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Enantioselective addition of thiophenylboronic acids to aldehydes using $ZnEt_2$/Schiff-base catalytic system

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ABSTRACT

Using Schiff-base amino alcohols as catalysts which were readily derived from natural amino acids in three steps, a series of valuable optically active thiophenyl methanols (**4a**–**4n**) were first obtained in good yields and high enantioselectivities (up to 96% ee) through the asymmetric addition of thiophenylboronic acid to aldehydes in the presence of $ZnEt_2$ in toluene.

1. Introduction

Catalytic asymmetric arylation of aldehydes has been widely studied as one of the most important methods for the synthesis of enantiopure diaryl methanols,[1] which are important intermediates for the synthesis of biologically and pharmaceutically active compounds.[2] Among these studies, the enantioselective addition of aryl organometallic reagents to aldehydes remains an intensively studied area. Since the pioneering work of Fu in 1997,[3] Pu's group and Bolm's group had developed a way of highly enantioselective phenyl transfer with diphenylzinc, respectively.[2a,4] Because of the advantageous features of organoboronic acids such as low toxicity and easy manipulation, they had been used as high efficient aryl transfer reagents in the enantioselective addition.[5] So recently, a series of ligands had been used to catalyze this type of reaction together with palladium or zinc reagents.[6]

Besides the phenyl addition products, the enantiopure thiophene methanols, which are important intermediates in manufacturing dyes, aroma compounds, and pharmaceuticals, also would be a series of valuable compounds to make.[7] However, only one example using thiophenylboronic acid as a substrate to prepare chiral thiophene methanol has been reported in 2007 by Bolm's group,[5f] in which they used a complicated ferrocene as catalyst. As we know, this catalyst was synthesized from ferrocenecarboxylic acid in more than five steps.[8] Therefore it is still desirable to develop or find more efficient systems for the asymmetric addition of thiophenylboronic acid to a variety of aldehydes. Herein, we report the new application result of a series of ligands for the catalytic, enantioselective thiophenyl transfer reaction in the presence of $ZnEt_2$.

2. Result and discussion

Based on the previous study of the $ZnEt_2$ catalytic system in our group,[9] we examined a series of ligands derived from natural amino acids to catalyze the asymmetric addition of thiophenylboronic acid to aldehydes. As a model reaction, we studied the reactivity of 2-chlorobenzaldehyde **3a** with 2.5 equiv of 2-thiophenylboronic acid **2**[10] in the presence of 10 mol % ligand at room temperature in toluene (Table 1). Fortunately, the oxazolidine **A**,[9e] Schiff-base amino alcohol **B1**[11], and camphorsulfonamide **C**[9b] were useful ligands in this reaction (Fig. 1). The best enantioselectivity of 66% ee was obtained when Schiff-base amino alcohol **B1** was used (Table 1, entry 2). To the best of our knowledge, the use of Schiff-base amino alcohols chiral ligands in the enantioselective thiophenyl transfer to aldehydes has not yet been reported.

After having identified an efficient catalyst **B1**, our focus was to optimize the reaction conditions. By increasing the amount of ligand, we found that 20 mol % of **B1** gave a higher ee value of 84%, but a further increase of **B1** amount in the reaction did not lead to a further improvement of ee value (Table 1, entries 4 and 5). The reaction gave a slightly higher ee when the reaction temperature was decreased from 20 to −40 °C, but a longer reaction time was needed and the yield decreased to 51%. According to the results reported by Bolm et al. in 2004, simple PEG ethers had beneficial effects on the catalyzed enantioselective processes.[5b] In our case, when 10 mol % DIMPEG and IMPEG were used as the additive, respectively, both of them could improve the ee values (Table 1, entries 9 and 10) and a better enantioselective excess of 91% was obtained when 10 mol % IMPEG was used.

