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Synthesis of α-Heteroarylpropanoic Acid via Asymmetric Hydroformylation Catalyzed by Rh(I)-(*R*,*S*)-BINAPHOS and the Subsequent Oxidation‡

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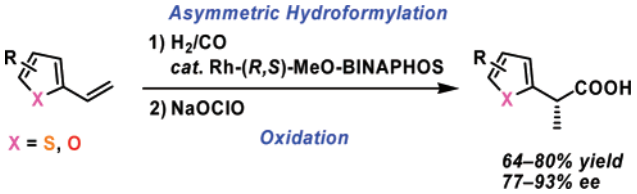

The asymmetric hydroformylation of vinyl heteroarenes (vinylfurans and vinylthiophenes) was investigated by using Rh(I)-BINAPHOS derivatives as a catalyst. The hydroformylation of vinylthiophenes **1** gave the corresponding branched aldehydes **2** with high enantiopurities as major products. Oxidation of the aldehydes **2** successfully afforded α-heteroarylpropanoic acids **4** in good yields. In addition, the aldehydes **2** were reduced to alcohols **5** without loss of enantiomeric excess.

Introduction

α-Heteroarylpropanoic acids are an important class of compounds due to their biological activities. For example, tiaprofenic acid is known as one of the most popular nonsteroidal anti-inflammatory drugs. Because their one enantiomer shows higher biological activity than the other, stereoselective synthetic routes for these compounds are of great interest.[1]

In recent years, various synthetic methods for racemic[2] or optically active[3] α-arylpropanoic acids have been developed. However, only a limited number of methods are applied to the synthesis of α-heteroarylpropanoic acids: stereospecific kinetic resolution by using lipases,[4] resolution of diastereomeric mixtures,[1] and stereoselective aromatic substitution with camphorsultam.[5]

Our strategy for enantioselective synthesis of α-heteroarylpropanoic acids is asymmetric hydroformylation[6] of vinylheteroarenes and the subsequent oxidation of the resulting optically active aldehydes. Previously, we have reported the enantioselective syntheses of hydratopic acid,[7] pyrrolidine carboxylic acid, and tetrahydrofuran carboxylic acid[8] via hydroformylation of the corresponding olefins by using Rh-BINAPHOS catalyst. In addition, recent reports show that the hydroformylation of

‡ This paper is dedicated to the memory of the late Professor Emeritus Yoshihiko Ito.

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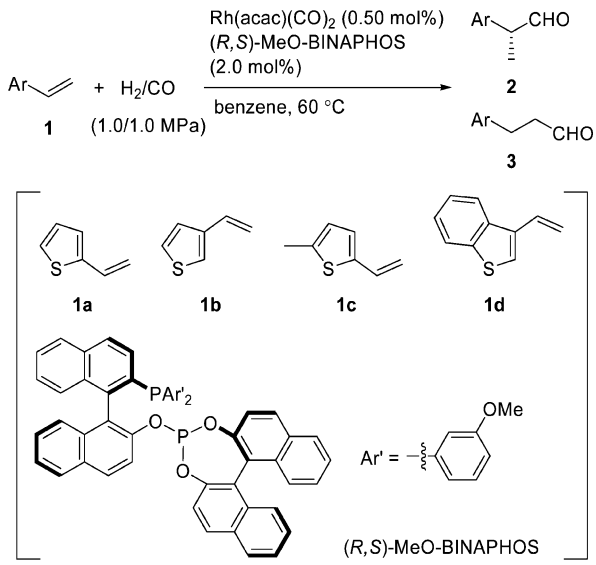
TABLE 1. Asymmetric Hydroformylation of Vinylthiophenes[a]



run	substrate	time (h)	2:3[b]	isolated yield of 2 (%)	ee of 2 (%)
1	**1a**	3	94:6	93	≥93 (*S*)[c]
2	**1b**	6	92:8	91	≥91 (*R*)[c]
3	**1c**	3	95:5	92	95 (*S*)[d]
4	**1d**	6	84:16	68	88 (*R*)[d]

[a] Reaction conditions: **1** (2.0 mmol), H_2 (1.0 MPa), CO (1.0 MPa), [Rh(acac)$(CO)_2$] (0.010 mmol), (*R*,*S*)-MeO-BINAPHOS (0.040 mmol) in benzene (1.0 mL) at 60 °C. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Not fully separated by HPLC. Therefore, the ee was estimated based on ee of its reduction product **5** (vide infra). [d] Determined by HPLC with CHIRALPAK IA column.

