) of compound **17** was obtained as a colorless oil, in addition to 150 mg of **12b** and 100 mg of **13**.[25] Compound **12b**: ^{1}H NMR (250 MHz) δ 8.09 (d, 2H, J = 8.8 Hz), 7.90 (t, 1H, J = 7.5 Hz), 7.83 (dd, 1H, J = 7.5 and 1.7 Hz), 7.58 (dd, 1H, J = 7.5 and 1.7 Hz), 6.90 (d, 2H, J = 8.8 Hz), 1.00 (s, 9H), 0.26 (s, 6H). Anal. Calcd for $C_{18}H_{22}NO_2BrSi$: C, 55.10; H, 5.65; N, 3.57. Found: C, 54.92; H, 5.51; N, 3.50. Compound **13**: ^{1}H NMR (250 MHz) δ 8.38 (d, 2H, J = 7.8 Hz), 7.67 (t, 2H, J = 7.8 Hz), 7.50 (d, 2H, J = 7.8 Hz). Anal. Calcd for $C_{10}H_6N_2Br_2$: C, 38.20; H, 1.91; N, 8.92. Found: C, 38.33; H, 1.72; N, 8.68.

Bis(6-bromo-2-pyridyl)methoxy[4-((*tert*-butyldimethylsilyl)oxy)phenyl]methane (18). A suspension of sodium hydride (as an 80% suspension in oil, 111 mg, 3.7 mmol) and compound **17** (1.36 g, 2.47 mmol) in dry THF (20 mL) was stirred for 15 min at rt. After addition of a large excess of methyl iodide (920 μL, 14.77 mmol), the yellow solution was stirred for 12 h at rt. The solution was treated with saturated aqueous NH_4Cl (20 mL). After evaporation of THF, the aqueous layer was extracted with Et_2O (3 × 30 mL). Drying ($MgSO_4$) and evaporation of Et_2O afforded 1.41 g of a yellow precipitate that was chromatographed on silica gel (eluent EtOAc/hexane 1/9) to give 1.16 g (83%) of compound **18** as a white solid and 150 mg of **19** as byproduct. Compound **18**: mp 151 °C; ^{1}H NMR (400 MHz) δ 7.63 (dd, 2H, J = 7.8 and 0.8 Hz), 7.50 (t, 2H, J = 7.8 Hz), 7.33 (dd, 2H, J = 7.8 and 0.8 Hz), 7.23 (d, 2H, J = 8.8 Hz), 6.77 (d, 2H, J = 8.8 Hz), 3.18 (s, 3H), 0.97 (s, 9H), 0.20 (s, 6H). Anal. Calcd for $C_{24}H_{28}N_2O_2Br_2Si$: C, 51.08; H, 5.00; N, 4.96. Found: C, 51.18; H, 4.93; N, 4.82. Compound **19**: ^{1}H NMR (400 MHz) δ 7.62 (d, 2H, J = 7.8 Hz), 7.50 (t, 2H, J = 7.8 Hz), 7.33 (d, 2H, J = 7.8 Hz), 7.32 (d, 2H, J = 8.9 Hz), 6.85 (d, 2H, J = 8.9 Hz), 3.80 (s, 3H), 3.19 (s, 3H). Anal. Calcd for $C_{19}H_{16}N_2O_2Br_2$: C, 49.17; H, 3.47; N, 6.04. Found: C, 49.42; H, 3.27; N, 5.71.

Bis[6-(1-oxo-2,2-dimethypropyl)-2-pyridyl]methoxy[4-((*tert*-butyldimethylsilyl)oxo)phenyl]methane (20). To a suspension of compound **18** (414 mg, 0.773 mmol) in Et_2O (10 mL) under N_2 was added a solution of butyllithium in hexane (880 μL, 2.5 M, 2.2 mmol) at −78 °C. The yellow solution obtained was stirred for 30 min at this temperature before pivalonitrile (243 μL, 2.2 mmol) was added. After being stirred at −78 °C for 2 h, the orange solution was warmed to rt over a period of 1 h and kept at this temperature for a further 1 h. The resulting dark brown solution was treated with saturated aqueous NH_4Cl (15 mL) to give a clear yellow solution. After separation of the phases, the aqueous layer was extracted with Et_2O (2 × 15 mL). Drying ($MgSO_4$) and evaporation of Et_2O afforded 450 mg of a thick brown oil. The crude product purified by chromatography on silica gel (eluent EtOAc/hexane 1.5/8.5) gave 350 mg (83%) of the desired diketone **20**: IR ($CHCl_3$) 1686 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.79–7.71 (m, 6H), 7.41 (d, 2H, J = 8.7 Hz), 6.79 (d, 2H, J = 8.7 Hz), 3.19 (s, 3H), 1.14 (s, 18H), 0.97 (s, 9H), 0.17 (s, 6H).

