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New chiral 2,2′-bipyridine diols as catalysts for enantioselective addition of diethylzinc to benzaldehyde

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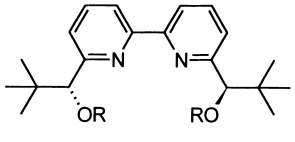
Abstract

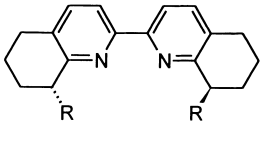
New C_2-symmetric chiral 2,2′-bipyridine diols were prepared from readily available homochiral materials such as menthone and camphor. Their catalytic activities in the reaction of diethylzinc with benzaldehyde to give 1-phenyl-1-propanol were studied. In all cases, the yields were good and enantioselectivities up to 95% were observed.

1. Introduction

The presence of a C_2 symmetry axis within a chiral auxiliary can serve the very important function of dramatically reducing the number of possible competing diastereomeric transition states.[1] Many C_2-symmetric chiral N,N bidentate ligands such as semicorrines and bisoxazolines are found to be highly effective chiral controllers in asymmetric reactions.[2–4] Although bipyridines are structurally similar to these ligands and are well known to form complexes with various metal ions,[5] relatively few C_2-symmetric bipyridine ligands were reported and used in asymmetric catalysis.[6,7] One reason associated with this problem is the lack of an efficient synthetic route to them.



1



2

Bolm et al. reported the synthesis of the C_2-symmetric chiral bipyridine ligands **1** through asymmetric reduction of prochiral ketones and studied their use in various asymmetric reactions.[8,9] Katsuki et al.

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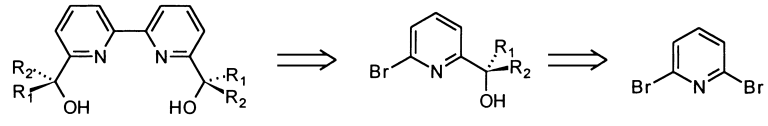
reported the synthesis of chiral bipyridine **2** from 2,3-cyclohexenopyridine and its use in asymmetric cyclopropanation.[10] We recently reported the use of Bolm's ligand **1** (R=Me) in asymmetric cyclopropanation and allylation reactions.[11,12] In order to increase the scope of chiral bipyridine ligands in asymmetric reactions, we report here the synthesis of new C_2-symmetric chiral bipyridine ligands based on homocoupling of readily available chiral pyridylalcohols and a study of their catalytic activities in the asymmetric diethylzinc addition to aldehydes.

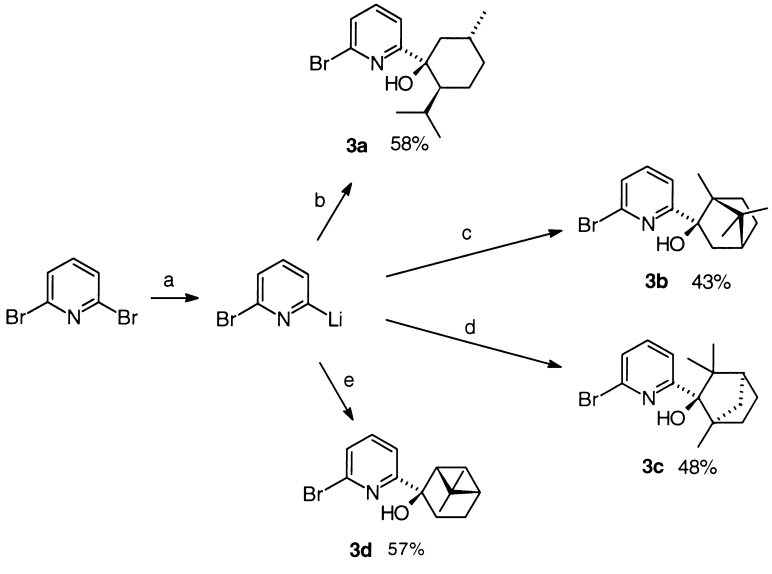
2. Results and discussion

Bromopyridylalcohols **3** could be obtained from the commercially available 2,6-dibromopyridine. C_2-Symmetric 2,2′-bipyridines **4** could then be obtained by metal-mediated homocouplings of **3** (Scheme 1).



Scheme 1.