After the identification of the Schiff-base amino alcohol **B1** as the most efficient ligand among **A**, **B1,** and **C**, a series of similar Schiff-base amino alcohols were also screened to identify the most efficient one in this series and the result is shown in Table 2. This series of Schiff-base amino alcohols **B2**, **B3**, **B4**, **B5,** and **B6** were

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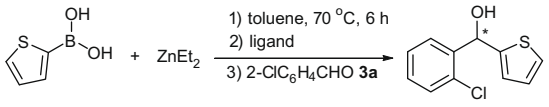
Table 1
Asymmetric aryl transfer to 2-chlorobenzaldehyde using 2-thiophenylboronic acid[a]



2 4a

Entry	Ligand (mol %)	Temp/time (°C/h)	Yield[b] (%)	ee[c] (%)
1	**A** (10)	20/12	49	60
2	**B1** (10)	20/12	61	66
3	**C** (10)	20/12	58	40
4	**B1** (20)	20/10	71	84
5	**B1** (30)	20/10	68	84
6	**B1** (5)	20/12	58	45
7	**B1** (20)	−10/12	66	84
8	**B1** (20)	−40/24	51	85
9[d]	**B1** (20)	20/8	74	91
10[e]	**B1** (20)	20/8	72	90

[a] Reactions were performed with 1.2 equiv of 2-thiophenylboronic acid and 3.6 equiv of $ZnEt_2$ in toluene.
[b] Isolated yields.
[c] The enantiomeric excess was determined by HPLC analysis on a Chiralpak column.
[d] Using 10 mol % IMPEG as an additive.
[e] Using 10 mol % DIMPEG as an additive.

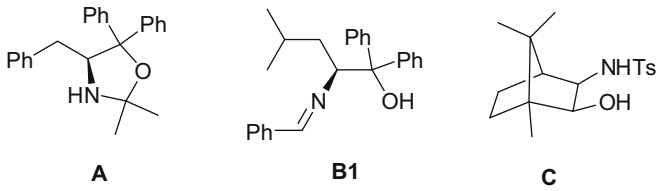
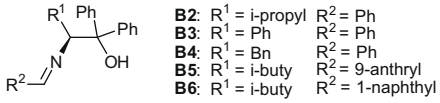
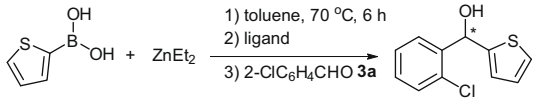


Figure 1. Chiral ligands tested.

Table 2
Asymmetric aryl transfer to 2-chlorobenzaldehyde using 2-thiophenylboronic acid with different Schiff-base amino alcohol ligands[a]





2 4a

Entry	Ligand (mol %)	Temp/time (°C/h)	Yield[b] (%)	ee[c] (%)
1	**B2** (20)	20/8	75	89
2	**B3** (20)	20/8	70	68
3[d]	**B4** (20)	20/8	nd	40
4	**B5** (20)	20/8	74	92
5	**B6** (20)	20/8	70	91

[a] Reactions were performed with 1.2 equiv of 2-thiophenylboronic acid and 3.6 equiv of $ZnEt_2$ in toluene, using 10 mol % IMPEG as an additive.
[b] Isolated yields.
[c] The enantiomeric excess was determined by HPLC analysis on a Chiralpak column.
[d] nd, Not determined.

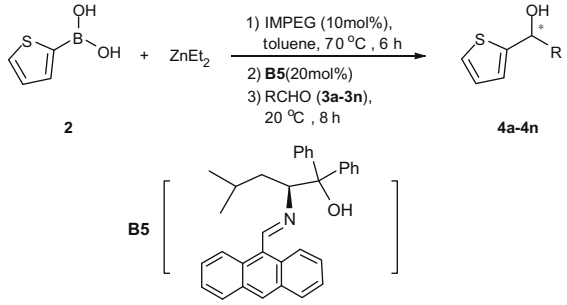
prepared from natural amino acids in three simple steps[9f] with high yields. It was found that the structure of the ligand could be highly influential on the enantioselectivity of the product. Simply attaching a bulky substituent at the R^1 position led to a dramatic decrease in enantioselectivity, such as **B4** gave only 40% ee. However, slightly increased ee values were observed when a bulky substituent was attached at the R^2 position. Both **B5** and **B6** proved to be most reactive and selective ligands for this thiophenyl transfer reaction (Table 2, entries 4 and 5). It was proposed that the strong steric-hindrance effect provided by both of isopropyl and anthryl/naphthyl made **B5** and **B6** to show a higher catalyst effect. Since ligand **B5** gave the highest ee value of 92% together with highest overall yield, catalyst **B5** was chosen for the thiophenylboronic acid to aldehydes addition.