Bis[6-(1-oxo-2,2-dimethylpropyl)-2-pyridyl]methoxy(4-hydroxyphenyl)methane (26). To a solution of **20** (460 mg, 0.8 mmol) in EtOH (10 mL) was added 2 M HCl (6 mL). The resulting solution was stirred for 12 h at rt. After evaporation of EtOH, the aqueous phase was neutralized with 10% aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was dried ($MgSO_4$), and the solvent was evaporated, affording 360 mg (97%) of the desired product **26**: IR ($CHCl_3$) 1669 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.79–7.72 (m, 6H), 7.45 (d, 2H, J = 8.7 Hz), 6.81 (d, 2H, J = 8.7 Hz), 5.70 (br s, 1H), 3.19 (s, 3H), 1.14 (s, 18H).

(*R*,*R*)*-Bis[6-(1-hydroxypropyl)-2-pyridyl]methoxy(4-hydroxyphenyl)methane [(*R*,*R*)*-3a]. A solution of dike-

(25) Garber, T.; Rillema, D. P. *Synth. Commun.* **1990**, *20*, 1233.

tone **15** (0.498 g, 0.961 mmol) in dry THF (4 mL) was treated with (−)-$(Ipc)_2BCl$ (1.48 g, 4.6 mmol) at rt under N_2. The resulting clear solution was stirred for 2 days. After addition of propionaldehyde (332 μL, 4.6 mmol) at 0 °C, the solution was stirred at this temperature for 4 h and then for 24 h at rt. After addition of 6 M NaOH (15 mL) at rt, the solution was stirred for an additional 1 h and extracted with Et_2O (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and the solvents evaporated under vacuum, affording a yellow oil that was treated with ethanol/5 M aqueous HCl 1/1 (20 mL). The resulting solution was stirred at rt for 3 h. After evaporation of ethanol, the acidic aqueous layer was washed with Et_2O (2 × 30 mL) to extract α-pinene. After neutralization of the aqueous layer with 6 M aqueous NaOH (pH 6−7), a white precipitate was formed that was extracted with Et_2O (2 × 40 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was evaporated under vacuum to give 361 mg (94%) of ***(R,R)*-3a**: ^1H NMR (250 MHz) δ 7.670 (t, 1H, J = 7.80 Hz), 7.660 (t, 1H, J = 7.80 Hz), 7.590 (d, 1H, J = 7.75 Hz), 7.420 (d, 1H, J = 7.75 Hz), 7.26 (d, 2H, J = 8.50 Hz), 7.09 (d, 1H, J = 7.60 Hz), 7.05 (d, 1H, J = 7.60 Hz), 6.676 (d, 2H, J = 8.50 Hz), 4.81 (br s, 2H, OH), 4.70−4.58 (m, 2H), 3.14 (s, 3H), 1.90−1.71 (m, 2H), 1.70−1.51 (m, 2H), 0.89−0.775 (m, 6H) (phenolic OH not observed).

***(R,R)*-Bis[6-(1-methoxypropyl)-2-pyridyl]methoxy(4-methoxyphenyl)methane [*(R,R)*-23a].** This compound was prepared using the same method as for **8** from a suspension of sodium hydride (as an 80% suspension in oil, 26 mg, 0.875 mmol), alcohol **3a** (100 mg, 0.25 mmol), and methyl iodide (200 μL, 3.21 mmol) in THF (2 mL). Chromatography (silica gel, eluent EtOAc/hexane 2/8) yielded 80 mg (72%) of the desired product ***(R,R)*-23a**: $[\alpha]^{20}_D$ − 61° ($CHCl_3$, c 1.27); ^1H NMR (250 MHz) δ 7.635 (t, 2H, J = 7.7 Hz), 7.495 (d, 2H, J = 7.7 Hz), 7.400 (d, 2H, J = 8.80 Hz), 7.215 (d, 1H, J = 7.7 Hz), 7.205 (d, 1H, J = 7.7 Hz), 6.815 (d, 2H, J = 8.80 Hz), 4.130 (br t, 2H, J = 6.20 Hz), 3.785 (s, 3H), 3.235 (s, 3H), 3.230 (s, 3H), 3.205 (s, 3H), 1.750−1.615 (m, 4H), 0.785 (t, 6H, J = 7.35 Hz). The ^1H NMR spectrum recorded at 400 MHz resulted in poor resolution in the lower field part of the spectrum but allowed the identification of separate triplets for the methyl protons of the two ethyl groups, at δ 0.785 and 0.780, respectively.