2-vinylfuran[9] and 2-vinylthiophene[10] with Rh catalysts gives the corresponding branched aldehydes as main products. However, to the best of our knowledge, there have been only a few reports of asymmetric hydroformylation of vinylheteroarenes. Stille reported the asymmetric hydroformylation of 5-benzoyl-2-vinylthiophene with Pt(II)-BPPM/$SnCl_2$ catalyst,[11] although the reaction rate was not satisfactory and triethyl orthoformate was necessary to avoid racemization of the product. Recently, we have demonstrated the asymmetric hydroformylation of vinylfurans with Rh-BINAPHOS catalyst,[12] and synthesized the corresponding aldehydes in good yields and with high enantioselectivity. It should be noted that optically active α-heteroarylpropanals, the products of asymmetric hydroformylation, could be useful as chiral building blocks not only for α-heteroarylpropanoic acid but also for the synthesis of other biologically active compounds. For example, 2-(2-furyl)propanal could be a starting material for monensin, a polyether antibiotic.[13] In addition, 2-(2-furyl)propanol, the reduction product of 2-(2-furyl)propanal, could be transformed into a series of antitumor, 1,10-*seco*-eudesmanolides.[14]

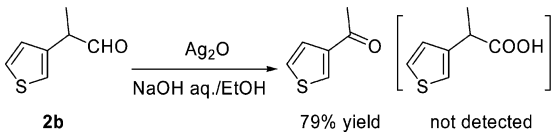
The subsequent oxidation of α-heteroarylpropanal to α-heteroarylpropanoic acids is also a challenging target. Oxidation of α-(5-acetoxyfuran-2-yl)propanal to the corresponding carboxylic acid by sodium chlorite has been reported.[15] However, α-thienylpropanoic acids have never been synthesized from α-thienylpropanals.

In this paper, we report the synthesis of α-heteroarylpropals using asymmetric hydroformylation of vinylheteroarenes catalyzed by Rh-BINAPHOS complex and the subsequent oxidation of the resulting optically active aldehydes without racemization at the asymmetric center.

Results and Discussion

Asymmetric Hydroformylation. First, the hydroformylation of vinylthiophenes was investigated. The results are summarized in Table 1. The reaction was carried out in the presence of Rh(acac)$(CO)_2$ (0.50 mol %) and (*R*,*S*)-MeO-BINAPHOS (2.0 mol %) in benzene under H_2/CO pressure (1.0 MPa/1.0 MPa). The ratio of branched product **2** and linear product **3** was determined by ^{1}H NMR spectroscopic analysis of the reaction mixture. Hydroformylation of 2-vinylthiophene (**1a**) resulted in a quantitative conversion within 3 h, and no hydrogenated or polymerized products were detected (Table 1, run 1). The branched aldehyde, 2-(2-thienyl)propanal (**2a**), was regioselectively formed (**2a**/**3a** = 94/6) and isolated in a high yield (93%) by silica gel column chromatography. Although the precise enantiomeric excess (ee) of **2a** was undetermined because of incomplete separation by chromatography, the ee should be ≥93% for *S*-isomer (vide infra). The reaction of 3-vinylthiophene (**1b**) gave branched aldehyde **2b** in high regio- and enantioselectivity [**2b**/**3b** = 92/8, ≥91% ee for *R*-isomer (vide infra)], while the complete conversion required longer reaction time than that for **1a** (Table 1, run 2). Substituted vinylthiophenes were also employable. Hydroformylation of 5-methyl-2-vinylthiophene (**1c**) gave the branched aldehyde **2c** (**2c**/**3c** = 95/5) with a high ee of 95% in 92% yield (Table 1, run 3). In the case of benzoannulated derivatives **1d**, the resulting reaction mixture contained the aldehydes **2d** and **3d** as exclusive products after the complete conversion. However, the isolated yield was moderate, which should be due to decomposition of the aldehydes during the purification process. The regioselectivity was slightly lower than those for the other substrates.

Oxidation of Aldehydes. Next, we investigated the oxidation of the hydroformylation products. Oxidation of the isolated branched aldehydes **2b** by using silver oxide,[16] which is effective for oxidation of α-arylpropanals, gave methyl 3-thienyl ketone, as a result of loss of one carbon unit (eq 1).[17]



(1)

The use of other oxidation reagents such as Jones reagent,[7] pyridinium dichromate,[8] and potassium permanganate also resulted in the formation of the ketone. When using sodium

