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Synthesis of novel chiral oligopyridine derivative ligands for the enantioselective addition of diethylzinc to benzaldehyde

Hiyoshizo Kotsuki,[a,*] Hiroyuki Hayakawa,[a] Hirotaka Tateishi,[a] Masahiro Wakao [a] and Motoo Shiro [b]

[a] *Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780-8520, Japan*
[b] *Rigaku Corporation, Matsubara-cho, Akishima, Tokyo 196, Japan*

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Abstract

Several chiral dipyridine and dithiophene derived ligands have been prepared from readily available homochiral materials such as ethyl L-lactate and naproxene methyl ester, based on the dialkylation strategy using heterocyclic organometallic reagents. Each of these chiral ligands was used for the catalytic enantioselective addition of diethylzinc to benzaldehyde. The best result was obtained for **3**: 70% ee was achieved. A plausible mechanism for this asymmetric induction is offered, based on X-ray crystallographic data.

1. Introduction

Asymmetric metal catalysis is now recognized as an important method of producing organic molecules in enantiomerically pure form.[1] Accordingly, a great deal of effort has been devoted to introducing new chiral metal catalysts, in which designing effective chiral ligands plays an essential role.[2] Nitrogen heterocyclic derivatives, such as pyridines and oligopyridines, are some of the most attractive ligands, and are gathering considerable attention not only from the standpoint of asymmetric synthesis but also in the fields of coordination[3] and supramolecular chemistry.[4] In our own efforts to investigate new catalytic asymmteric transformations,[5] we recently reported the novel synthesis of C_2-symmetric chiral pyridine ligands and their use in the asymmetric alkylation of benzaldehyde with diethylzinc (Eq. 1).[6] Unfortunately, the catalytic use of these ligands only modestly enforced the desired chiral induction [40–41% enantiomeric excess (ee)]. This result undoubtedly can be ascribed to the distance between the stereogenic carbon centers and the pyridine coordination sites.

* Corresponding author. E-mail: kotsuki@cc.kochi-u.ac.jp

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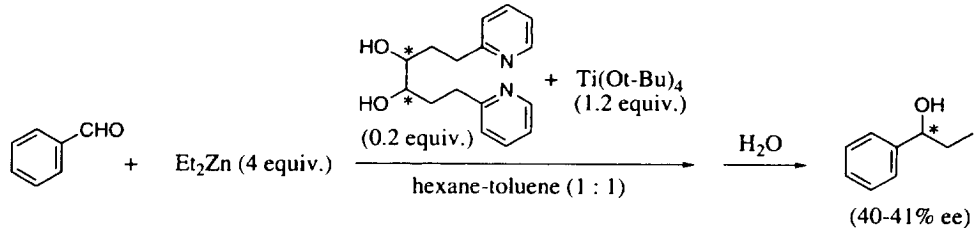


(1)

We have developed a facile new method to synthesize chiral oligopyridine ligands[7] by incorporating the pyridine functional group in close proximity to the stereogenic carbon centers by taking advantage of readily available chiral materials. The catalytic effects of the products obtained in this study have been assessed in the addition of diethylzinc to benzaldehyde.

2. Results and discussion

2.1. Preparation of chiral ligands

As the most straightforward approach, we adopted a dialkylation strategy, starting from commercially available homochiral esters such as ethyl L-lactate (**1**)[8] with an excess of the lithiopyridine species (Scheme 1). Thus, treating **1** with 3.6 equiv. of 2-lithiopyridine, which was prepared from 2-bromopyridine by transmetallation with *n*-BuLi,[8] in THF at −78°C produced the desired dipyridine **2a** along with the pyridylketone **2b**[9] in yields of 52 and 19%, respectively. Selective protection of the secondary alcohol group of **2a** with *tert*-butyldimethylchlorosilane or acetic anhydride gave both the corresponding dipyridylsilyl ether **3** and dipyridyl monoacetate **4** in high yields. Furthermore, methylation of a free tertiary alcohol group in **3** (MeI/NaH) followed by desilylation with 40% HF in aqueous CH_3CN produced the dipyridyl secondary alcohol **6**.