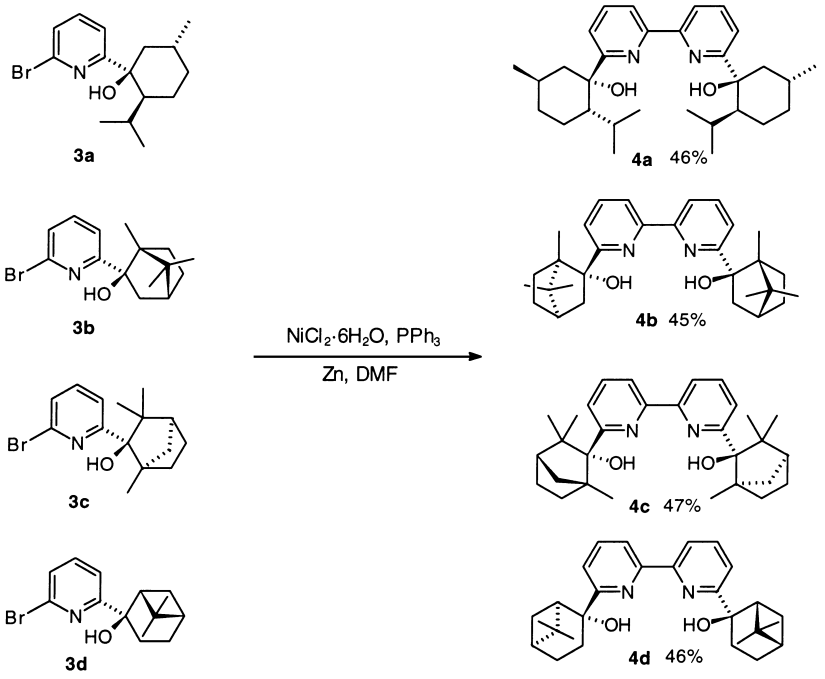
The synthesis of bromopyridylalcohols **3a**–**d** started from monolithiation of 2,6-dibromopyridine in ether followed by trapping with optically active naturally occurring ketones (Scheme 2). Compounds **3a**–**d** were obtained as single diastereomers as shown by GLC and NMR analysis of the product mixtures. The configurations are reported in Scheme 2. Similar observations had been observed previously with condensation of 2-pyridyllithium with the same chiral ketones.[13,14] The yields were 43–58% based on 2,6-dibromopyridine, depending only slightly on the nature of ketone.



Scheme 2. (a) *n*-BuLi, Et_2O, −78→−40°C; (b) menthone, −78°C→rt; (c) camphor, −78°C→rt; (d) fenchone, −78°C→rt; (e) nopinone, −78°C→rt

The optically active C_2-symmetric 2,2′-bipyridines of type **4** were then synthesized by nickel(0)-mediated homocoupling of **3a**–**d** (Scheme 3).[15,16] As with the previously reported homocoupling, no

protection of the hydroxy groups was required.[8] The yields of bipyridines for all the reactions were 45–47% after column chromatography.



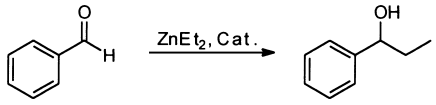
Scheme 3.

Having prepared these 2,2′-bipyridine diol ligands, we tested their properties as catalysts for the addition of diethylzinc to benzaldehyde (Table 1).[17] In all cases, the yields of the isolated 1-phenyl-1-propanol were good and the enantioselectivities obtained were also high. Catalyst **4a** induces the formation of the (*S*)-enantiomer in 82% ee (entry 1) while **4b**–**d** induce the formation of (*R*)-enantiomer in 92, 77 and 79% ee, respectively (entries 3, 11 and 12). Temperature and solvent have great effects on both the rate and enantioselectivity. Lowering the temperature from 22 to 0°C leads to slightly slower reactions but to an increase of asymmetric induction from 81 to 85% ee for **4a** (entry 2) and from 92 to 95% ee for **4b** (entry 4). Toluene (entry 3), hexane (entry 7) and THF (entry 8) gave similar results while CH_2Cl_2 (entry 9) and CH_3CN (entry 10) decreased the enantioselectivity and the rate as well. Changing the amount of catalyst from 2 to 8 mol% had only a small effect on the enantioselectivity (entries 3, 5 and 6). More remarkable is that all the reactions were completed within an hour at room temperature with 5 mol% catalysts. These observed reaction rates are very fast when compared with pyridylalcohol type ligands reported previously.[7a,9a,13,14] Use of pyridylalcohol prepared from 2-bromopyridine and chiral ketones for ethylation of benzaldehyde were reported previously by Chelucci and Dimitrov independently.[13,14] Our results here are much better in terms of rate and enantioselectivity.

With bipyridine **4b** being the best ligand, other aldehydes were also tested (Table 2). Several observations were noticed: in all cases, chemical yields of the alcohols were good; the enantioselectivities were all lower than benzaldehyde; all the reactions required more time for completion; not all substrates favor the (*R*)-configuration isomer. The observation of (*S*)-configuration products with cyclohexanecarboxaldehyde and 1-naphthaldehyde is not easy to understand, but it may be due to the bulkiness of the substrate, which changes the structure of the active catalyst upon coordination.