Having optimized the reaction conditions, a variety of aldehydes were investigated to explore the substrate scope. As shown in Table 3, most of them were proved to be excellent aryl acceptors for this thiophenyl transfer reaction, and provided the corresponding products in good to high yields, and with excellent ee values (up to 96% ee).

Reactions of benzaldehyde gave an excellent ee value of 93% with a good yield of 82% (Table 3, entry 1). Regardless of the electronic and steric properties of the substituents, the aromatic aldehydes **3b–l** underwent the reactions to yield the optically active adducts **4b–l** in good yields and 81–96% ee. The position of the substituent group on the aromatic aldehydes only slightly influenced the enantioselectivity of the reaction: 2-methoxy-, 3-methoxy-, and 4-methoxyphenyl-substituted aldehydes reacted smoothly with thiophenylboronic acid to afford the desired secondary methanols with similar enantioselectivities (Table 3, entries 8–10).

Furthermore, other aldehydes were also screened in this reaction.[12] The reaction of bulky aldehyde such as 2-naphthaldehyde (Table 3, entry 13) provided product **4m** in 88% ee with a yield of 68%. The heteroaromatic aldehyde, 2-furaldehyde, was also

Table 3
Enantioselective thiophenyl transfer to aldehydes using **B5** as the chiral ligands[a]



2 4a-4n

Entry	R in RCHO	Product	Yield[b] (%)	ee[c] (%)
1	Phenyl	**4a**	82	93
2	2-Chlorophenyl	**4b**	74	92
3	3-Chlorophenyl	**4c**	72	81
4	4-Chlorophenyl	**4d**	83	85
5	4-Fluorophenyl	**4e**	79	92
6	2-Methylphenyl	**4f**	67	94
7	4-Methylphenyl	**4g**	83	84 (*R*)[d]
8	2-Methoxyphenyl	**4h**	79	95
9	3-Methoxyphenyl	**4i**	77	93
10	4-Methoxyphenyl	**4j**	81	96
11	2-Bromophenyl	**4k**	61	95
12	4-Bromophenyl	**4l**	85	92
13	2-Naphthyl	**4m**	68	88
14	2-Furyl	**4n**	77	82

[a] All the reactions proceeded as described in Section 4.2.
[b] Isolated yields.
[c] The enantionmeric excess was determined by HPLC analysis on a Chiralpak column.
[d] The absolute configuration of **4g** was assigned based on the comparison to the literature data.[5f]

shown to be an efficient reagent, affording the addition product in 82% ee (Table 3, entry 14).

3. Conclusion

In summary, we have extended the applicability of $ZnEt_2$/Schiff-base catalytic system for the arylation of aldehydes. A series of readily available and inexpensive Schiff-base amino alcohols have been identified as efficient chiral ligands in the thiophenyl transfer to aldehydes. When a new Schiff-base B5 was used as ligand, the results indicated that thiophenylboronic acid could be a suitable substrate to synthesize optically active thiophenyl methanol derivatives.