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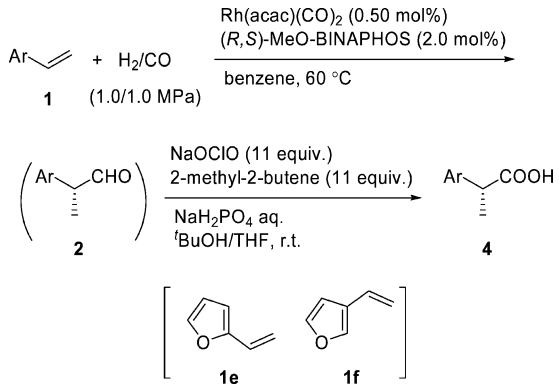
TABLE 2. Asymmetric Hydroformylation and Subsequent Oxidation of Vinylheteroarenes[a]



run	substrate	yield of **4** (%)	ee of **4** (%)
1	**1a**	80[b]	93 (*S*)[e]
2	**1b**	71[c]	91 (*R*)[e]
3	**1c**	64[c]	83 (*S*)[e]
4	**1d**	69[c]	92 (*R*)[f]
5	**1e**	69[c]	77 (*S*)[g]
6	**1f**	—[d]	

[a] Reaction conditions: **1** (1.0 mmol), H_2 (1.0 MPa), CO (1.0 MPa), [Rh(acac)(CO)$_2$] (0.0050 mmol), (*R*,*S*)-MeO-BINAPHOS (0.020 mmol) in benzene (0.50 mL) at 60 °C for 3−6 h, then NaOClO (11 mmol), 2-methyl-2-butene (5.5 mL of 2 M THF solution, 11 mmol), aqueous $NaH_2PO_4 \cdot 2H_2O$ (1.77 mmol in 2 mL of H_2O), ^{t}BuOH (10 mL) at room temperature for 30 min. [b] Isolated yield. [c] NMR yield by using naphthalene as an internal standard. [d] The desired oxidation product was not detected. [e] Determined by GC with Chirasil DEX CB column. [f] Determined by HPLC with CHIRALPAK IA column. [g] Determined by HPLC with CHIRALPAK IB column.

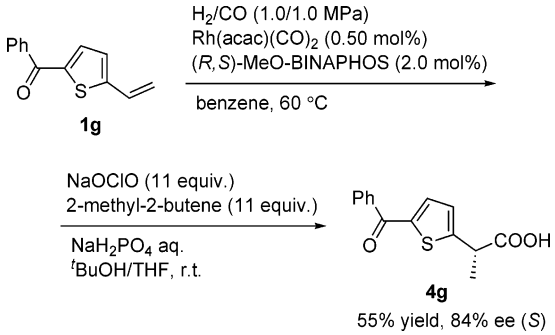
hypochlorite, a complex mixture was obtained, without the desired carboxylic acid. After optimizing the reaction conditions, we found that the use of sodium chlorite brought the successful oxidation to give the corresponding α-thienylpropanoic acid in moderate to good yields.[15] The results of hydroformylation of vinylthiophenes **1** and the subsequent oxidation without the isolation of aldehydes are summarized in Table 2. The ee values of the obtained carboxylic acids were generally high, which indicates that the oxidation proceeded without any (or with few) loss in ee from aldehydes (vide supra).

We also investigated the hydroformylation of vinylfurans and their subsequent oxidation (Table 2, runs 5 and 6). When 2-vinylfuran was employed, the corresponding carboxylic acid was obtained in moderate yield (69%) with 77% ee for the *R*-isomer (run 5). In contrast, oxidation of the hydroformylation product from 3-vinylfuran gave the complex mixture without the desired carboxylic acid (run 6).

On the basis of the successful synthesis of enantio-enriched α-thienylpropanoic acids, we demonstrated the asymmetric synthesis of tiaprofenic acid. By using (*R*,*S*)-MeO-BINAPHOS ligand in the hydroformylation step, (*S*)-tiaprofenic acid with 84% ee was obtained in 55% yield (Scheme 1).

Reduction of Aldehydes. The subsequent reduction after the asymmetric hydroformylation of vinylthiophenes was also demonstrated (Table 3). According to our previous report of asymmetric hydroformylation of vinylfurans and the subsequent reduction,[12] the crude mixture of hydroformylation was treated with $NaBH_4$ in ethanol at −78 °C. The reduction caused a slight reduction in enantioselectivity as compared to that of aldehydes **2** (vide supra), producing the enantio-enriched alcohols **5** in high

SCHEME 1. Asymmetric Synthesis of (*S*)-Tiaprofenic Acid (4g)