Although these C_2-symmetric bipyridine ligands can function as N,N bidentate ligands, studies by

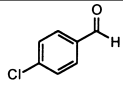
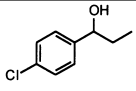
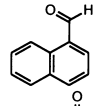
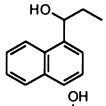
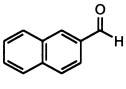
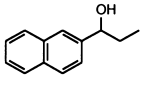
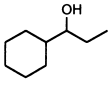
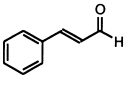
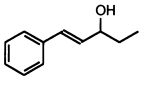
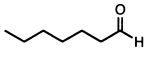
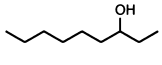
Table 1
Enantioselective addition of diethylzinc to benzaldehydes catalyzed by bipyridines **4a**–**d**[a]



Entry	Catalyst	Solvent	Time (h)[b]	Temp. (°C)	Yield (%)[c]	Ee (%)[d]
1	**4a**	Toluene	0.5	22	74	81 (S)
2	**4a**	Toluene	3	0	77	85 (S)
3	**4b**	Toluene	0.5	22	78	92 (R)
4	**4b**	Toluene	1	0	86	95 (R)
5[e]	**4b**	Toluene	1	22	86	91 (R)
6[f]	**4b**	Toluene	0.5	22	84	91 (R)
7	**4b**	THF	3	22	77	91 (R)
8	**4b**	Hexane	0.5	22	78	92 (R)
9	**4b**	CH_2Cl_2	5	22	36	43 (R)
10	**4b**	CH_3CN	5	22	30	23 (R)
11	**4c**	Toluene	0.5	22	82	77 (R)
12	**4d**	Toluene	0.5	22	86	79 (R)

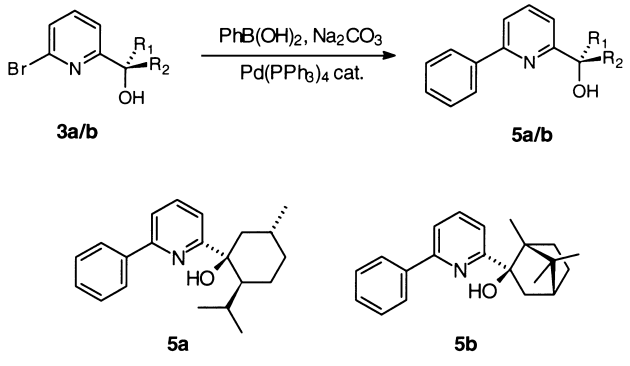
[a]Reactions were run with 5 mol% ligands unless otherwise stated. [b]Reactions were monitored by GC. [c]Isolated yield after chromatography. [d]Determined by GC analysis using a chiral column (Chrompack Chirasil-DEX CB column). Absolute configuration was determined by comparing the sign of specific rotation.[18] [e]Reactions were run with 2 mol% catalyst. [f]Reactions were run with 8 mol% catalyst.

Table 2
Enantioselective addition of diethylzinc to aldehydes catalyzed by **4b**[a]

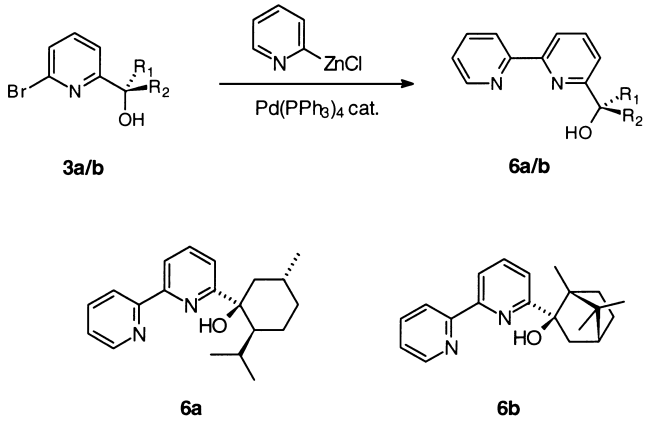
Substrate	Product	Time (h)[b]	Yield (%)[c]	Ee (%)[d]
		7	68	54 (R)
		7	52	20 (S)
		7.5	67	68 (R)
		6	66	80 (S)
		2.5	54	44 (R)
		6	74	47 (R)

[a]Reactions were run with 5 mol% ligands. [b]Reactions were monitored by GC. [c]Isolated yield after chromatography. [d]Determined by GC analysis using a chiral column (Chrompack Chirasil-DEX CB column). Absolute configuration was determined by comparing the sign of specific rotation.[18]

Bolm et al. on a related ligand have shown that it is not essential to have C_2 symmetry for achieving high enantioselectivity in the alkylation of aldehyde.[9a] Optically active pyridylalcohols with aromatic substituents in the 6-position of the heterocycle were equally efficient. In order to reveal more details of the nature of the active catalytic species, we prepared the phenyl substituted pyridylalcohols **5a** and **5b** and pyridyl substituted pyridylalcohols **6a** and **6b** to compare them with **4a** and **4b**, respectively. Ligands **5a** and **5b** were prepared by palladium(0)-catalyzed cross couplings of bromopyridines **3a** and **3b** with phenylboronic acid (Scheme 4),[9a,19] whereas bipyridines **6a** and **6b** were prepared by cross coupling of **3a** and **3b** with 2-pyridylzinc chloride using catalytic amounts of tetrakis(triphenylphosphine)palladium(0) (Scheme 5).[9a]



Scheme 4.