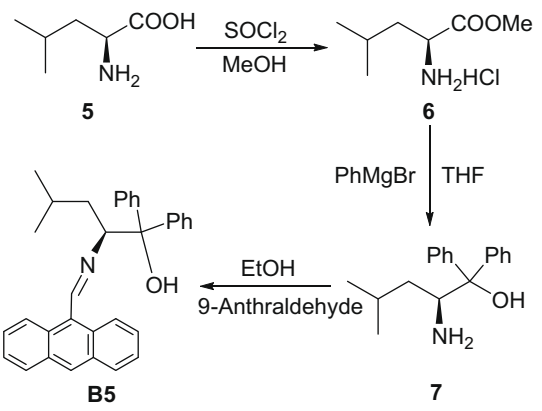
4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere condition, and solvents were dried according to established procedures. Reactions were monitored by thin layer chromatography (TLC), column chromatography purifications were carried out using silica gel. All aldehydes, thiophene, and aminoacids were purchased from Acros or Fluka. Diethylzinc was prepared from EtI with Zn and then was diluted with toluene to 1.0 M. Melting points are uncorrected and were recorded on an X-4 melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using Bruker 300 MHz. IR spectra were obtained on a FTIR spectrometer. Optical rotations were recorded on a Perkin–Elmer 341 polarimeter. HR-MS was measured with an APEX II 47e mass spectrometer and EI was recorded on a TRACE DSQ Gas Chromatography–Mass spectrometer. The ee value determination was carried out using chiral HPLC with Daicel Chiralpak OD-H, AS-H, or AD-H column on Waters with a 996 UV-detector.

4.2. Procedure for the preparation of ligand B5[9f,13]

As in Scheme 1, compound **7** was prepared according to known procedures in two steps from L-leucine.[12] Then to a solution of **7** (1.07 g, 4 mmol) in 40 ml 95% EtOH was added 9-anthraldehyde (0.82 g, 4 mmol). The resulting solution was stirred for 24 h at room temperature, then the reaction mixture was vacuum filtered to provide crude product which was purified by recrystallization from ethyl acetate–hexane and gave the pure product **B5** as a yellow solid (1.57 g) with the yield of 86%.



Scheme 1. The synthesis of chiral Schiff-base amino alcohol ligand **B5**.

4.2.1. (*S*,*E*)-2-(Anthracen-9-ylmethyleneamino)-4-methyl-1,1-diphenylpentan-1-ol B5

Mp 175 °C; $[\alpha]_D^{20} = -136$ (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91–0.93 (d, *J* = 6.6 Hz, 3H), 1.09–1.11 (d, *J* = 6.6 Hz, 3H), 1.36–1.45 (m, 1H), 1.69–1.77 (m, 1H), 1.98–2.07 (m, 1H), 4.03 (s, 1H), 4.76–4.80 (m, 1H), 7.14–7.25 (m, 3H), 7.28–7.34 (m, 3H), 7.37–7.44 (m, 4H), 7.67–7.73 (m, 4H), 7.78–7.81 (m, 2H),7.93–7.95 (d, *J* = 8.4 Hz, 1H), 8.41 (s, 1H), 9.38 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 21.2; 24.1; 24.4; 38.4; 76.5; 76.6; 79.8; 123.6; 124.5; 125.2; 125.5; 125.7; 126.1; 126.5; 126.6; 126.6; 128.4; 128.6; 128.7; 129.2; 129.3; 129.6; 131.1; 144.2; 147.7; 161.8; ESI-MS: *m*/*z* (%) 458.6 [M+]; IR (KBr); 3507, 2955, 1644, 1448, 1175, 1047, 909, 734, 702 cm^{-1}. HRMS-EI (*m*/*z*): calcd for $C_{33}H_{31}NO$: 457.2406; found: 457.2476, 0.4 ppm.

4.3. General procedure for the enantioselective addition of thiophenylboronic acid to aldehydes

The general procedure: under an argon atmosphere, a well-dried 5-ml vial was charged with thiophenylboronic acid **2** (32 mg, 0.24 mmol) and 10% IMPEG (FW = 1100 g/mol, 0.02 mmol, 22 mg), and then Et_2Zn (0.72 ml, 0.72 mmol, 1.0 M solution in toluene) was added using a syringe. The mixture was stirred for 6 h at 70 °C and subsequently cooled to room temperature. Then the mixture was added into another vial containing ligand **B5** (18 mg, 0.04 mmol) using a syringe and was stirred for 30 min at room temperature. Then, the mixture was cooled to 0 °C and stirred for another 10 min followed by the addition of aldehyde (0.2 mmol). After stirring for 8 h at room temperature, the reaction was quenched with saturated ammonium chloride and extracted with ether and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product. After column chromatography on silica gel eluted with 5–10% ethyl acetate in petroleum ether, the optically active product was isolated. The enantiomeric purity of the product was determined by using HPLC. The absolute configuration of adducts was assigned by comparison to the literature data.[5f]