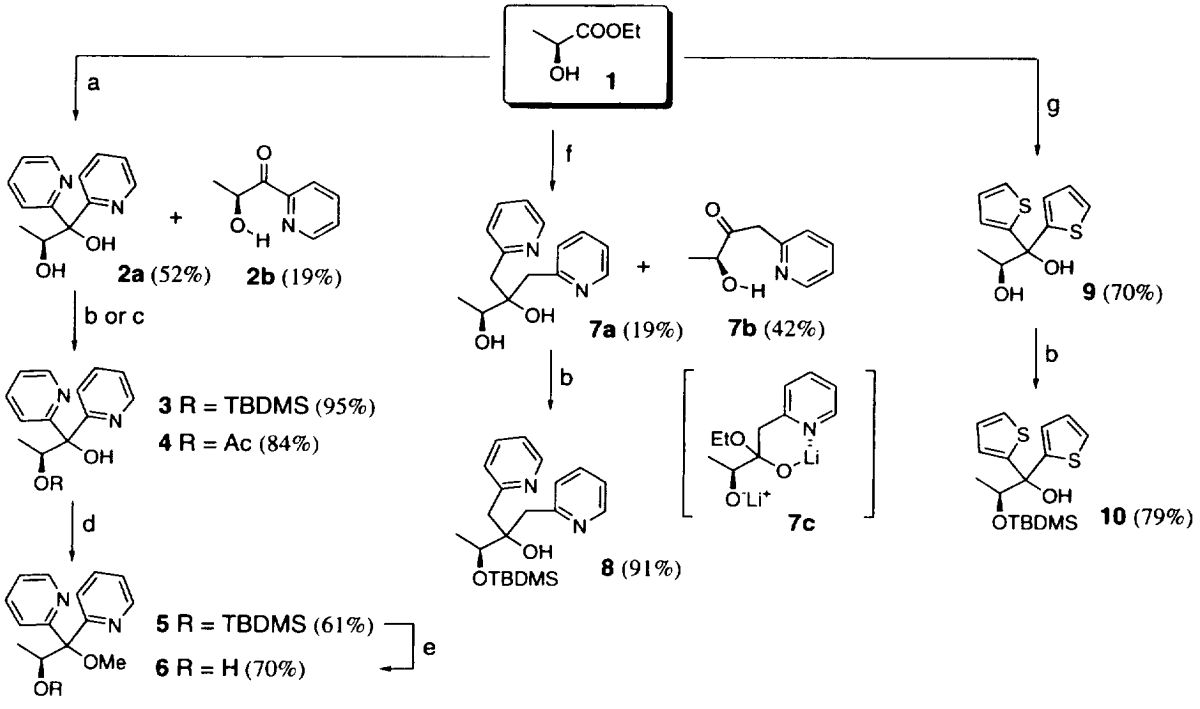
In order to survey our new chiral ligands systematically, we also prepared larger homologs, such as **7a** and **8**, using 2-picolyllithium[10] in place of 2-lithiopyridine. The only problem in this sequence was the formation of the undesired ketone **7b** as the major by-product of the first step. This accounts for the peculiar structure of the carbon tetrahedral intermediate **7c**, which is stabilized by six-membered intramolecular coordination of lithium at the pyridyl nitrogen. Unfortunately, all attempts to reconvert **7b** to **7a** were unsuccessful, due to the fairly unstable nature of **7b**.[9]

Although the metal coordination character of thiophene is not well understood,[11,12] characterization of its behavior would be informative. Thus, similar treatment of **1** with 2-thienyllithium[9] gave the dithienyl analog **9**, which was further converted to the monosilyl-protected alcohol **10**.

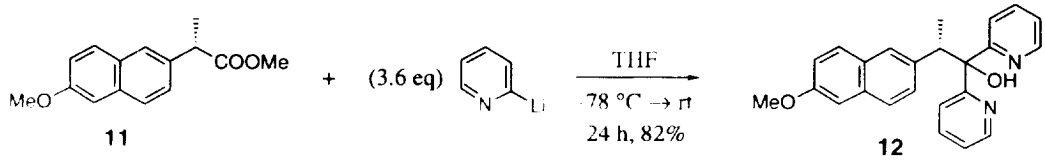
Besides using **1** as a chiral resource,[13] we were also interested in naproxene methyl ester **11**,[14] since it is anticipated that the electron-rich naphthalene ring system within this molecule might exert some influence on the enantiodifferentiating process, perhaps via a π–π stacking interaction. Thus, following the established strategy as described above, **11** was alkylated with 2-lithiopyridine to give **12** in 82% yield (Scheme 2).

2.2. Catalytic reactions

With a variety of chiral pyridine and thiophene derivative ligands in hand, we then proceeded to evaluate the feasibility of using them in the asymmetric catalytic alkylation of benzaldehyde with diethylzinc.[15] By analogy to previously reported examples using several chiral pyridine catalysts,[16]



Scheme 1. Reagents and conditions: (a) 2-lithiopyridine (3.6 equiv.), THF, rt; (b) TBDMSCl, imidazole, DMF, rt; (c) Ac_2O, cat. 4-dimethylaminopyridine, pyridine, rt; (d) NaH, THF, then MeI, rt; (e) 40% aq. HF, CH_3CN, rt; (f) 2-picolyllithium (3.0 equiv.), THF, rt; (g) 2-thienyllithium (3.6 equiv.), THF, rt

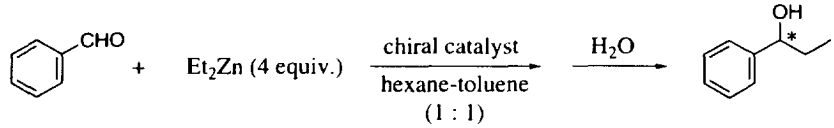


Scheme 2.

we expected that comparable catalytic activity should be obtained for our new ligands. In general, the reaction was carried out in hexane–toluene at room temperature using 4 equiv. of diethylzinc in the presence of 0.2 equiv. of the catalyst, and the results are summarized in Table 1.