SCHEME 2. Determination of Absolute Configuration of 5c and 5d

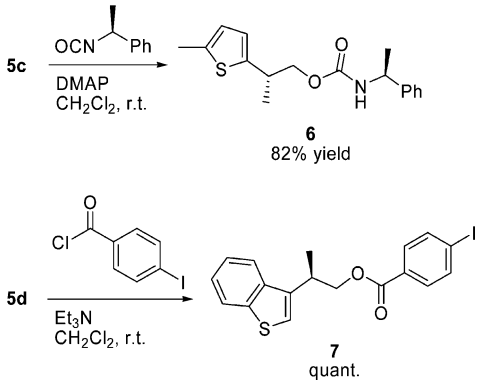
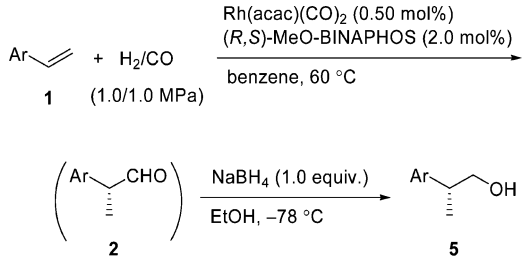


TABLE 3. Asymmetric Hydroformylation and Subsequent Reduction of Vinylthiophenes[a]



run	substrate	isolated yield of **5** (%)	ee of **5** (%)[b]
1	**1a**	91	93 (*S*)
2	**1b**	85	91 (*R*)
3	**1c**	89	93 (*S*)
4	**1d**	55	85 (*R*)

[a] Reaction conditions: **1** (2.0 mmol), H_2 (1.0 MPa), CO (1.0 MPa), [Rh(acac)(CO)$_2$] (0.010 mmol), (*R*,*S*)-MeO-BINAPHOS (0.040 mmol) in benzene (1.0 mL) at 60 °C for 3−6 h, then $NaBH_4$ (2.0 mmol), EtOH (4.0 mL) at −78 °C. [b] Determined by HPLC with CHIRALPAK IA column.

yields (Table 3, runs 1−3). When using **1d** as a starting material, the yield and the ee of alcohol **5d** (55% yield, 85% ee (*R*), see Table 3, run 4) slightly decreased from those of the aldehyde intermediate (68% yield, 88% ee (*R*), see Table 1, run 4).

Determination of Absolute Configurations. The absolute configuration of major enantiomers of **5a** and **5b** was found to be *S* and *R*, respectively, based on the sign of specific rotation.[18] The configuration of the major enantiomer of **5c** was determined to be *S* through X-ray crystallographic analysis of its (*S*)-1-phenylethylcarbamate derivative **6** (Scheme 2). The configuration of the major enantiomer of **5d** was also determined to be

R by X-ray crystallographic analysis of its *p*-iodobenzoate derivative **7**.

Thus, the absolute configurations of aldehydes **2** and carboxylic acids **4** were determined based on those of the reduction products **5**. Finally, the sense of enantioface selection in hydroformylation of vinylthiophenes is the same as that observed for styrenes.

Conclusion

The syntheses of optically active α-heteroarylpropanoic acid were achieved. The hydroformylation of vinylthiophenes **1** with Rh-BINAPHOS derivatives and the subsequent oxidation of the aldehydes **2** with NaOClO successfully afforded α-heteroarylpropanoic acids **4** in good yields and enantiopurities. In addition, the branched aldehydes **2** were reduced with $NaBH_4$ to alcohols **5** without loss of ee. The methodology we developed provides an effective synthetic route to α-heteroarylpropanoic acids **4**, which would be advantageous to the conventional process of optical resolution of the racemic mixture,[4] or to the usage of an equimolar amount of chiral axiliaries.[1,5]

Experimental Section

Typical Procedure for Asymmetric Hydroformylation of Vinylthiophenes. A solution of [Rh(acac)$(CO)_2$] (2.8 mg, 0.010 mmol), (*R*,*S*)-MeO-BINAPHOS (33 mg, 0.040 mmol), and vinylthiophene **1** (2.0 mmol) in benzene (1.0 mL) was degassed by freeze−thaw−pump cycles and was transferred into a 50 mL autoclave under Ar. Hydrogen (1.0 MPa) and carbon monoxide (1.0 MPa) were charged, and the resulting mixture was stirred at 60 °C for the appropriate time. After the H_2/CO pressure was released, an aliquot of the resulting mixture was analyzed by ^{1}H NMR to determine the ratios of the aldehydes **3** and **4**. The crude product was purified by silica gel column chromatography.

