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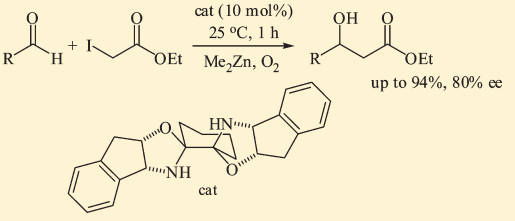
Bisoxazolidine-Catalyzed Enantioselective Reformatsky Reaction

Christian Wolf* and Max Moskowitz

Department of Chemistry, Georgetown University, Washington, D.C. 20057, United States

Supporting Information

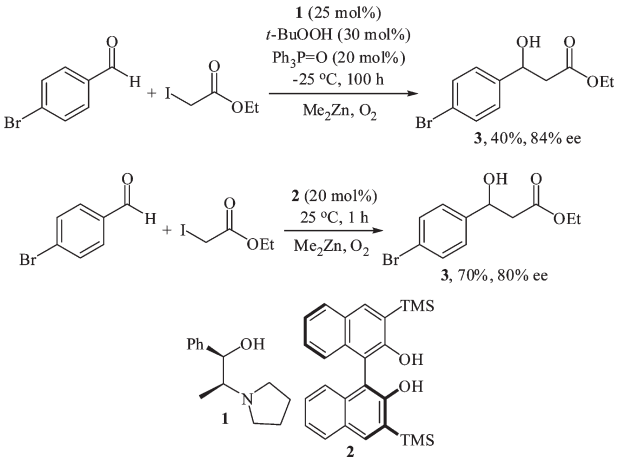
ABSTRACT: A readily available chiral bisoxazolidine catalyzes the asymmetric Reformatsky reaction between ethyl iodoacetate and aldehydes. In the presence of 10 mol % of the ligand, dimethylzinc, and air, this method produces ethyl 3-hydroxy-3-(4-aryl)propanoates in high yields and in 75 to 80% ee at room temperature within 1 h. In contrast to aromatic substrates, relatively low ee's are obtained with aliphatic aldehydes.



The classical Reformatsky reaction produces β-hydroxy esters through insertion of zinc into α-halo esters and subsequent nucleophilic addition of the zinc enolate to aldehydes or ketones. Since its introduction in 1887, this reaction has become one of the most successful carbon−carbon bond formation methods, and it has found numerous synthetic applications which can certainly be attributed to the remarkable functional group tolerance and generally mild reaction conditions.[1] The advance of procedures that generate zinc enolates under homogeneous conditions, for example in the presence of dimethylzinc, set the stage for asymmetric variants.[2] Until recently, few examples of diastereoselective[3] and enantioselective[4] Reformatsky reactions were known, and ee's obtained were generally low unless stoichiometric amounts of chiral ligands were used. A breakthrough in the development of catalytic enantioselective procedures was made in 2008 when Cozzi and Feringa reported that ephedrine and BINOL derivatives **1** and **2** effectively catalyze the Me_2Zn-promoted addition of ethyl iodoacetate to aromatic aldehydes in the presence of air or *tert*-butyl hydroperoxide which accelerate the zinc enolate generation.[5] Employing 25 mol % of *N*-pyrrolidinylephedrine and catalytic amounts of triphenylphosphine oxide in the Reformatsky reaction between ethyl iodoacetate and benzaldehyde, Cozzi's group obtained ethyl 3-hydroxy-3-(4-bromophenyl)propanoate, **3**, in 40% yield and 84% ee after 100 h. Feringa et al. were able to produce **3** in the presence of 20 mol % of **2** in 70% yield and 80% ee (Scheme 1).[6]

A few years ago, we reported the synthesis of bisoxazolidine **4** from aminoindanol and cyclohexadione, and since then we have shown several applications of this C_2-symmetric *N*,*O*-diketal in asymmetric catalysis (Figure 1).[7] This ligand catalyzes the dimethylzinc-mediated enantioselective alkynylation of a wide range of aldehydes toward propargylic alcohols with excellent yields and ee's.[8] It has also been used successfully in the alkylation of aldehydes with Me_2Zn and Et_2Zn,[9] and in the asymmetric Henry reaction which can be performed either in the presence of excess of dimethylzinc or catalytic amounts of copper(I) acetate.[10] Most recently, we have demonstrated the usefulness of ligand **4** in the nitroaldol reaction of trifluoromethyl ketones and α-keto esters and an asymmetric Friedel−Crafts reaction.[11]

Scheme 1. Asymmetric Reformatsky Reaction Using 1 and 2



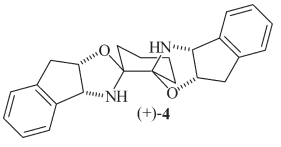


Figure 1. Structure of bisoxazolidine **4**.