Scheme 5.

Ligands **5a**, **5b**, **6a** and **6b** were all active in catalyzing ethylation of benzaldehyde. With **5a** and **5b**, the enantiomeric excesses were 76% (*S*) and 78% (*R*), respectively, and complete conversion of benzaldehyde was achieved within 1.5 h for both ligands. Since the configurations of the products are the same as their bipyridine counterparts and the enantioselectivities, though a bit lower, are comparable to those with bipyridines, the results seem to suggest that ligands **4a**–**d** function as pyridylalcohol (N,O) ligands. In view of the high concentration of diethylzinc in the reaction mixture, we believe that the remaining N,O-part of the ligand coordinates to other zinc atoms during reaction and the two N,O units probably function independently. Further comparison of results with **6a** and **6b** provides more information. Ethylation of benzaldehyde with **6a** and **6b** gave 21% (*R*) and 65% (*R*) and complete conversions of benzaldehyde were achieved in 1 and 3 h, respectively. Although **6a** and **6b** are closer in structure to **4a** and **4b** than **5a** and **5b**, respectively, ligand **6a** gave the (*R*)-alcohol as the major product, in contrast to **4a** and **5a**, whereas

6b gave a lower ee than **5b**. Similar results have also been observed previously with other pyridylalcohols and bipyridylalcohols.[7a] The result here hints at a different mechanism for reactions with ligands **6a** and **6b**.

In summary, we have successfully synthesized four new C_2-symmetric 2,2′-bipyridine diol ligands in good yields using organometallic addition of chiral ketones and homocoupling of bromopyridine intermediates. These ligands are good catalysts for addition of diethylzinc to aldehydes. Enantiomeric excesses of up to 95% were observed. Comparison of reactivity and enantioselectivity of ligands **4a**, **5a**, **6a** and **4b**, **5b**, **6b** indicated that bipyridines **4** function as N,O ligands in diethylzinc addition reactions. We are continuing our efforts to study the use of these ligands in other catalytic asymmetric reactions.

3. Experimental

3.1. General methods

Toluene was distilled under N_2 from sodium. Dichloromethane and acetonitrile were distilled over calcium hydride. Diethyl ether and THF were distilled under N_2 over sodium/benzophenone. Chemicals were of reagent-grade quality obtained commercially. Infrared spectra in the range of 500–4000 cm^{-1} as Nujol matrices or KBr plates were recorded on a Perkin–Elmer model FTIR-1600 spectrometer. Proton and ^{13}C NMR spectra were recorded on a Varian 300 MHz Mercury instrument. Positive ion FAB mass spectra as 3-nitrobenzylalcohol matrices were recorded on a Finnagin MAT 95 spectrometer. Electron ionization mass spectra were recorded on a Hewlett–Packard 5890II GC instrument coupled with a 5970 mass selective detector. Elemental analyses were performed on a Vario EL elemental analyser. Optical rotation was measured by JASCO DIP-370 digital polarimeter. Melting point was measured by Electrothermal digital melting point apparatus.

3.2. General procedures for the synthesis of N,O ligands *3a–d*

To an ether solution (100 ml) of 2,6-dibromopyridine (20 mmol, 4.74 g) was added a 1.6 M solution of *n*-butylithium (14 ml) in hexane (22 mmol) at −78°C, over 30 min. This was allowed to warm to −45°C slowly and stirred for 15 min; a clear yellow solution was obtained. The mixture was cooled back to −78°C and chiral ketone (20 mmol) in dry ether (10 ml) was added dropwise over 10 min. The solution was allowed to warm to room temperature over 1 h and stirred for another 2.5 h. Water (50 ml) was then added. The layers were separated and the aqueous layer was extracted with ether (three times by 50 ml). The combined organic layers were washed with brine (50 ml) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (19:1 petroleum ether:ethyl acetate). All ligands were characterized by spectral (IR, ^1H NMR, ^{13}C NMR and MS) and elemental analyses.