2-(2-Thienyl)propanal (2a). Following the typical procedure with 2-vinylthiophene (**1a**), the crude product was purified by silica gel column chromatography (hexane:EtOAc = 10:1, R_f 0.42) to give **2a** as a colorless oil: yield 262 mg (93% yield). Spectroscopic data were identical with those in the literature.[19]

2-(3-Thienyl)propanal (2b). Following the typical procedure with 3-vinylthiophene (**1b**), the crude product was purified by silica gel column chromatography (hexane:EtOAc = 10:1, R_f 0.38): yield 255 mg (91% yield). Spectroscopic data were identical with those in the literature.[18,19]

2-(5-Methylthiophen-2-yl)propanal (2c). Following the typical procedure with 5-methyl-2-vinylthiophene (**1c**), the crude product was purified by silica gel column chromatography (hexane:EtOAc = 10:1, R_f 0.42): yield 281 mg (92% yield) as a colorless oil; 95% ee for (*S*)-**2c** [HPLC with CHIRALPAK IA column, hexane, 1.0 mL/min, t_R = 17.9 min for (*R*)-**2c** and 19.5 min for (*S*)-**2c**]; $[\alpha]^{20}_D$ −78.8 (*c* 1.39, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.61 (d, J = 1.8 Hz, 1H), 6.70 (d, J = 3.4 Hz, 1H), 6.67 (m, 1H), 3.77 (q, J = 6.7 Hz, 1H), 2.46 (s, 3H), 1.47 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 199.2, 139.7, 137.5, 125.4, 125.3, 47.9, 15.2, 15.1. Anal. Calcd for $C_8H_{10}OS$: C 62.30, H 6.54. Found: C 62.01, H 6.65.

2-(Benzo[*b*]thiophen-3-yl)propanal (2d). Following the typical procedure with 3-vinylbenzo[*b*]thiophene (**1d**), the crude product was purified by silica gel column chromatography (hexane:EtOAc = 5:1, R_f 0.31): yield 258 mg (68% yield); colorless oil; 88% ee for (*R*)-**2d** [HPLC with CHIRALPAK IA column, hexane:$CHCl_3$ = 99:1, 1.0 mL/min, t_R = 23.6 min for (*S*)-**2d** and 26.0 min for (*R*)-**2d**]; $[\alpha]^{17}_D$ −31.4 (*c* 0.29, $CHCl_3$); IR (neat) 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.67 (d, J = 2.1 Hz, 1H), 7.91−7.88 (m, 1H), 7.78−7.75 (m, 1H), 7.43−7.37 (m, 2H), 7.27 (m, 1H), 4.05 (qdd, J = 7.0, 1.9, 0.8 Hz, 1H), 1.58 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 199.9, 140.6, 138.0, 132.3, 124.7, 124.4, 123.6, 123.0, 121.5, 46.7, 13.6. Anal. Calcd for $C_{11}H_{10}OS$: C 69.44, H 5.30. Found: C 69.20, H 5.49.

Oxidation of 2-(3-Thienyl)propanal (2b) by Silver Oxide. Silver oxide (61 mg, 266 μmol) was suspended in a solution of NaOH (10 mg) in H_2O (1.0 mL). To this suspension was added a solution of **2b** (36 mg, 253 μmol) in EtOH (1.0 mL), and the resulting mixture was stirred at 40 °C overnight. The reaction mixture was acidified with 1 M aqueous HCl (15 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give methyl 3-thienyl ketone (25 mg, 79% yield).

Typical Procedure for Asymmetric Hydroformylation and Subsequent Oxidation. A solution of [Rh(acac)$(CO)_2$] (1.4 mg, 0.0050 mmol), (*R*,*S*)-MeO-BINAPHOS (17 mg, 0.020 mmol), and olefin **1** (1.0 mmol) in benzene (0.50 mL) was degassed by freeze−thaw−pump cycles, then was transferred into a 50 mL autoclave under Ar. Hydrogen (1.0 MPa) and carbon monoxide (1.0 MPa) were charged and the resulting mixture was stirred at 60 °C for the appropriate time. After the H_2/CO pressure was released, the reaction mixture was transferred into a 20 mL Schlenk tube, then ^{t}BuOH (10 mL), 2-methyl-2-butene (2.0 M in THF, 5.5 mL, 11 mmol), and NaH_2PO_4·$2H_2O$ (276 mg, 1.77 mmol) in H_2O (2.0 mL) were added. The mixture was cooled to 0 °C, then NaOClO (994 mg, 11.0 mmol) in 2 mL of H_2O was added. After being stirred for 30 min at room temperature, the reaction was quenched with saturated aqueous Na_2SO_3 (10 mL). The aqueous phase was acidified with 1 M aqueous HCl (10 mL) and extracted with three portions of EtOAc (10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated. An aliquot of the resulting mixture was analyzed by ^{1}H NMR to determine the yield of carboxylic acid **4** (naphthalene as an internal standard) and by HPLC or by GC to determine the ee of carboxylic acid **4**.