4.3.1. (Phenyl)-(2′-thienyl)methanol 4a

Yield (82%), 93% ee determined by HPLC analysis (Chiralpak AS-H column, IPA:hexane = 2:98, 0.5 ml/min, 254 nm UV detection). Retention time: t_{minor} = 35.5 min and t_{major} = 39.9 min; white solid, mp 37–38 °C, $[\alpha]_D^{20} = -3.6$ (*c* 1.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 2.60–2.61 (d, *J* = 3.6 Hz, 1H); 5.98–5.99 (d, *J* = 3 Hz, 1H); 6.84–6.85 (m, 1H); 6.90–6.93 (dd, J^1 = 3.6 Hz, J^2 = 1.5 Hz, 1H); 7.22–7.24 (dd, J^1 = 1.5 Hz, J^2 = 3.6 Hz, 1H); 7.30–7.34 (m, 3H); 7.40–7.42 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): 72.4; 124.9; 125.4; 126.3; 126.7; 128.0; 128.6; 143.1; 148.2; IR (KBr): 3271, 1450, 1159, 1017, 824, 702 cm^{-1}; MS: *m*/*z* (%) 190 [M+], 110 (35), 104 (100), 84 (52), 83 (53), 76 (33).

4.3.2. (2-Chlorophenyl)-(2′-thienyl)methanol 4b

Yield (74%), 92% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:hexane = 5:95, 1.0 ml/min, 254 nm UV detection). Retention time: t_{minor} = 12.8 min and t_{major} = 14.0 min; gray oil, $[\alpha]_D^{20} = -31$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 2.75 (br s, 1H); 6.38 (s, 1H); 6.88–6.94 (m, 2H); 7.20–7.25 (m, 2H); 7.28–7.34 (m, 2H); 7.66–7.69 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): 68.9; 125.3; 125.5; 126.7; 127.2; 127.5; 129.1; 129.6; 132.2; 140.5; 146.3; IR (KBr): 3355, 1440, 1016, 751, 703 cm^{-1}; MS: *m*/*z* (%) 224 [M+], 224 (38), 139 (71), 113 (30), 111 (37), 85 (100).

4.3.3. (3-Chlorophenyl)-(2′-thienyl)methanol 4c

Yield (72%), 81% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:hexane = 5:95, 1.0 ml/min, 254 nm UV detection). Retention time: t_{minor} = 15.4 min and t_{major} = 16.4 min; gray oil,

$[\alpha]_D^{20} = -13$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.79 (br s, 1H); 5.95 (s, 1H); 6.85–6.86 (d, J = 3.3 Hz, 1H); 6.91–6.94 (dd, J^1 = 3.6 Hz, J^2 = 1.5 Hz, 1H); 7.23–7.28 (m, 4H); 7.41 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): 71.6; 124.4; 125.2; 125.8; 126.4; 126.8; 128.1; 129.8; 134.4; 145.0; 147.3; IR (KBr): 3407, 2921, 1602, 1488, 1459, 1434, 1258, 1037, 700 cm^{-1}; MS: *m*/*z* (%) 224 [M+], 111 (43), 85 (100), 84 (38).