3.2.1. N,O ligand *3a*

The above procedure was followed using (−)-menthone. After workup, it gave 3.62 g (58%) of **3a**: mp 43–45°C; $[\alpha]_D^{25}$=−5.2 (*c*=0.52, $CHCl_3$); IR (NaCl): 3447.3 m, 1581.9 m, 1553.1 s; ^1H NMR ($CDCl_3$): δ 0.62 (d, 3H, *J*=6.9 Hz), 0.76 (d, 3H, *J*=6.9 Hz), 0.80 (d, 3H, *J*=6.3 Hz), 1.10–1.30 (m, 2H), 1.40–1.60 (m, 4H), 1.70–2.0 (m, 3H), 4.15 (s, 1H), 7.28 (m, 2H), 7.48 (t, 1H, *J*=7.7 Hz); ^{13}C NMR ($CDCl_3$): δ 18.53, 21.80, 22.22, 23.59, 27.53, 28.33, 34.97, 49.48, 50.52, 77.54, 117.96, 125.54, 138.82, 139.93, 167.57;

MS (EI) *m/z* (rel. intensity): 311 and 313 (M^+, 11 and 11), 293 and 295 (14 and 14), 226 and 228 (48 and 47), 200 and 202 (base and 68), 184 and 186 (39 and 35).

3.2.2. *N,O ligand **3b***

The above procedure was followed using (*R*)-camphor. After workup, it gave 2.68 g (43%) of **3b**: mp 103–105°C; $[\alpha]_D^{25}$=−27.7 (*c*=0.51, $CHCl_3$); IR (KBr): 3455.7 s, 1577.8 s, 1550.1 vs; ^{1}H NMR ($CDCl_3$): δ 0.74 (s, 3H), 0.79 (s, 3H), 1.14 (s, 3H), 1.10–1.30 (m, 2H), 1.50–1.20 (m, 5H), 4.20 (s, 1H), 7.21 (d, 1H, *J*=7.7 Hz), 7.27 (d, 1H, *J*=7.7 Hz), 7.39 (t, 1H, *J*=7.7 Hz); ^{13}C NMR ($CDCl_3$): δ 9.79, 21.13, 21.18, 26.76, 30.67, 43.71, 45.16, 50.45, 53.54, 82.75, 119.14, 125.77, 137.74, 139.98, 165.35; MS (EI) *m/z* (rel. intensity): 309 and 311 (M^+, 8 and 9), 199 and 201 (base and 95).

3.2.3. *N,O ligand **3c***

The above procedure was followed using (1*R*)-(−)-fenchone. After workup, it gave 2.97 g (48%) of **3c**: mp 93–95°C; $[\alpha]_D^{25}$=−33.3 (*c*=0.52, $CHCl_3$); IR (KBr): 3400.0 s, 1577.8 vs, 1544.4 vs; ^{1}H NMR ($CDCl_3$): δ 0.46 (s, 3H), 0.99 (s, 3H), 1.00 (s, 3H), 1.15 (m, 1H), 1.35 (d, 1H, *J*=10.4 Hz), 1.49 (m, 1H), 1.80 (m, 2H), 2.30 (m, 2H), 5.00 (s, 1H), 7.3–7.50 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 17.05, 22.00, 24.33, 29.13, 32.37, 41.78, 46.09, 48.77, 52.05, 83.80, 121.43, 125.37, 137.29, 139.09, 164.34; MS (EI) *m/z* (rel. intensity): 309 and 311 (M^+, 3 and 2), 294 and 296 (6 and 6), 281 and 283 (9 and 8), 228 and 230 (base and 64).

3.2.4. *N,O ligand **3d***

The above procedure was followed using (1*R*)-(+)-nopinone. After workup, it gave 3.38 g (57%) of **3d** as a liquid: $[\alpha]_D^{25}$=+4.3 (*c*=0.56, $CHCl_3$); IR (KBr): 3444.4 s, 1572.2 s, 1550.0 vs; ^{1}H NMR ($CDCl_3$): δ 1.13 (d, 1H, *J*=10.2 Hz), 1.24 (s, 3H), 1.26 (s, 3H), 1.80–2.40 (m, 6H), 2.56 (m, 1H), 3.78 (s, 1H), 7.34 (d, 1H, *J*=7.7 Hz), 7.39 (d, 1H, *J*=7.7 Hz), 7.52 (t, 1H, *J*=7.7 Hz); ^{13}C NMR ($CDCl_3$): δ 23.39, 24.79, 27.60, 27.68, 29.32, 38.71, 39.93, 52.87, 78.88, 118.29, 125.88, 138.44, 140.50, 168.15; MS (EI) *m/z* (rel. intensity): 295 and 297 (M^+, 4 and 4), 278 and 280 (20 and 18), 213 and 215 (base and 88).