Bis[6-(1-methoxypropyl)-2-pyridyl]methoxy(4-methoxyphenyl)methane (23a). To a solution of diketone **15** (100 mg, 0.193 mmol) in ethanol (2 mL) was added sodium borohydride (20 mg, 0.53 mmol). The solution was stirred at 40 °C for 5 h. After the addition of 4 N HCl (5 mL), the solution was stirred for a further 5 h at rt. The resulting acidic solution was extracted with CH_2Cl_2 (10 mL). The aqueous layer was neutralized (pH = 6−7) with a solution of 10% aqueous $NaHCO_3$ and extracted twice with CH_2Cl_2 (10 mL). Drying ($MgSO_4$) and evaporation of the solvent yielded 75 mg (96%) of **3a**. The crude bisalcohol **3a** (100 mg, 0.25 mmol) was *O*-methylated analogous to **7**, using a suspension of sodium hydride (as an 80% suspension in oil, 26 mg, 0.875 mmol) and methyl iodide (200 μL, 3.21 mmol) in THF (2 mL). Chromatography on silica gel (eluent EtOAc/hexane 2/8) afforded 80 mg (72%) of the desired mixture of isomers **23a** as a colorless oil. By comparison with the ^1H NMR spectrum of ***(R,R)*-23a**, the signals for the two meso isomers were identified. The isomers could not be separated by HPLC using chiral columns AGD (with various ratios of phosphonate buffer pH 7,8 mmol/L:2-propanol as eluent) or CHIRALCEL OD (eluent 0.75% 2-propanol in hexane). ***(R,r,S)*-23a and *(R,s,S)*-23a**: ^1H NMR (250 MHz) δ 7.635 (t, 4H, J = 7.70 Hz), 7.495 (d, 2H, J = 7.70 Hz), 7.480 (d, 2H, J = 7.70 Hz), 7.465 (d, 2H, J = 8.80 Hz), 7.395 (d, 2H, J = 8.80 Hz), 7.215 (d, 2H, J = 7.70 Hz), 7.205 (d, 2H, J = 7.70 Hz), 6.815 (d, 4H, J = 8.80 Hz), 4.13, 4.12 (each t, 4H, J = 6.20 Hz), 3.785 (s, 6H), 3.235, 3.210, 3.205 (each s, 18H), 1.77−1.60 (m, 8H), 0.795, 0.770 (each t, 12H, J = 7.35 Hz). The ^1H NMR spectrum recorded at 400 MHz resulted in poor resolution in the lower field part of the spectrum but allowed for the identification of four separate singlets as the methoxy protons situated around δ 3.2 (at 3.240, 3.235, 3.210, and 3.207). Anal. Calcd for $C_{27}H_{34}N_2O_4$: C, 71.97; H, 7.61; N, 622. Found: C, 72.25; H, 7.33; N, 6.30.

***(R,R)*-Bis[6-(1-methoxy-2,2-dimethylpropyl)-2-pyridyl]-methoxy(4-methoxyphenyl)methane [*(R,R)*-23b].** Diketone **20** (67 mg, 0.117 mmol) was reduced analogous to **15** using (−)-$(Ipc)_2BCl$ (190 mg, 0.592 mmol) in THF (1 mL). After workup [as described for ***(R,R)*-3a**], a mixture of bisalcohol ***(R,R)*-3b** and α-pinene derivatives was obtained as a white solid. The product was *O*-methylated following the procedure described for alcohol **7** using a suspension of sodium hydride (as an 80% suspension in oil, 20 mg, 0.67 mmol) and methyl iodide (100 μL, 1.6 mmol) in THF (0.5 mL). Chromatography on silica gel (eluent EtOAc/hexane 1/9) gave 30 mg (50%) of ***(R,R)*-23b** as a colorless oil: $[\alpha]^{20}_D$ + 23° ($CHCl_3$, c 0.48). ^1H NMR (250 MHz) δ 7.64−7.47 (m, 4H), 7.39 (d, 2H, J = 8.9 Hz), 7.21 (dd, 1H, J = 7.7 and 0.8 Hz), 7.135 (dd, 1H, J = 7.15 and 1.6 Hz), 6.78 (d, 2H, J = 8.9 Hz), 3.90 (s, 1H), 3.86 (s, 1H), 3.78 (s, 3H), 3.195 (s, 3H), 3.17 (s, 3H), 3.165 (s, 3H), 0.80 (s, 9H), 0.74 (s, 9H).