Not surprisingly, the use of the unprotected diol **2a** showed very little catalytic activity (entry 1). Unlike our previous findings,[6] the addition of $Ti(O\text{-}t\text{-}Bu)_4$[17] to this system did not significantly improve the ee (entry 2). Fortunately, relatively high enantioselectivity (70% ee) was achieved when the monosilyl-protected dipyridine **3** was used as a chiral catalyst (entry 3). In this case, the use of less diethylzinc or the addition of $Ti(O\text{-}t\text{-}Bu)_4$ considerably reduced the yields and enantiomeric excesses (entries 4 and 5).[18] As expected, using acetate **4** was inefficient, owing to its lability as a protective group, and using the fully protected **5** was also fruitless (entries 6 and 7). The less efficient the chiral catalysts (like **6**, **7a**, and **8**) the more unfavorable the asymmetric environment around the chelating hydroxyl and nitrogen groups (entries 8–10). The marked difference in catalytic activity between **3** and its thiophene analog **10** clearly demonstrates the non-chelating character of the thiophene sulfur (compare entries 3 and 11). Contrary to our expectations, a disappointingly low catalytic activity was observed for **12** (6% ee) compared with that of **3** (70% ee), implying that the naphthalene ring did not make an important contribution to the required stereocontrol (entry 12). In any event, it is surprising that replacing only the *tert*-butyldimethylsilyloxy

Table 1
Enantioselective addition of diethylzinc to benzaldehyde in the presence of several chiral catalysts



Entry	Catalyst[a]	Additive[b]	Time (h)	Yield (%)[c]	ee (%)[d]	Abs. Config.[e]
1	**2a**	--	48	64	2	*S*
2	**2a**	Ti(O*t*-Bu)$_4$	48	88	12	*R*
3	**3**	--	10	90	70	*S* ⇦
4[f]	**3**	--	24	37	66	*S*
5	**3**	Ti(O*t*-Bu)$_4$	48	84	51	*S*
6	**4**	--	48	10	3	*S*
7	**5**	--	48	84	2	*S*
8	**6**	--	48	91	2	*S*
9	**7a**	--	72	77	8	*S*
10	**8**	--	120	90	6	*R*
11	**10**	--	72	55	2	*S*
12	**12**	--	24	100	6	*S*

a) 0.2 equiv. of the catalyst was used. b) 1.2 equiv. of the additive was used. c) Isolated yields. d) Determined by HPLC (DAICEL Chiralcel OB). e) Determined by optical rotation. f) 2 equiv. of Et_2Zn was used.

group of **3** with a naphthalene ring at the stereogenic carbon center decreased the enantioselectivity considerably, and at present, we cannot explain this.

X-Ray crystallographic structure analysis was then performed to gain insight into the best results obtained with the monosilyl-protected dipyridine **3**. The ORTEP depiction is shown in Fig. 1. Evidently, this molecule has a relatively rigid conformation, caused by intramolecular hydrogen bonding between the adjacent hydroxyl group and one of the pyridine rings. The hydrogen bond distance between N(1) and O(2) is 2.61 Å. Support for this hydrogen bonding in solution comes from the ^{1}H NMR spectrum, which shows a large downfield shift of the OH resonance for **3** (δ=5.94 in $CDCl_3$).

Although we cannot preclude the possibility that the solid state conformation may be quite different from that found in solution, we believed that initially diethylzinc should react with **3** to form an organozincate complex that maintains the original spatial arrangement. Following the proposed mechanism described in the literature,[5,19] the reaction in the presence of **3** can be considered to proceed through a six-centered transition state, in which benzaldehyde is attacked on its *si*-face to form (*S*)-1-phenyl-1-propanol, as illustrated in Scheme 3. The 70% ee in this reaction indicates that some isomerization of the intermediate complex took place by switching the coordination pattern to the second pyridyl ligand.

In conclusion, we have developed a facile method for deriving a variety of chiral oligopyridine derivative ligands by applying the polyalkylation strategy to readily available homochiral esters. Thus, our initial purpose of improving the stereocontrol in the formation of 1-phenyl-1-propanol was achieved by incorporating a pyridine unit near the stereogenic carbon center (70% ee). It is noteworthy that the