3.3. *General procedures for synthesis of bipyridines **4a–d***

To a solution of $NiCl_2 \cdot 6H_2O$ (6 mmol, 1.43 g) in degassed DMF (30 ml) at 70°C under N_2, triphenylphosphine (24 mmol, 6.30 g) was added to give a blue solution. Zinc powder (13 mmol, 0.87 g) was then added and the resulting mixture was stirred for 1 h which resulted in the formation of a dark-brown mixture. N,O ligand **3** (5 mmol) in degassed DMF (5 ml) was added slowly and the mixture was stirred for another 3 h. The mixture was then allowed to cool to room temperature and 5% aqueous NH_3 (50 ml) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (three times by 70 ml). The combined organic layers were washed with water (three times by 50 ml) and once with brine (50 ml). Drying with Na_2SO_4 and removal of the solvent under reduced pressure yielded a pale yellow solid. This was purified by column chromatography (25:1 petroleum ether:ethyl acetate) to give a white solid which was characterized by IR, ^{1}H NMR, ^{13}C NMR, CHN, MS and elemental analyses.

3.3.1. *Bipyridine **4a***

The above general procedure was followed using N,O ligand **3a**. The usual workup gave 0.53 g (46%) of **4a**: mp 159–161°C; $[\alpha]_D^{25}$=−40.5 (*c*=0.50, CCl_4); IR (KBr): 3380.6 s, 1577.8 s; ^{1}H NMR ($CDCl_3$): δ 0.63 (d, 6H, *J*=6.69 Hz), 0.77 (d, 6H, *J*=6.9 Hz), 0.84 (d, 6H, *J*=6.6 Hz), 1.00 (m, 2H), 1.20 (m, 2H), 1.32 (m, 2H), 1.48–1.73 (m, 8H), 1.78–2.02 (m, 4H), 5.35 (s, 2H), 7.30 (d, 2H, *J*=7.7 Hz), 7.79 (t, 2H, *J*=7.7

Hz), 8.24 (d, 2H, *J*=7.7 Hz); ^{13}C NMR ($CDCl_3$): 18.67, 20.08, 22.50, 23.77, 27.64, 28.69, 35.38, 50.01, 50.85, 77.36, 118.79, 119.49, 137.89, 152.65, 164.72; positive ion FAB mass spectra *m/z*: 465 (M^++H). Anal. calcd for $C_{30}H_{44}N_2O_2$: C, 77.54; H, 9.54; N, 6.03. Found: C, 77.58; H, 9.41; N, 6.01.

*3.3.2. Bipyridine **4b***

The above general procedure was followed using N,O ligand **3b**. The usual workup gave 0.52 g (45%) of **4b**: mp 232–234°C; $[\alpha]_D^{25}$=−59.8 (*c*=0.51, CCl_4); IR (KBr): 3466.7 s, 3433.4 vs, 1566.7 vs; ^{1}H NMR ($CDCl_3$): δ 0.82 (s, 6H), 0.85 (s, 6H), 1.22 (s, 6H), 1.16–1.34 (m, 4H), 1.68–1.82 (m, 4H), 1.87 (t, 2H, *J*=4.4 Hz), 2.16 (d, 2H, *J*=14.0 Hz), 2.22–2.34 (s, 2H), 5.20 (s, 2H), 7.41 (d, 2H, *J*=7.7 Hz), 7.74 (t, 2H, *J*=7.7 Hz), 8.19 (d, 2H, *J*=7.7 Hz); ^{13}C NMR ($CDCl_3$): δ 10.11, 21.30, 21.42, 27.11, 30.90, 44.12, 45.46, 50.58, 53.55, 82.89, 118.75, 120.70, 136.74, 153.25, 162.90; positive ion FAB mass spectra *m/z*: 461 (M^++H). Anal calcd for $C_{30}H_{40}N_2O_2$: C, 78.22, H, 8.75; N, 6.08. Found: C, 76.48; H, 8.46; N, 5.46.

*3.3.3. Bipyridine **4c***

The above general procedure was followed using N,O ligand **3c**. The usual workup gave 0.54 g (47%) of **4c**: mp 176–178°C; $[\alpha]_D^{25}$=+27.2 (*c*=0.51, CCl_4); IR (KBr): 3366.7 s, 3300.1 s, 1572.3 vs; ^{1}H NMR ($CDCl_3$): δ 0.52 (s, 6H), 1.02 (s, 6H), 1.05 (s, 6H), 1.20 (m, 2H), 1.40 (m, 2H), 1.50 (m, 2H), 1.85 (m, 4H), 2.35 (m, 4H), 6.10 (s, 2H), 7.57 (d, 2H, *J*=7.7 Hz), 7.80 (t, 2H, *J*=7.7 Hz), 8.22 (d, 2H, *J*=7.7 Hz); ^{13}C NMR ($CDCl_3$): δ 17.30, 22.41, 24.51, 29.48, 32.60, 42.08, 46.10, 48.88, 52.08, 83.84, 118.45, 123.16, 136.16, 152.41, 161.63; positive ion FAB mass spectra *m/z*: 461 (M^++H). Anal. calcd for $C_{30}H_{40}N_2O_2$: C, 78.22; H, 8.75; N, 6.08. Found: C, 78.79, H, 8.65; N, 5.41.