Bis[6-(1-methoxy-2,2-dimethylpropyl)-2-pyridyl]-methoxy(4-methoxyphenyl)methane (23b). Diketone **20** (46 mg, 80 μmol) was reduced using sodium borohydride (10 mg, 0.257 mmol) in ethanol (1 mL) to yield **3b** (28 mg, 76%). The crude bisalcohol **3b** was *O*-methylated in the same manner as for **7** using a suspension of sodium hydride (as an 80% suspension in oil, 12 mg, 0.4 mmol) and methyl iodide (60 μL, 0.96 mmol) in THF (2 mL). Chromatography on silica gel (eluent EtOAc/hexane 1/9) afforded 21 mg (72%) of the desired product **23b** as a colorless oil. The product consisted of a mixture of stereoisomers. By comparison with the spectrum of ***(R,R)*-23b**, signals for the two meso isomers were identified. ***(R,r,S)*-23b and *(R,s,S)*-23b**: ^1H NMR (250 MHz) δ 7.64−7.47 (m, 8H), 7.42 (d, 4H, J = 8.9 Hz), 7.175 (dd, 4H, J = 7.5 and 1.2 Hz), 6.81 (d, 4H, J = 8.9 Hz), 3.86, 3.825 (each s, 4H), 3.79 (s, 6H), 3.19, 3.16, 3.12, (each s, 18H), 0.80, 0.78 (each s, 36H). Anal. Calcd for $C_{31}H_{42}N_2O_4$: C, 73.49; H, 8.36; N, 5.53. Found: C, 73.30; H, 8.31; N, 5.46.

Bis[6-(1-methoxypropyl)-2-pyridyl][4-((*tert*-butyldimethylsilyl)oxy)phenyl]methanol (25a). To a solution of *rac*-1-(6-bromopyridin-2-yl)-1-methoxypropyl methyl ether (**24a**, 300 mg, 1.3 mmol) in dry THF was added a solution of 2.5 M butyllithium in hexane (570 μL, 1.43 mmol) at −78 °C. The resulting clear yellow solution was stirred for 1 h at this temperature, before ester **11** (183 mg, 0.65 mmol) was added. After stirring at −78 °C for 1 h, the solution was allowed to reach rt over a period of 30 min. The solution was stirred for a further 12 h at rt. After treatment with saturated NH_4Cl (7 mL) and phase separation, the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated, affording 300 mg of a crude product as an orange oil. Purification by chromatography on silica gel (eluent EtOAc/hexane 0.5/9.5) yielded 135 mg (46%) of **25a** and 50 mg of **12c**. Compound **12c**: ^1H NMR (400 MHz) δ 8.09 (d, 2H, J = 8.75 Hz), 7.89 (t, 1H, J = 7.65 Hz), 7.84 (dd, 1H, J = 7.65 and 1.3 Hz), 7.58 (dd, 1H, J = 7.65 and 1.3 Hz), 6.90 (d, 2H, J = 8.75 Hz), 4.30 (app t, 1H, J = 6.0 Hz), 3.34 (s, 3H), 1.91−1.80 (m, 2H), 1.00 (s, 9H), 0.95 (t, 3H, J = 7.40 Hz), 0.26 (s, 6H). Compound **25a** (as a mixture of stereoisomers): ^1H NMR (400 MHz) δ 7.745, 7.730, 7.725 (each dd, 2H, J = 7.65 and 1.0 Hz), 7.675 (t, 2H, J = 7.65 Hz), 7.26 (dd, 2H, J = 7.65 and 1.0 Hz), 7.11 (d, 2H, J = 8.6 Hz), 7.02, 7.00 (each s, 1H), 6.71 (d, 2H, J = 8.65 Hz), 4.19−4.15 (m, 2H), 3.280, 3.275, 3.270, 3.265 (each s, 6H), 1.81−1.71 (m, 4H), 0.95 (s, 9H), 0.835, 0.810, 0805 (each t, 6H, J = 7.40 Hz), 0.20 (s, 6H).