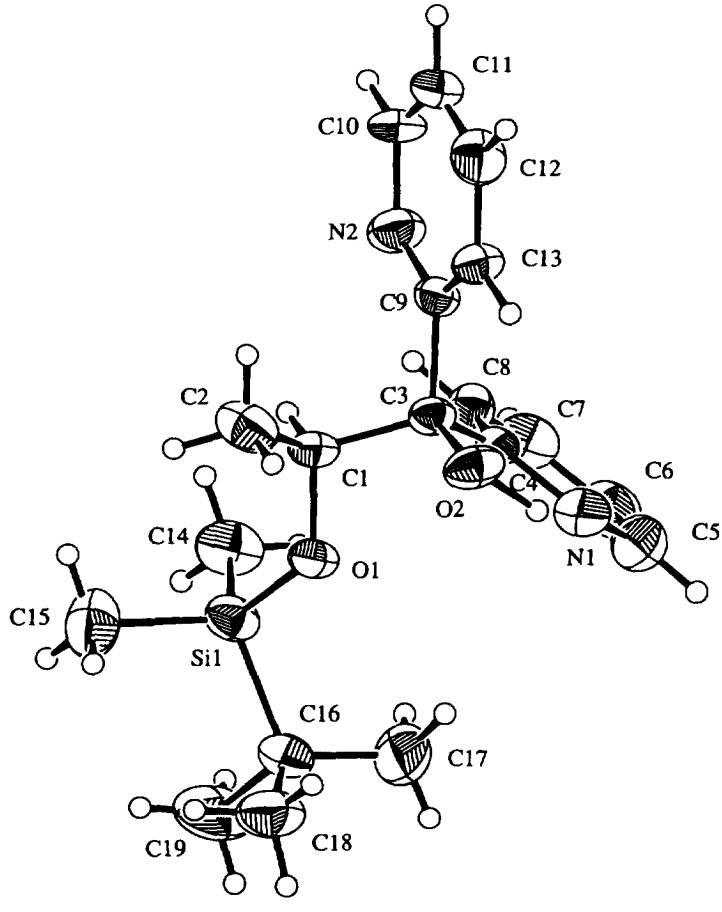
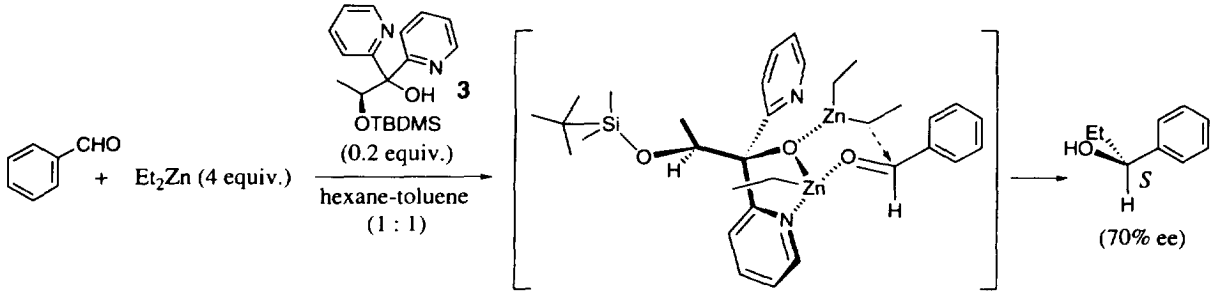


Fig. 1. X-Ray crystal structure of **3**



Scheme 3. Plausible mechanism for the enantioselective alkylation of benzaldehyde with diethylzinc

asymmetric environment with a pyridyl coordination sphere significantly influenced the stereocontrol of the ethylation of benzaldehyde.

3. Experimental section

General procedures were as described previously.[6] All NMR were recorded in $CDCl_3$ solution at 90 MHz for ^1H NMR and 22.6 MHz for ^{13}C NMR.

3.1. (S)-1,1-Di(2-pyridyl)propane-1,2-diol 2a

A solution of 2.56M *n*-BuLi in hexane (14 ml, 36 mmol) was added to a solution of 2-bromopyridine (5.69 g, 36 mmol) in THF (15 ml) at −78°C and the mixture was stirred at this temperature for 10 min. Then a solution of ethyl (*S*)-lactate **1** (1.18 g, 10 mmol) in THF (20 ml) was added dropwise at −78°C and the mixture was allowed to warm to rt and stirred for 24 h. After quenching with aq. KOH, the precipitate was removed by filtration through Celite. The filtrate was extracted with AcOEt, dried (Na_2SO_4), and concentrated. The crude product was purified by silica gel column chromatography (hexane:AcOEt=4:1 to 1:1) to give **2a** (1.2 g, 52%) as colorless needles and the ketone **2b** (0.29 g, 19%) as a colorless oil. Mp 62.0–62.5°C (from Et_2O–pentane); R_f 0.26 (hexane:AcOEt=1:1); $[\alpha]_D^{26}$ +29.2 (c 1.00, $CHCl_3$); FTIR (KBr) ν 3432, 3248, 1589, 1466, 1441, 1138 cm^{-1}; ^1H NMR δ 1.03 (3H, d, J=6.4 Hz), 4.50 (1H, br), 4.67 (1H, q, J=6.4 Hz), 6.50 (1H, br), 7.1–7.3 (2H, m), 7.5–7.9 (4H, m), 8.4–8.6 (2H, m); ^{13}C NMR δ 17.3, 73.8, 78.6, 121.6, 122.3, 122.4, 122.6, 136.7, 136.9, 146.8, 147.3, 160.7, 162.7. Anal. calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17%. Found: C, 67.79; H, 5.91; N, 12.28%.