*3.3.4. Bipyridine **4d***

The above general procedure was followed using N,O ligand **3d**. The usual workup gave 0.50 g (46%) of **4d**: mp 142–144°C; $[\alpha]_D^{25}$=−19.1 (*c*=0.51, CCl_4); IR (KBr): 3444.2 s, 1570.8 s; ^{1}H NMR ($CDCl_3$): δ 0.87 (m, 2H), 1.28 (s, 6H), 1.30 (s, 6H), 1.90–2.30 (m, 12H), 2.62 (m, 2H), 4.70 (s, 2H), 7.50 (d, 2H, *J*=7.7 Hz), 7.82 (d, 2H, *J*=7.7 Hz), 8.29 (t, 2H, *J*=7.7 Hz); ^{13}C NMR ($CDCl_3$): δ 23.50, 25.05, 27.77, 29.90, 38.91, 40.10, 53.55, 78.86, 118.86, 119.79, 137.22, 153.55, 165.67; positive ion FAB mass spectra *m/z*: 433 (M^++H). Anal. calcd for $C_{28}H_{36}N_2O_2$: C, 77.74; H, 8.39; N, 6.48. Found: C, 77.76, H, 8.86; N, 6.67.

*3.4. General procedures for the synthesis of N,O ligands **5a**,**b***

A solution of N,O ligand **3** (5.76 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.17 mmol, 0.2 g) in toluene (12 ml) was treated with a solution of Na_2CO_3 (11.53 mmol, 1.22 g) in H_2O (6 ml) followed by a solution of phenylboronic acid (6.92 mmol, 0.84 g) in MeOH (3 ml). The mixture was stirred at 85°C for 4 h under N_2. After cooling to room temperature, a solution of concentrated aqueous NH_3 (2.9 ml) in saturated aqueous Na_2CO_3 (29 ml) was added and the mixture was extracted with CH_2Cl_2 (three times by 50 ml). The combined organic layers were washed with brine (50 ml) and dried with Na_2SO_4. Removal of the solvent under reduced pressure gave a crude product which was purified by chromatography (25:1, petroleum ether:ethyl acetate). This product was characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and CHN.

*3.4.1. N,O ligand **5a***

Following the above procedure using N,O ligand **3a** and the usual workup gave 0.84 g (47%) of **5a**: mp 102–103°C; $[\alpha]_D^{25}$=−35.5 (*c*=0.51, CCl_4); IR (KBr): 3377.8 s, 1572.2 s; ^{1}H NMR ($CDCl_3$): δ 0.69 (d, 3H, *J*=7.1 Hz), 0.84 (d, 3H, *J*=7.1 Hz), 0.91 (d, 3H, *J*=7.1 Hz), 1.07 (m, 1H), 1.26 (m, 1H), 1.38 (m,

1H), 1.56–1.80 (m, 4H), 1.84–2.10 (m, 2H), 5.66 (s, 1H), 7.27 (d, 1H, *J*=7.7 Hz), 7.45 (m, 3H), 7.64 (d, 1H, *J*=7.7 Hz), 7.78 (t, 1H, *J*=7.7 Hz), 8.03 (d, 2H, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 18.57, 22.05, 22.39, 23.63, 27.51, 28.53, 35.30, 50.01, 50.73, 77.08, 117.54, 117.97, 126.64, 128.52, 128.93, 137.56, 138.45, 154.18, 164.83; MS (EI) *m/z* (rel. intensity): 309 (M^+, 23), 266 (17), 224 (85), 198 (64), 169 (31), 154 (base). Anal. calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.71; H, 8.43; N, 4.32.

*3.4.2. N,O ligand **5b***

Following the above procedure using N,O ligand **3b** and the usual workup gave 0.94 g (53%) of **5b**: mp 88–89°C; $[\alpha]_D^{25}$=−61.4 (*c*=0.51, CCl_4); IR (KBr): 3377.8 s, 1572.2 s; ^{1}H NMR ($CDCl_3$): δ 0.88 (s, 3H), 0.92 (s, 3H), 1.30 (s, 3H), 1.24–1.40 (m, 3H), 1.76–1.96 (m, 2H), 2.14–2.40 (m, 2H), 5.45 (s, 1H), 7.36–7.52 (m, 4H), 7.64 (d, 1H, *J*=7.7 Hz), 7.74 (t, 1H, *J*=7.7 Hz), 8.01 (d, 2H, *J*=6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 10.17, 21.30, 21.44, 27.15, 30.89, 44.22, 45.45, 50.58, 53.55, 82.85, 118.15, 118.94, 126.67, 128.60, 128.96, 136.45, 138.72, 154.64, 163.13; MS (EI) *m/z* (rel. intensity): 307 (M^+, 27), 264 (12), 198 (base), 169 (31), 154 (52). Anal. calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.17; H, 8.02; N, 4.01.