Bis[6-(1-methoxy-2,2-dimethylpropyl)-2-pyridyl][4-((*tert*-butyldimethylsilyl)oxy)phenyl]methanol (25b). Compound **25b** was obtained using the same procedure describe above, from a solution of *rac*-1-(6-bromopyridine-2-yl)-2,2-dimethypropyl methyl ether (**24b**, 1g, 3.86 mmol) in dry THF (20 mL), a solution of 2.5 M butyllithium in hexane (1.70 mL, 4.25 mmol), and ester **11** (542 mg, 1.93 mmol). Chromatography on silica gel (eluent EtOAc/hexane 0.5/9.5) yielded 507 mg (44%) of **25b** (as a mixture of stereoisomers): ^1H NMR (400 MHz) δ 7.73−7.61 (m, 4H), 7.23−6.92 (m, 5H), 6.71 (br d, 2H, J = 8.7 Hz), 3.92, 3.91, 3.89, 3.86 (each s, 2H), 3.22, 3.20, 3.18 (each s, 6H), 0.95 (s, 9H), 0.81, 0.80, 0.78 (each s, 18H), 0.16 (s, 6H).

Bis[6-(1-methoxypropyl)-2-pyridyl]methoxy(4-methoxyphenyl)methane (23a). To a solution of compound **25a** (139 mg, 0.26 mmol) in ethanol (2 mL) was added 1 M HCl (2 mL). After stirring for 12 h at rt, the solution was neutralized with a solution of 10% aqueous K_2CO_3 (pH = 7). After evaporation of EtOH, the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). Drying ($MgSO_4$) and evaporation of the solvent afforded 100 mg of a white solid which was methylated in the same manner as **7** using sodium hydride (as an 80% suspension in oil, 20 mg, 0.67 mmol) and methyl iodide (160 μL, 2.57 mmol) in dry THF (1 mL). Yield: 80 mg (69%) of **23a** as a colorless oil after chromatography on silica gel (eluent EtOAc/hexane 2/8). Anal. Calcd for $C_{27}H_{34}N_2O_4$: C, 71.97; H, 7.61; N, 6.22. Found: C, 72.33; H, 7.22; N, 6.05.

Bis[6-(1-methoxy-2,2-dimethylpropyl)-2-pyridyl]methoxy(4-hydroxyphenyl)methane (23b). Compound **23b** was prepared in the same manner as **23a**, from **25b** (500 mg, 0.84 mmol) in ethanol (2 mL) and 1 M HCl (3 mL). The white solid obtained after workup (220 mg) was methylated using sodium hydride (as an 80% suspension in oil, 40 mg, 1.33 mmol) and methyl iodide (150 μL, 2.41 mmol) in dry THF (2 mL). Chromatography (silica gel, eluent EtOAc/hexane 1/9) yielded **23b** (200 mg, 47%).

Ethyl 4-Benzoxybenzoate (30). A solution of ethyl 4-hydroxybenzoate (500 mg, 3.00 mmol) and sodium hydride (as an 80% suspension in oil, 100 mg, 3.31 mmol) in DMF (5 mL) was stirred for 10 min under N_2 at rt. Benzyl chloride (380 mg, 3.00 mmol) was added, and after the solution was stirred at rt under N_2 for 12 h, water (30 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic phases were washed with water (2 × 30 mL) and dried ($MgSO_4$), and the solvent was evaporated under vacuum. The crude product was chromatographed on silica gel with EtOAc/hexane 1/9 as eluent, giving 400 mg (52%) of **30**: ^1H NMR (250 MHz) δ 8.00 (d, 2H, J = 8.8 Hz), 7.45–7.32 (m, 5H), 7.00 (d, 2H, J = 8.8 Hz), 5.12 (s, 2H), 4.35 (q, 2H, J = 7.5 Hz), 1.38 (t, 3H, J = 7.5 Hz); ^{13}C NMR (62.9 MHz) δ 166.34, 162.41, 138.24, 131.5, 128.68, 128.20, 127.50, 123.20, 114.44, 70.60, 60.66, 14.40; IR ($CHCl_3$, cm^{-1}) 1713, 1607, 1580, 1510, 1278, 1251, 1168, 1103, 1024. Anal. Calcd for $C_{16}H_{16}O_3$: C, 75.00; H, 6.25. Found: C, 74.94; H, 6.14.