2-(2-Thienyl)propanoic Acid (4a). Following the typical procedure with 2-vinylthiophene (**1a**), the crude product was purified by silica gel column chromatography (hexane:EtOAc = 3:1, R_f 0.18): yield 124 mg (80% yield); spectroscopic data were identical with those in the literature;[20] 93% ee for (*S*)-**4a** [GC with Chirasil DEX CB column, 150 °C, t_R= 18.7 min for (*R*)-**4a** and 19.8 min for (*S*)-**4a**].

2-(3-Thienyl)propanoic acid (4b). According to the typical procedure, 3-vinylthiophene (**1b**) was hydroformylated and further oxidized: 71% NMR yield; spectroscopic data were identical with those in the literature;[21] 92% ee for (*R*)-**4b** [GC with Chirasil DEX CB column, 150 °C, t_R = 19.0 min for (*S*)-**4b** and 20.4 min for (*R*)-**4b**].

2-(5-Methylthiophen-2-yl)propanoic Acid (4c). According to the typical procedure, 5-methyl-2-vinylthiophene (**1c**) was hydroformylated and further oxidized: 64% NMR yield; 83% ee for (*S*)-**4c** [GC with Chirasil DEX CB column, 150 °C, t_R = 22.2 min for (*R*)-**4c** and 24.8 min for (*S*)-**4c**].

The authentic sample was synthesized by the following procedure. In a 20 mL Schlenk tube, 2-(5-methylthiophen-2-yl)propanal (255 mg, 1.7 mmol) and ^{t}BuOH (10 mL), 2-methyl-2-butene (2.0 M in THF, 5.5 mL, 11 mmol), and NaH_2PO_4·$2H_2O$ (276 mg, 1.8 mmol) in H_2O (2 mL) were added. The mixture was cooled to 0 °C, then NaOClO (994 mg, 11 mmol) in H_2O (2 mL) was added. After being stirred for 30 min, the reaction was quenched with saturated aqueous Na_2SO_3 (10 mL). The aqueous phase was acidified with 1 M aqueous HCl (10 mL) and extracted with three portions of EtOAc (10 mL). The combined organic phases were

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dried over $MgSO_4$, filtered, and evaporated. The crude mixture was purified by the recycling preparative HPLC: yield 172 mg (61% yield); IR (neat) 2923, 1712 cm^{-1}; $[\alpha]^{23}_D$ −5.1 (*c* 2.86, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.75 (d, J = 3.4 Hz, 1H), 6.61−6.59 (m, 1H), 3.94 (q, J = 7.3 Hz, 1H), 2.44 (d, J = 0.9 Hz, 3H), 1.57 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.9, 139.5, 139.1, 125.0, 124.7, 40.8, 18.8, 15.2. Anal. Calcd for $C_8H_{10}O_2S$: C 56.44, H 5.92. Found: C 56.18, H 6.01.

2-(Benzo[*b*]thiophen-3-yl)propanoic Acid (4d). According to the typical procedure, 3-vinylbenzo[*b*]thiophene (**1d**) was hydroformylated and further oxidized: 69% NMR yield; 92% ee for (*R*)-**4d** [HPLC with CHIRALPAK IA column, hexane:2-propanol:TFA = 98:2:0.1, 1.0 mL/min, t_R = 15.2 min for (*S*)-**4d** and 16.3 min for (*R*)-**4d**].

The authentic sample was synthesized by the following procedure. In a 20 mL Schlenk tube, 2-(benzo[*b*]thiophen-3-yl)propanal (226 mg, 70 mmol) and ^{t}BuOH (10 mL), 2-methyl-2-butene (2.0 M in THF, 5.5 mL, 11 mmol), and $NaH_2PO_4 \cdot 2H_2O$ (276 mg, 1.8 mmol) in H_2O (2 mL) were added. The mixture was cooled to 0 °C, then NaOClO (994 mg, 11.0 mmol) in H_2O (2 mL) was added. After stirring for 30 min, the reaction was quenched with saturated aqueous Na_2SO_3 (10 mL). The aqueous phase was acidified with 1 M aqueous HCl (10 mL) and extracted with three portions of EtOAc (10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated. The crude mixture was purified by the recycling preparative HPLC: yield 216 mg (88% yield); IR (neat) 2937, 1709 cm^{-1}; $[\alpha]_D$ −24.6 (*c* 1.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.86 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.41−7.34 (m, 3H), 4.17 (q, J = 7.1 Hz, 1H), 1.67 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.6, 140.5, 138.0, 134.2, 124.6, 124.3, 123.2, 123.0, 121.9, 39.3, 17.3. HRMS calcd for $C_{11}H_{10}O_2S$ 206.0402, found 206.0408.