Ketone **2b**: R_f 0.37 (hexane:AcOEt=1:1); $[\alpha]_D^{24}$ −55.9 (c 1.27, $CHCl_3$); FTIR (neat) ν 3445, 1703, 1584, 976 cm^{-1}; ^1H NMR δ 1.52 (3H, d, J=6.8 Hz), 4.30 (1H, br), 5.36 (1H, q, J=6.8 Hz), 7.51 (1H, ddd, J=7.7, 4.7, 1.8 Hz), 7.88 (1H, dt, J=7.7, 1.8 Hz), 8.09 (1H, ddd, J=7.7, 1.8, 1.0 Hz), 8.68 (1H, ddd, J=4.7, 1.8, 1.0 Hz); ^{13}C NMR δ 20.8, 70.6, 122.9, 127.5, 137.1, 148.7, 151.2, 201.9. No satisfactory HRMS data were obtained due to the unusual instability.[9]

3.2. (S)-2-tert-Butyldimethylsilyloxy-1,1-di(2-pyridyl)propan-1-ol 3

A mixture of **2a** (250 mg, 1.1 mmol), imidazole (110 mg, 1.6 mmol), and TBDMSCl (240 mg, 1.6 mmol) in DMF (1.1 ml) was stirred at rt for 4 h. The mixture was quenched with H_2O and extracted with AcOEt. The combined extracts were washed with H_2O and brine. The organic phase was dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel column chromatography (hexane:AcOEt=19:1 to 9:1) to give **3** (360 mg, 95%) as colorless plates. Mp 54.5–57.0°C (from pentane); R_f 0.30 (hexane:AcOEt=9:1); $[\alpha]_D^{26}$ +44.6 (c 1.01, $CHCl_3$); FTIR (KBr) ν 3304, 1589, 1468, 1437 cm^{-1}; ^1H NMR δ −0.35 (3H, s), 0.00 (3H, s), 0.65 (9H, s), 1.03 (3H, d, J=6.2 Hz), 5.12 (1H, q, J=6.2 Hz), 5.94 (1H, br), 7.0–7.3 (2H, m), 7.5–7.7 (2H, m), 7.8–8.1 (2H, m), 8.5–8.6 (2H, m); ^{13}C NMR δ −5.3, −4.0, 17.8, 18.0, 25.7 (×3), 74.6, 81.1, 121.3, 121.7, 121.9 (×2), 136.2, 136.4, 147.0, 147.8, 162.16, 162.22. Anal. calcd for $C_{19}H_{28}N_2O_2Si$: C, 66.24; H, 8.20; N, 8.14%. Found: C, 66.52; H, 8.04; N, 8.09%.

3.3. (S)-1-Hydroxy-1,1-di(2-pyridyl)-2-propyl acetate 4

A mixture of **2a** (230 mg, 1 mmol), a catalytic amount of 4-dimethylaminopyridine, and Ac_2O (204 mg, 2 mmol) in pyridine (5 ml) was stirred at rt for 24 h. The mixture was quenched with H_2O and extracted with AcOEt. The combined extracts were washed with aq. NaOH, H_2O, and brine. The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified by preparative TLC (hexane:AcOEt=1:1) to give **4** (229 mg, 84%) as a pale orange oil. R_f 0.46 (hexane:AcOEt=9:1); $[\alpha]_D^{26}$ −2.85 (c 1.05, $CHCl_3$); FTIR (neat) ν 3329, 1736, 1589, 1572, 1244 cm^{-1}; ^1H NMR δ 1.12 (3H, d, J=6.4 Hz), 1.72 (3H, s), 6.28 (1H, q, J=6.4 Hz), 6.67 (1H, s), 7.0–7.3 (2H, m), 7.5–7.8 (2H, m), 7.8–8.0 (2H, m), 8.4–8.6 (2H, m); ^{13}C NMR δ 14.0, 20.6, 75.4, 79.5, 121.1 (×2), 122.0, 122.2, 136.4, 136.6, 146.9, 147.6, 160.5 (×2), 169.8; MS *m/z* (rel. intensity) 273 (M^++1, 54), 255 (10), 213 (36), 185 (100), 80 (5), 78 (6), 41 (7). HRMS calcd for $C_{15}H_{16}N_2O_3$+H: 273.1239. Found: 273.1249.