Polymer-Supported Ethyl 4-Hydroxybenzoates 28a–d. A solution of ethyl 4-hydroxybenzoate (83 mg, 0.50 mmol) and sodium hydride (as an 80% suspension in oil, 23 mg, 0.77 mmol) in DMF (5 mL) was stirred for 30 min at rt under N_2. Chloromethylated polystyrene **4a** (0.5 mmol of chloromethyl groups) was added, and the resulting mixture was stirred for 2 days. The polymer was removed by filtration and washed in succession with MeOH, MeOH–H_2O (1/1), acetone, CH_2Cl_2, and MeOH. The polymers were dried at rt under vaccum, for at least 12 h. Polymers **4b–d** were treated in the same way. The IR spectra of the polymers obtained (**28a–d**) showed peaks corresponding to polystyrene and characteristic peaks appearing at the same frequency as in the monomeric model **30**. IR (KBr, cm^{-1}): 1715, 1607, 1507, 1278, 1251, 1168.

Polymer-Supported Ligand 2 (31a–d). Polymers **31a–d** were prepared by the same procedure as that used for the preparation of the polymers **28a–d**. IR spectra of the polymers obtained showed peaks corresponding to the polystyrene structure and characteristic peaks of the ligand **2**. IR (KBr, cm^{-1}): 1587, 1509, 1240, 1173, 1081. Polymer **31a**. Anal. Found: N, 1.72 corresponding to 0.61 mmol of ligand/g of polymer. Polymer **31b**. Anal. Found: N, 1.80 corresponding to 0.65 mmol of ligand/g of polymer. Polymer **31c**. Anal. Found: N, 1.56 corresponding to 0.56 mmol of ligand/g of polymer. Polymer **31d**. Anal. Found: N, 5.14 corresponding to 1.84 mmol of ligand/g of polymer. These values were in good agreement with values obtained from the weight increase of the polymers upon reaction.

Polymer-Supported Ligand 3a (32a). A solution of **3a** (360 mg, 0.88 mmol) and potassium carbonate (245 mg, 1.77 mmol) in DMF (20 mL) was stirred for 30 min at rt under N_2. Chloromethylated polystyrene **4b** (700 mg, 1.26 mmol of chloromethyl groups) was added, and the resulting mixture was stirred for 2 days at 80 °C. The polymer was removed by filtration and washed in succession with MeOH, MeOH–H_2O (1/1), acetone, CH_2Cl_2, and MeOH. The polymers were dried at rt under vacuum, for at least 12 h, resulting in 770 mg of a polymer containing 0.43% N corresponding to 0.12 mmol of ligand **3a**/g of polymer.

Polymer-Supported Ligand 26 (33). This polymer was prepared in the same manner as **28** from **26** (395 mg, 0.86 mmol), sodium hydride (as an 80% suspension in oil, 31 mg, 1.03 mmol), and chloromethylated polystyrene **4d** (195 mg, 0.96 mmol of chloromethyl groups) in DMF (2 mL). Washings and drying afforded 442 mg of a polymer containing 3.59% N corresponding to 1.28 mmol of ligand **26**/g of polymer. IR (KBr): 1678 cm^{-1}.

Polymer-Supported Ligand 3b (32b). To a suspension of polymer **33** (414 mg, 0.53 mmol of ligand **26**) in dry THF (5 mL) was added a solution of (−)-$(Ipc)_2BCl$ (623 mg, 1.94 mmol) in THF (4 mL). The resulting solution was stirred under N_2 for 3 days. After addition of methanol (3 mL), the suspension was stirred for a further 1 h. The polymer was removed by filtration was washed in succession with MeOH, MeOH–THF (1/1), MeOH–H_2O (1/1), and MeOH. Drying at rt under vacuum for 12 h afforded 410 mg of a white polymer.

Acknowledgment. Dynospheres from Pharmacia AB, DVB from Casco Nobel, and Bonopore from Nobel Chemicals were generous gifts. This work was supported by the Swedish Research Council for Engineering Sciences and by the Swedish Natural Science Research Council. We thank Dr. Jack duFlos, INSA, Rouen, France, and Ms. Kerstin Nordström for kind help with HPLC.

JO940752+