2-(2-Furyl)propanoic Acid (4e). According to the typical procedure, 2-vinylfuran (**1e**) was hydroformylated and further oxidized. Spectroscopic data were identical with those in the literature:[22] 69% NMR yield; 77% ee for (*S*)-**4e** [HPLC with CHIRALPAK IB column, hexane:2-propanol:TFA = 98:2:0.1, 1.0 mL/min, t_R = 11.6 min for (*S*)-**4e** and 12.7 min for (*R*)-**4e**].

2-(5-Benzoylthiophen-2-yl)propanoic Acid (Tiaprofenic Acid, 4g). According to the typical procedure, 5-benzoyl-2-vinylthiophene (**1g**) was hydroformylated and oxidized:[1] 55% NMR yield; spectroscopic data were identical with those in the literature; 84% ee for (*S*)-**4g** [HPLC with CHIRALPAK IB column, hexane:2-propanol: TFA = 95:5:0.1, 1.0 mL/min, t_R = 14.3 min for (*S*)-**4g** and 15.6 min for (*R*)-**4g**].

Typical Procedure for Hydroformylation and Subsequent Reduction. A solution of $[Rh(acac)(CO)_2]$ (2.8 mg, 0.010 mmol), (*R*,*S*)-MeO-BINAPHOS (33 mg, 0.040 mmol), and vinylthiophene **1** (2.0 mmol) in benzene (1.0 mL) was degassed by freeze−thaw−pump cycles, then was transferred into a 50 mL autoclave under Ar. Hydrogen (1.0 MPa) and carbon monoxide (1.0 MPa) were charged and the mixture was stirred at 60 °C for the appropriate time. After the H_2/CO pressure was released, the reaction mixture was transferred into a 20 mL Schlenk tube, and EtOH (4.0 mL) was added. Powdered $NaBH_4$ (76 mg, 2.0 mmol) was added at −78 °C, and the resulting mixture was stirred overnight. The reaction was quenched with H_2O (3 mL) and extracted with three portions of EtOAc (10 mL). The organic layers were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography to give the corresponding alcohol.

2-(2-Thienyl)propanol (5a). Following the typical procedure with 2-vinylthiophene (**1a**), the crude product was purified by silica gel column chromatography (hexane:EtOAc = 5:1, R_f 0.23): yield 259 mg (91% yield); spectroscopic data were identical with those in the literature;[18] 93% ee for (*S*)-**5a** [HPLC with CHIRALPAK IA column, hexane:$CHCl_3$ = 80:20, 1.0 mL/min, t_R = 16.8 min for (*R*)-**5a** and 19.7 min for (*S*)-**5a**]; $[\alpha]^{18}_D$ +18.1 (*c* 12.5, $CHCl_3$) (lit.[18] $[\alpha]^{25}_D$ −6.2 (*c* 19, $CHCl_3$) for (*R*)-**5a** (31% ee)).

2-(3-Thienyl)propanol (5b). Following the typical procedure with 3-vinylthiophene as olefin (**1b**), the product was purified by silica gel column chromatography (hexane:CH_2Cl_2:EtOAc = 5:5:1, R_f 0.39): yield 246 mg (85% yield); spectroscopic data were identical with those in the literature;[18] 89% ee for (*R*)-**5b** [HPLC with CHIRALPAK IA column, hexane:$CHCl_3$ = 80:20, 1.0 mL/min, t_R = 17.8 min for (*S*)-**5b** and 19.6 min for (*R*)-**5b**]; $[\alpha]^{20}_D$ +15.7 (*c* 12.3, $CHCl_3$) (lit.[18] $[\alpha]^{25}_D$ −2.0 (*c* 11, $CHCl_3$) for (*S*)-**5b** (12.6% ee)).

2-(5-Methylthiophen-2-yl)propanol (5c). Following the typical procedure with 5-methyl-2-vinylthiophene (**1c**), the product was purified by silica gel column chromatography (hexane:EtOAc = 4:1, R_f 0.18): yield 274 mg (89% yield); colorless oil; 93% ee for (*S*)-**5c** [HPLC with CHIRALPAK IA column, hexane:$CHCl_3$ = 80:20, 1.0 mL/min, t_R = 17.8 min for (*R*)-**5c** and 19.6 min for (*S*)-**5c**]; $[\alpha]^{20}_D$ +21.4 (*c* 1.76, $CHCl_3$); IR (neat) 3361 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.67 (d, J = 3.4 Hz, 1H), 6.61−6.59 (m, 1H), 3.69 (dd, J = 10.8, 5.7 Hz, 1H), 3.62 (dd, J = 10.7 Hz, 7.2 Hz, 1H), 3.18−3.12 (m, 1H), 2.45 (s, 3H), 1.31 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 144.9, 137.9, 124.7, 123.7, 68.8, 38.2, 18.4, 15.2. Anal. Calcd for $C_8H_{12}OS$: C 61.50, H 7.74. Found: C 61.32, H 7.86.