4.3.4. (4-Chlorophenyl)-(2′-thienyl)methanol 4d

Yield (83%), 85% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:hexane = 2:98, 1.0 ml/min, 254 nm UV detection). Retention time: t_{minor} = 30.2 min and t_{major} = 35.6 min; yellow solid, mp 55–56 °C, $[\alpha]_D^{20} = -19$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.73 (br s, 1H); 5.96 (s, 1H); 6.84–6.85 (d, J = 3.6 Hz, 1H); 6.91–6.94 (dd, J^1 = 3.6 Hz, J^2 = 1.5 Hz, 1H); 7.24–7.26 (dd, J^1 = 1.2 Hz, J^2 = 3.9 Hz, 1H); 7.28–7.31 (dd, J^1 = 2.7 Hz, J^2 = 3.6 Hz, 2H); 7.32–7.35 (dd, J^1 = 2.7 Hz, J^2 = 3.6 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): 71.6; 125.1; 125.7; 126.8; 127.7; 128.7; 133.7; 141.5; 147.6; IR (KBr): 3356, 1490, 1089, 1011, 829, 704 cm^{-1}; MS: *m*/*z* (%) 224 [M+], 139 (77), 111 (64), 85 (100), 84 (46).

4.3.5. (4-Fluorophenyl)-(2′-thienyl)methanol 4e

Yield (79%), 92% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:hexane = 5:95, 1.0 ml/min, 254 nm UV detection). Retention time: t_{minor} = 13.7 min and t_{major} = 15.0 min; white solid, mp 47–48 °C, $[\alpha]_D^{20} = -15$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.47–2.48 (d, J = 2.7 Hz, 1H); 6.03–6.04 (d, J = 3 Hz, 1H); 6.87–6.88 (m, 1H); 6.93–6.96 (dd, J^1 = 3.6 Hz, J^2 = 1.5 Hz, 1H); 7.02–7.07 (m, 2H); 7.25–7.28 (m, H); 7.39–7.42 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): 71.7; 115.2, 115.5; 124.9; 125.6; 126.7; 128.0, 128.1; 138.9, 138.9; 147.9; 160.8, 164.0; IR (KBr): 3384, 2921, 1604, 1508, 1226, 1156, 1037, 837, 703 cm^{-1}; MS: *m*/*z* (%) 207 [M+], 207 (38), 192 (56), 191 (100).

4.3.6. (2-Methylphenyl)-(2′-thienyl)methanol 4f

Yield (67%), 94% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:hexane = 5:95, 1.0 ml/min, 254 nm UV detection). Retention time: t_{minor} = 12.6 min and t_{major} = 14.5 min; colorless oil, $[\alpha]_D^{20} = -24$ (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.27 (s, 3H); 2.33 (br s, 1H); 6.20–6.21 (d, J = 3.3 Hz, 1H); 6.81–6.83 (m, 1H); 6.91–6.94 (dd, J^1 = 3.6 Hz, J^2 = 1.5 Hz, 1H); 7.13–7.16 (m, 1H); 7.20–7.28 (m, 3H); 7.60–7.63 (dd, J^1 = 1.8 Hz, J^2 = 5.4 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): 19.1; 69.2; 125.3; 125.6; 126.3; 126.6; 127.9; 130.5; 135.0; 141.1; 147.3; IR (KBr): 3367, 1460, 1228, 1035, 746, 702 cm^{-1}; MS: *m*/*z* (%) 204 [M+], 119 (100), 91 (21).

4.3.7. (*R*)-(4-Methylphenyl)-(2′-thienyl)methanol 4g

Yield (83%), 84% ee determined by HPLC analysis (Chiralpak AD-H column, IPA: hexane = 5:95, 1.0 ml/min, 254 nm UV detection). Retention time: t_{minor} = 15.2 min and t_{major} = 17.6 min; white solid, mp 38–39 °C, $[\alpha]_D^{20} = -16$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.34 (s, 3H); 2.39–2.43 (d, J = 9.6 Hz, 1H); 6.00 (s, 1H); 6.85–6.87 (m, 1H); 6.91–6.94 (dd, J^1 = 3.6 Hz, J^2 = 1.5 Hz, 1H); 7.15–7.18 (d, J = 5.1 Hz, 2H); 7.23–7.25 (m, 1H); 7.30–7.33 (d, J = 8.1 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): 21.2; 72.3; 124.8; 125.3; 126.3; 126.6; 129.2; 137.8; 140.3; 148.4; IR (KBr): 3414, 1611, 1512, 1248, 1176, 1032, 834, 705, 577 cm^{-1}; MS: *m*/*z* (%) 204 [M+], 203 (52), 188 (61), 187 (100).