*3.5. General procedures for the synthesis of bipyridine ligands **6a**,**b***

A solution of 2-bromopyridine (1.1 g, 7 mmol) in THF (30 ml) at −78°C was treated slowly with a 2.5 M solution of *n*-butyllithium in *n*-hexane (2.8 ml, 7 mmol). The resulting red-brown solution was stirred at this temperature for 30 min and transferred through a cannula into a cold (−78°C) solution of dry $ZnCl_2$ (0.96 g) in THF (20 ml) ($ZnCl_2$ was used after fusion by flame-drying under reduced pressure). The color of the solution remained the same at this temperature. After warming to room temperature, the mixture was stirred until the color changed to yellow-brown. This mixture was transferred into a stirred solution of N,O ligand **3** (3.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.4 mmol, 0.4 g) in THF (20 ml). After stirring for 16 h at room temperature, 100 ml of saturated aqueous $NaHCO_3$ was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (three times by 50 ml) and the combined organic layers were washed with brine (50 ml) and dried with Na_2SO_4. The solvent was removed under reduced pressure to give a crude product which was purified by chromatography on a silica gel column (10:1, petroleum ether:triethyl amine). Product was characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and CHN.

*3.5.1. Bipyridine ligand **6a***

The above procedure was followed using ligand **3a**. The usual workup gave 0.85 g (78%) of **6a**: mp 77–78°C; $[\alpha]_D^{25}$=−28.7 (*c*=0.52, CCl_4); IR (KBr): 3366.7 s, 1577.8 s, 1562.6 s; ^{1}H NMR ($CDCl_3$): δ 0.69 (d, 3H, *J*=6.9 Hz), 0.84 (d, 3H, *J*=6.9 Hz), 0.91 (d, 3H, *J*=6.6 Hz), 1.08 (m, 1H), 1.27 (m, 1H), 1.40 (m, 1H), 1.56–1.80 (m, 4H), 1.84–2.08 (m, 2H), 5.46 (s, 1H), 7.28–7.40 (m, 2H), 7.78–7.90 (m, 2H), 8.32 (d, 1H, *J*=7.7 Hz), 8.41 (d, 1H, *J*=8.0 Hz), 8.69 (d, 1H, *J*=4.4 Hz); ^{13}C NMR ($CDCl_3$): δ 18.55, 22.03, 22.38, 23.61, 27.48, 28.55, 35.28, 50.00, 50.68, 77.16, 118.75, 119.24, 120.80, 123.61, 136.69, 137.76, 148.94, 153.13, 155.36, 164.49; MS (EI) *m/z* (rel. intensity): 310 (M^+, 36), 267 (34), 225 (base), 199 (83), 170 (32), 155 (86). Anal. calcd for $C_{20}H_{26}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.12; H, 8.47; N, 8.74.

*3.5.2. Bipyridine ligand **6b***

The above procedure was followed using ligand **3b**. The usual workup gave 0.95 g (88%) of **6b**: mp 97–99°C; $[\alpha]_D^{25}$=−49.6 (*c*=0.52, CCl_4); IR (KBr): 3388.9 s, 1577.8 s, 1560.7 s; ^{1}H NMR ($CDCl_3$): δ

0.89 (s, 3H), 0.93 (s, 3H), 1.30 (s, 3H), 1.20–1.45 (m, 2H), 1.70–2.00 (m, 3H), 2.20–2.40 (m, 2H), 5.21 (s, 1H), 7.32 (m, 1H), 7.48 (d, 1H, J=7.7 Hz), 7.78–7.85 (m, 2H), 8.30–8.40 (m, 2H), 8.67 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 9.94, 21.16, 21.29, 26.96, 30.75, 43.97, 45.35, 50.44, 53.42, 82.77, 118.81, 120.46, 120.67, 123.57, 136.59, 136.69, 148.88, 153.52, 155.48, 162.67; MS (EI) *m/z* (rel. intensity): 308 (M^+, 20), 265 (12), 199 (base), 170 (21), 155 (34). Anal. calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.88; H, 7.92; N, 8.56.

3.6. General procedures for the addition of diethylzinc to aldehydes

Chiral ligand (0.05 mmol, 5 mol%) in dry toluene (1.0 ml) was cooled to 0°C and 1 M diethylzinc in hexane (1.5 mmol, 1.5 ml) was added slowly. The mixture was allowed to stir at room temperature for 30 min. Freshly distilled aldehyde (1 mmol) was added and the reaction was monitored by GC. After the reaction was completed, it was quenched by addition of 2 N HCl (5 ml). The layers were separated and the aqueous layer was extracted with ether (three times by 20 ml). The combined organic layers were dried by Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography. Enantiomeric excesses for the products were determined by chiral GC with a Chrompack Chirasil-DEX CB column.

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