2-(Benzo[*b*]thiophen-3-yl)propanol (5d). Following the typical procedure with 3-vinylbenzo[*b*]thiophene (**1d**), the crude product was purified by silica gel column chromatography (hexane:EtOAc = 5:1, R_f 0.16): yield 203 mg (55% yield); colorless oil; 85% ee for (*R*)-**5d** [HPLC with CHIRALPAK IA column, hexane:$CHCl_3$ = 80:20, 1.0 mL/min, t_R = 19.3 min for (*S*)-**5c** and 24.5 min for (*R*)-**5c**]. $[\alpha]^{17}_D$ −13.3 (*c* 1.9, $CHCl_3$); IR (neat) 3354 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.89−7.87 (m, 1H), 7.83−7.81 (m, 1H), 7.42−7.34(m, 2H), 7.21 (s, 1H), 3.90 (dd, J = 10.8, 6.0 Hz, 1H), 3.81 (dd, J = 10.7, 6.1 Hz, 1H), 3.49−3.42 (m, 1H), 1.44 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 140.6, 138.6, 138.5, 124.4, 123.9, 122.9, 121.7, 121.1, 67.3, 35.8, 17.1. HRMS calcd for $C_{11}H_{12}OS$ 192.0609, found 192.0601.

Determination of Absolute Configuration of (*S*)-5c. To a solution of **5c** (26 mg, 169 μmol, 93% ee) and DMAP (12.3 mg, 101 μmol) in CH_2Cl_2 (0.50 mL) was added (*S*)-(−)-(1-isocyanatoethyl)benzene (30 μL, 214 μmol). The mixture was stirred for 16 h at room temperature, then 1 M aqueous $NaHCO_3$ (3 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by silica gel column chromatography (hexane:EtOAc = 10:1, R_f 0.17) to give **6** as a colorless solid: yield 42 mg (82% yield). The solid was recrystallized from ether/hexane. The absolute configuration was confirmed by X-ray crystal analysis. Mp 121−124 °C; ^1H NMR ($CDCl_3$) δ 7.35−7.24 (m, 5H), 6.63−6.59 (br, 1H), 6.58−6.55 (br, 1H), 5.03−4.93 (br, 1H), 4.88−4.80 (br, 1H), 4.16−4.08 (m, 2H), 3.30−3.21 (m, 1H), 2.44 (s, 3H), 1.48 (d, J = 6.4 Hz, 3H), 1.30 (d, J = 5.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.5, 144.6, 143.5, 137.6, 128.6, 127.3, 125.9, 124.5, 123.3, 69.8, 50.6, 35.0, 22.4, 18.9, 15.3. HRMS calcd for $C_{17}H_{21}O_2NS$ 303.1293, found 303.1305.

Determination of Absolute Configuration of (*R*)-5d. To a solution of **5d** (21 mg, 110 μmol, 85% ee) and Et_3N (20 μL, 144 μmol) in CH_2Cl_2 (0.20 mL) was added *p*-iodobenzoic acid chloride (40 mg, 149 μmol) in CH_2Cl_2 (0.50 mL). The mixture was stirred for 2 h at room temperature, then 1 M aqueous $NaHCO_3$ (1 mL) was added. The aqueous layer was extracted with CH_2Cl_2 three times, and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give **7** as a colorless solid in a yield of 47 mg (quantitative yield). The obtained solid was recrystallized from ether/hexane. A part of the large single crystal was used for X-ray analysis, and the absolute configuration was confirmed by

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anomalous dispersion effects. HPLC analysis of the rest of the large single crystal revealed that the single crystal was the major isomer. HPLC with CHIRALPAK IC column, hexane:2-propanol = 98:2, 1.0 mL/min, t_R = 7.2 min for ester from (*S*)-**5d** and 7.8 min for ester from (*R*)-**5c**; mp 89−94 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H), 7.43−7.35 (m, 2H), 7.25 (s, 1H), 4.65 (dd, J = 10.8, 5.7 Hz, 1H), 4.37 (dd, J = 10.8, 7.6 Hz, 1H), 3.74−3.68 (m, 1H), 1.53 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.0, 140.5, 138.4, 137.72, 133.70, 131.0, 129.6, 124.4, 124.0, 122.9, 121.7, 121.2, 100.8, 69.2, 32.6, 17.4. HRMS calcd for $C_{18}H_{15}O_2SI$ 421.9838, found 421.9855.

Supporting Information Available: General experimental procedures, syntheses of 3-vinylfuran (**1f**), ^{1}H and ^{13}C NMR spectra for synthesized compounds, and crystallographic information files (CIF) for **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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