3.4. (S)-2-tert-Butyldimethylsilyloxy-1,1-di(2-pyridyl)-1-methoxypropane 5

A solution of **3** (70 mg, 0.2 mmol) in THF (2 ml) was added to a suspension of NaH (16 mg, 0.4 mmol; 60% dispersion in a mineral oil) in THF (6 ml) at 0°C and the mixture was stirred at rt for 30 min. Then to this mixture was introduced MeI (57 mg, 0.4 mmol) at 0°C and the mixture was stirred at rt for 15 h. After quenching with water, the mixture was extracted with AcOEt. The extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by preparative TLC (hexane:AcOEt=5:1) to give **5** (44 mg, 61%) as a colorless solid. Mp 62.0–63.0°C (unrecrystallized); R_f 0.18 (hexane:AcOEt=5:1); $[\alpha]_D^{26}$ −13.4 (c 0.75, $CHCl_3$); FTIR (neat) ν 1588, 1462, 1431 cm^{-1}; ^1H NMR δ 0.00 (3H, s), 0.11 (3H, s), 0.73 (9H, s), 1.07 (3H, d, J=6.4 Hz), 3.47 (3H, s), 5.48 (1H, q, J=6.4 Hz), 7.0–7.3 (2H, m), 7.5–7.8 (4H, m), 8.4–8.7 (2H, m); ^{13}C NMR δ −4.8, −4.0, 18.0, 18.6, 25.7, 25.8 (×2), 54.2, 72.9, 87.5, 121.5, 122.3, 124.1 (×2), 135.1, 135.8, 148.1, 148.4, 160.0, 161.9; MS *m/z* (rel. intensity) 359 (M^++1, 100), 343 (55), 327 (31), 301 (85), 269 (24), 200 (52), 185 (30), 159 (10), 73 (19), 57 (6), 41 (9). Anal. calcd for $C_{20}H_{30}N_2O_2Si$: C, 67.00; H, 8.43; N, 7.81%. Found: C, 67.09; H, 8.55; N, 7.88%.

3.5. (S)-1,1-Di(2-pyridyl)-1-methoxypropan-2-ol 6

A solution of **5** (50 mg, 0.14 mmol) in MeCN (3 ml) was treated carefully with 40% aq. HF (20 drops) at 0°C and the mixture was stirred at rt for 72 h. After completion of the reaction, the mixture was basified by addition of aq. NaOH and thoroughly extracted with AcOEt. The combined extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by preparative TLC (AcOEt only) to give **6** (24 mg, 70%) as a colorless oil. R_f 0.46 (AcOEt); $[\alpha]_D^{27}$ −2.66 (c 1.13, $CHCl_3$); FTIR (neat) ν 3380, 1589, 1572, 1464, 1433 cm^{-1}; ^1H NMR δ 1.07 (3H, d, J=6.4 Hz), 3.36 (3H, s), 5.15 (1H, q, J=6.4 Hz), 5.97 (1H, br s), 7.0–7.4 (3H, m), 7.5–7.8 (3H, m), 8.4–8.6 (2H, m); ^{13}C NMR δ 16.3, 53.4, 71.8, 85.0, 121.9, 122.0, 122.2, 124.0, 136.2, 136.5, 147.4, 148.3, 161.9, 162.3; MS *m/z* (rel. intensity) 245 (M^++1, 87), 229 (18), 201 (100), 185 (73), 169 (86), 122 (5), 78 (15), 51 (5), 45 (56). HRMS calcd for $C_{14}H_{16}N_2O_2$+H: 245.1290. Found: 245.1292.

3.6. (S)-1-(2-Pyridyl)-2-(2-pyridylmethyl)butane-2,3-diol 7a

A solution of LDA (30 mmol), prepared from *i*-Pr_2NH (4.2 ml, 30 mmol) and 1.13M *n*-BuLi in hexane (26.5 ml, 30 mmol), in THF (20 ml) was added to a solution of 2-picoline (2.96 ml, 30 mmol) in THF (10 ml) at −78°C and the mixture was allowed to warm to 0°C. After stirring for 1 h, to this mixture at −78°C was added a solution of **1** (1.13 ml, 10 mmol) in THF (10 ml) and the mixture was allowed to warm to rt and stirred for 2 days. After quenching with aq. KOH, the precipitate was removed by filtration through Celite. The filtrate was extracted with AcOEt, dried (Na_2SO_4), and concentrated. The crude product was purified by preparative TLC (AcOEt only) to give **7a** (490 mg, 19%) as a pale yellow oil and the unstable ketone **7b** (693 mg, 42%) as an unstable yellow oil. R_f 0.31 (hexane:acetone=1:1); $[\alpha]_D^{26}$ −26.1 (c 1.42, $CHCl_3$); FTIR (neat) ν 3347, 1595, 1570, 1476, 1437 cm^{-1}; ^1H NMR δ 1.25 (3H, d, J=6.4 Hz), 2.71 (1H, d, J_{AB}=13.6 Hz), 3.06 (2H, s), 3.13 (1H, d, J_{AB}=13.6 Hz), 3.47 (1H, q, J=6.4 Hz), 7.0–7.3 (4H, m), 7.4–7.7 (2H, m), 8.4–8.6 (2H, m); ^{13}C NMR δ 16.5, 41.8, 43.4, 71.1, 77.6, 121.2 (×2), 124.8, 125.3, 136.3, 136.5, 148.0, 148.1, 158.8, 159.3; MS *m/z* (rel. intensity) 259 (M^++1, 100), 241 (24), 223 (32), 213 (34), 194 (8), 166 (59), 148 (8), 120 (7), 94 (16), 41 (6). HRMS calcd for $C_{15}H_{18}N_2O_2$+H: 259.1446. Found: 259.1462.