4.3.8. (2-Methoxyphenyl)-(2′-thienyl)methanol 4h

Yield (79%), 95% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:hexane = 5:95, 1.0 ml/min, 254 nm UV detection). Retention time: t_{major} = 19.9 min and t_{minor} = 21.4 min; brown oil, $[\alpha]_D^{20} = -20$ (*c* 0.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 3.44 (br s, 1H); 3.80 (s, 3H); 6.18 (s, 1H); 6.82–6.83 (m, 1H); 6.88–6.94 (m, 2H); 6.96–6.98 (dd, J^1 = 0.9 Hz, J^2 = 6.6 Hz, 1H); 7.19–7.32 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 55.5; 69.4; 111.0; 120.9; 124.3; 124.7; 126.6; 127.6; 129.1; 131.2; 148.0; 156.6; IR (KBr): 3417, 2936, 1597, 1490, 1462, 1244, 1027, 756, 703 cm^{-1}; MS: *m*/*z* (%) 220 [M+], 220 (42), 135 (100).

4.3.9. (3-Methoxyphenyl)-(2′-thienyl)methanol 4i

Yield (77%), 93% ee determined by HPLC analysis (Chiralpak OD-H column, IPA:hexane = 10:90, 1.0 ml/min, 254 nm UV detection). Retention time: t_{major} = 16.7 min and t_{minor} = 18.4 min; yellow solid, mp 55–56 °C, $[\alpha]_D^{20} = -10$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.75 (br s, 1H); 3.76 (s, 3H); 5.96 (s, 1H); 6.80–6.86 (m, 2H); 6.89–6.92 (dd, J^1 = 3.6 Hz, J^2 = 1.5 Hz, 1H); 6.97–6.99 (m, 2H); 7.22–7.24 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): 55.3; 72.3; 111.7; 113.5; 118.7; 124.9; 125.4; 126.7; 129.6; 144.8; 145.0; 159.7; IR (KBr): 3414, 1602, 1488, 1260, 1150, 1038, 755, 703 cm^{-1}; MS: *m*/*z* (%) 220 [M+], 220 (43), 135 (100).

4.3.10. (4-Methoxyphenyl)-(2′-thienyl)methanol 4j

Yield (81%), 96% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:hexane = 5:95, 1.0 ml/min, 254 nm UV detection). Retention time: t_{minor} = 23.5 min and t_{major} = 26.9 min; yellow solid, mp 51–52 °C, $[\alpha]_D^{20} = -16$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.73 (br s, 1H); 3.77 (s, 3H); 5.94 (s, 1H); 6.82–6.87 (m, 3H); 6.90–6.92 (dd, J^1 = 3.6 Hz, J^2 = 1.2 Hz, 1H); 7.21–7.23 (dd, J^1 = 1.2 Hz, J^2 = 3.9 Hz, 1H); 7.30–7.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): 55.3; 72.0; 113.9; 124.7; 125.2; 126.7; 127.7; 135.6; 148.6; 159.3; IR (KBr): 3356, 1575, 1430, 1195, 1016, 703 cm^{-1}; MS: *m*/*z* (%) 220 [M+], 220 (30), 135 (100), 109 (33).

4.3.11. (2-Bromophenyl)-(2′-thienyl)methanol 4k

Yield (61%), 95% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:hexane = 5:95, 1.0 ml/min, 254 nm UV detection). Retention time: t_{minor} = 14.8 min and t_{major} = 16.7 min; brown oil, $[\alpha]_D^{20} = -49$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.74 (br s, 1H); 6.36 (s, 1H); 6.90–6.93 (m, 2H); 7.13–7.18 (m, 1H); 7.23–7.26 (dd, J^1 = 1.5 Hz, J^2 = 3.3 Hz, 1H); 7.32–7.38 (m, 1H); 7.50–7.53 (dd, J^1 = 0.9 Hz, J^2 = 7.2 Hz, 1H); 7.66 (d, J = 1.5 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): 71.1; 122.4; 125.5; 125.6; 126.7; 127.9; 127.9; 129.4; 132.8; 142.1; 146.3; IR (KBr): 3356, 1467, 1437, 1012, 749, 703 cm^{-1}; MS: *m*/*z* (%) 270 [M+], 189 (77), 185 (45), 183 (45), 85 (100), 84 (69).