Ketone **7b**: R_f 0.47 (AcOEt); FTIR (neat) ν 3360, 1721, 1649, 1597 cm^{-1}; ^1H NMR δ 1.40 (3H, d, J=7.0 Hz), 3.95 (1H, d, J_{AB}=14.3 Hz), 4.17 (1H, d, J_{AB}=14.3 Hz), 4.31 (1H, q, J=7.0 Hz), 6.9 (1H, br),

7.1–7.3 (2H, m), 7.5–7.8 (1H, m), 8.4–8.6 (1H, m); MS *m/z* (rel. intensity) 165 (M^+, 11), 120 (33), 93 (100), 78 (2), 65 (9). HRMS: calcd for $C_9H_{11}NO_2$: 165.0789. Found: 165.0814.

*3.7. (S)-3-*tert*-Butyldimethylsilyloxy-1-(2-pyridyl)-2-(2-pyridylmethyl)butan-2-ol* **8**

This sample was prepared from **7a** (70 mg, 0.27 mmol) as described for the synthesis of **3**. Compound **8** (91 mg, 91%) was obtained as a colorless oil. R_f 0.45 (Et_2O:MeOH=49:1); $[\alpha]_D^{27}$ +31.2 (c 0.88, $CHCl_3$); FTIR (neat) ν 3316, 1595, 1570, 1474, 1435, 1100 cm^{-1}; ^1H NMR δ −0.03 (3H, s), 0.00 (3H, s), 0.89 (9H, s), 1.25 (3H, d, J=6.4 Hz), 2.95 (1H, d, J_{AB}=13.8 Hz), 3.06 (2H, s), 3.17 (1H, d, J_{AB}=13.8 Hz), 3.78 (1H, q, J=6.4 Hz), 6.52 (1H, br), 7.0–7.7 (6H, m), 8.3–8.5 (2H, m); ^{13}C NMR δ −4.6, −4.0, 18.2, 18.3, 26.1 (×3), 41.8, 42.1, 73.6, 77.5, 120.9 (×2), 125.4, 125.5, 135.7, 135.9, 147.8, 148.0, 159.7, 159.9; MS *m/z* (rel. intensity) 373 (M^++1, 98), 357 (38), 315 (43), 280 (33), 223 (50), 213 (100), 148 (6), 120 (18), 93 (22), 73 (12), 57 (5), 41 (41). HRMS calcd for $C_{21}H_{32}N_2O_2Si$+H: 373.2311. Found: 373.2305

3.8. (S)-1,1-Di(2-thienyl)propane-1,2-diol **9**

To a solution of thiophene (1.82 g, 21.6 mmol) in THF (20 ml) at −78°C was added a solution of 2.53M *n*-BuLi in hexane (8.5 ml, 21.6 mmol) and the mixture was allowed to warm to 0°C and stirred for 30 min. To this solution at −78°C was added dropwise a solution of **1** (708 mg, 6 mmol) in THF (10 ml) and the mixture was allowed to warm to rt and stirred for 24 h. After quenching with aq. KOH, the insoluble substance was removed by filtration through Celite. The filtrate was extracted with AcOEt, dried (Na_2SO_4), and concentrated. The crude product was purified by silica gel column chromatography (hexane:AcOEt=4:1 to 2:1) to give **9** (1.01 g, 70%) as a pale yellow oil. R_f 0.30 (hexane:AcOEt=2:1); $[\alpha]_D^{26}$ −37.9 (c 1.08, $CHCl_3$); FTIR (neat) ν 3428, 1437, 1364 cm^{-1}; ^1H NMR δ 1.17 (3H, d, J=6.4 Hz), 2.20 (1H, br), 3.47 (1H, s), 4.42 (1H, q, J=6.4 Hz), 6.9–7.1 (3H, m), 7.1–7.3 (3H, m); ^{13}C NMR δ 16.7, 74.5, 78.9, 124.3 (×2), 124.6, 125.1, 126.5, 126.7, 147.5, 149.4; MS *m/z* (rel. intensity) 222 (M^+−18, 0.2), 195 (46), 179 (47), 169 (10), 147 (3), 134 (8), 111 (100), 83 (11), 69 (7), 51 (3), 45 (17), 43 (13). HRMS calcd for $C_{11}H_{12}O_2S_2$: 240.0279. Found: 240.0275.