4.3.12. (4-Bromophenyl)-(2′-thienyl)methanol 4l

Yield (85%), 92% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:hexane = 5:95, 1.0 ml/min, 254 nm UV detection). Retention time: t_{minor} = 15.6 min and t_{major} = 18.6 min; yellow solid, mp 63–64 °C, $[\alpha]_D^{20} = -17$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.78 (br s, 1H); 5.93 (s, 1H); 6.83–6.84 (m, 1H); 6.90–6.93 (dd, J^1 = 3.6 Hz, J^2 = 1.5 Hz, 1H); 7.23–7.28 (m, 3H); 7.43–7.47 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): 71.7; 121.8; 125.1; 125.8; 126.8; 128.0; 131.6; 142.0; 147.5; IR (KBr): 3357, 1485, 1401, 1071, 1008, 825, 704 cm^{-1}; MS: *m*/*z* (%) 270 [M+], 185 (44), 183 (47), 111 (50), 85 (100), 84 (41).

4.3.13. (2-Naphthyl)-(2′-thienyl)methanol 4m

Yield (68%), 88% ee determined by HPLC analysis (Chiralpak AS-H column, IPA:hexane = 2:98, 1.0 ml/min, 254 nm UV detection). Retention time: t_{minor} = 25.3 min and t_{major} = 30.0 min; brown oil, mp 70–71 °C, $[\alpha]_D^{20} = -57$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 2.90 (br s, 1H); 6.05 (s, 1H); 6.81–6.82 (d, J = 3.3 Hz, 1H); 6.85–6.88 (dd, J^1 = 3.6 Hz, J^2 = 1.2 Hz, 1H); 7.15–7.20 (m, 1H); 7.40–7.45 (m, 3H); 7.72–7.78 (m, 3H); 7.82 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): 72.5; 124.6; 125.0; 125.2; 125.6; 126.2; 126.3; 126.8; 127.8; 128.2; 128.4; 133.1; 133.3; 140.6; 148.0; IR (KBr): 3376, 3056, 1601, 1508, 1364, 1230, 1118, 1020, 823, 757, 703, 478 cm^{-1};

MS: *m*/*z* (%) 240 [M+], 240 (78), 155 (100), 129 (51), 128 (50), 127 (40), 110 (57).

4.3.14. (2-Furanyl)-(2′-thienyl)methanol 4n

Yield (77%), 82% ee determined by HPLC analysis (Chiralpak AD-H column, IPA:hexane = 2:98, 1.0 ml/min, 254 nm UV detection). Retention time: t_{major} = 34.5 min and t_{minor} = 36.2 min; brown solid, mp 31–32 °C, $[\alpha]_D^{20} = -11$ (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 2.72 (br s, 1H); 6.04 (s, 1H); 6.27–6.35 (m, 2H); 6.96–7.01 (m, 2H); 7.24–7.29 (m, 2H); 7.40 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): 66.3; 107.4; 110.3; 125.3; 125.6; 126.7; 142.6; 144.5; 154.9; IR (KBr): 3427, 3110, 1742, 1231, 1144, 1011, 704, 598 cm^{-1}; MS: *m*/*z* (%) 180 [M^+], 162 (100).

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12. (a) Under the same conditions, we also uesd **B5** in the addition of 2-thiophenylboronic acid to two aliphatic aldehydes: isobutyl-aldehyde and cyclohexanecarboxaldehyde. The enantioselectivities were determined by chiral HPLC on a Chiracel OD column and were found to be 40 and 61% ee, respectively.; (b) To evaluate the asymmetry-inducing ability of **B5**, the reaction of 2-chlorobenzaldehyde with phenyl-boronic acid was performed under the same conditions, and we obtained an ee value of 94% with a good yield of 91%.
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