*3.9. (S)-2-*tert*-Butyldimethylsilyloxy-1,1-di(2-thienyl)propan-1-ol* **10**

This sample was prepared from **9** (202 mg, 0.84 mmol) as described for the synthesis of **3**. Compound **10** (234 mg, 79%) was obtained as a colorless oil. R_f 0.38 (hexane:AcOEt=7:1); $[\alpha]_D^{26}$ −50.7 (c 1.03, $CHCl_3$); FTIR (neat) ν 3526, 1472, 1362 cm^{-1}; ^1H NMR δ −0.18 (3H, s), 0.05 (3H, s), 0.77 (9H, s), 1.11 (3H, d, J=6.2 Hz), 3.70 (1H, s), 4.40 (1H, q, J=6.2 Hz), 7.8–8.0 (3H, m), 8.0–8.2 (3H, m); ^{13}C NMR δ −5.3, −4.2, 17.9, 18.6, 25.7 (×3), 76.3, 79.1, 123.5, 124.0, 124.1, 124.3, 126.5 (×2), 148.2, 150.7; MS *m/z* (rel. intensity) 337 (M^+−17, 0.4), 297 (6), 279 (4), 213 (12), 205 (6), 195 (11), 159 (35), 141 (6), 111 (70), 103 (12), 97 (6), 83 (9), 73 (100), 59 (20), 45 (13). HRMS calcd for $C_{17}H_{26}O_2S_2Si$: 354.1144. Found: 354.1148.

3.10. Methyl (S)-(+)-2-(6-methoxy-2-naphthyl)-1-propanoate **11**

This sample was prepared from (*S*)-(+)-2-(6-methoxy-2-naphthyl)-1-propanonic acid according to the literature procedure.[14] Mp 93.0–94.0°C (from CH_2Cl_2:hexane) (lit.[14a] mp 88°C, lit.[14b] mp 91°C); R_f 0.77 ($CHCl_3$:MeOH=39:1); $[\alpha]_D^{25}$ +74.0 (c 1.00, $CHCl_3$) {lit.[14a] $[\alpha]_D^{23}$ +77 ($CHCl_3$), lit.[14b] $[\alpha]_D^{23}$ +72.2

(c 2.05, $CHCl_3$)}; FTIR (KBr) ν 1738, 1605, 1451, 1202, 1177; ^{1}H NMR δ 1.57 (3H, d, J=7.0 Hz), 3.65 (3H, s), 3.85 (1H, q, J=7.0 Hz), 3.89 (3H, s), 7.0–7.8 (6H, m); ^{13}C NMR δ 18.6, 45.4, 52.0, 55.3, 105.7, 118.9, 125.9, 126.1, 127.1, 128.9, 129.2, 133.7, 135.6, 157.6, 174.9.

3.11. (S)-1,1-Di(2-pyridyl)-2-(6-methoxy-2-naphthyl)propan-1-ol 12

This sample was prepared from **11** (977 mg, 4 mmol) as described for the synthesis of **2**. Compound **12** (1.22 g, 82%) was obtained as colorless needles. Mp 180.0–181.0°C (from Et_2O); R_f 0.28 (hexane:AcOEt=5:1); $[\alpha]_D^{27}$ −187.7 (c 1.01, $CHCl_3$); FTIR (KBr) ν 3320, 1632, 1607, 1588, 1391 cm^{-1}; ^{1}H NMR δ 1.22 (3H, d, J=7.0 Hz), 3.83 (3H, s), 4.39 (1H, q, J=7.0 Hz), 6.65 (1H, br s), 6.7–8.3 (13H, m), 8.60 (1H, ddd, J=4.8, 1.9, 1.0 Hz); ^{13}C NMR δ 16.5, 48.9, 55.2, 80.7, 105.4, 117.9, 121.5, 121.6 (×2), 121.8, 125.4, 127.8, 128.5, 128.6, 129.2, 132.9, 136.0, 136.6, 138.3, 146.5, 147.6, 156.9, 162.2, 163.4. Anal. calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56%. Found: C, 77.72; H, 5.96; N, 7.54%.

3.12. General procedure for the enantioselective addition of diethylzinc to benzaldehyde

A solution of 1.0M Et_2Zn in hexane (3.8 ml, 3.8 mmol) was added to a solution of chiral ligand (0.19 mmol) in toluene (4 ml) at −15°C and the resulting yellow solution was stirred at this temperature for 15 min before adding benzaldehyde (96 μl, 0.94 mmol). The mixture was gradually warmed to rt and stirred for the period described in Table 1. After quenching with 2M HCl, the precipitate was removed by filtration through Celite. The filtrate was extracted with AcOEt, dried (Na_2SO_4), and concentrated. The crude product was purified by preparative TLC (petroleum ether:AcOEt=5:1) to give 1-phenyl-1-propanol (R_f 0.26, petroleum ether:AcOEt=5:1) as a colorless oil. The enantiomeric excess (ee) of the product was determined with a Hitachi L-6200 HPLC using a Daicel Chiralcel OB column eluted with 1% *i*-PrOH in hexane, at a flow rate of 0.5 ml/min.

3.13. X-Ray crystallographic analysis of 3

Crystal data: $C_{19}H_{28}N_2O_2Si$, M=344.53, orthorhombic, space group $P2_12_12_1$(#19), a=15.118(2), b=16.516(2), c=8.062(1) Å, V=2012.9(4) Å^3, Z=4, D_{calc}=1.137 g/cm^3, μ(Cu-Kα)=11.24 cm^{-1}, number of observations 1262 (I>3.00σ(I)), R=0.049, R_w=0.072. Intensity data were collected on a Rigaku AFC5R diffractometer using Cu-Kα radiation (λ=1.54178 Å).

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