On the basis of the success with asymmetric reactions involving organozinc species, we decided to introduce **4** to the Reformatsky reaction. During optimization, we realized that 4-bromobenzaldehyde is significantly less prone to decomposition than benzaldehyde and therefore a better choice for method

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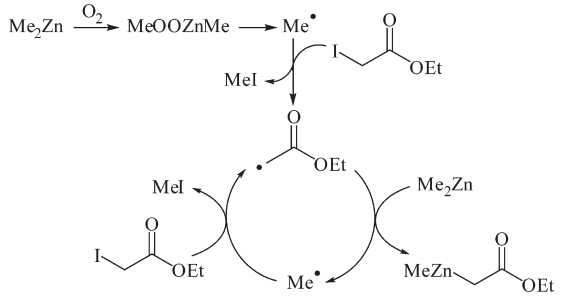
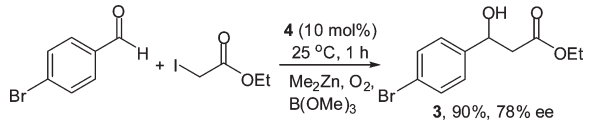


Figure 2. Radical generation and subsequent formation of the methylzinc enolate.

Scheme 2. Bisoxazolidine-Catalyzed Reformatsky Reaction with Bromobenzaldehyde



development. The Reformatsky reaction proved to be very sensitive to unusual parameters, such as the size of the flask used, the timing of the exposure to air, and the addition sequence of dimethylzinc. It is generally assumed that dimethylzinc and oxygen generate a methyl radical which initiates the formation of the Reformatsky reagent (Figure 2).[12] Because the oxygen has to diffuse into the reaction mixture to affect the radical process, the subsequent production of the intermediate methylzinc enolate is dependent on several parameters including flask size and reaction volume which determine the surface area at the gas−liquid interface. We found that a change in the parameters mentioned above and in the rate of addition of the aldehyde or in the amount of ethyl iodoacetate strongly affect yields. For example, when the amount of ethyl iodoacetate was reduced from 2 to 1 equiv, no product was isolated. Addition of stoichiometric amounts of trimethoxyborane led to a 10% increase in yield which may be attributed to formation of a borate complex with the Reformatsky product. This transmetalation process should facilitate catalyst turnover and avoid interference of the alkoxide formed with the catalytically active zinc complex. By contrast, we observed that the enantioselectivity of this reaction is considerably less sensitive, and variation of the reaction temperature between 0 and 35 °C did not change ee's.

Careful optimization of solvent, catalyst loading, introduction of air, concentration of ethyl iodoacetate, amount of dimethylzinc and trimethoxyborane, and the addition sequence of the latter and the substrate resulted in a procedure that gives ethyl 3-hydroxy-3-(4-bromophenyl)propanoate, **3**, in 90% yield and 78% ee (Scheme 2). Our method involves only 10 mol % of the ligand and is completed at room temperature within 1 h. However, a decrease in the temperature did not improve ee's any further.

We then continued with the screening of various aldehyde substrates (Table 1). Benzaldehyde gave ethyl 3-hydroxy-3-(4-bromophenyl)propanoate, **5**, in 79% yield and 77% ee (entry 1), and similar results were obtained with a range of other aromatic aldehydes. In general, yields up to 94% were achieved with this method while ee's varied between 75 and 80% (entries 1−11). Aliphatic substrates gave good yields but low to moderate ee's even at reduced temperatures and at higher catalyst loading, entries 12−14. The results obtained with both linear and branched aldehydes are comparable with those reported by Cozzi and Feringa.[5]

In summary, the bisoxazolidine-catalyzed asymmetric Reformatsky reaction produces 3-hydroxy-3-(4-aryl)propanoates in high yields and in 75 to 80% ee at room temperature within 1 h. Our method requires only 10 mol % of **4**, and the results compare well with previously reported procedures. However, effective asymmetric induction with aliphatic substrates remains a challenge, and future work is needed to further improve ee's.

EXPERIMENTAL SECTION

All commercially available reagents and solvents were used without further purification. NMR spectra were obtained at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). Chemical shifts are reported in ppm relative to TMS. Reaction products were purified by column chromatography on silica gel (particle size 32−63 μm). Aldehydes were purified prior to use by distillation under reduced pressure or by flash chromatography on silica gel using 4% ethyl acetate in hexanes as mobile phase.

General Reaction Procedure. A 150 mL three-neck flask was fitted with a $CaCl_2$ drying tube sealed with a stopper. Bisoxazolidine **4** (9.6 mg, 0.024 mmol) was dissolved in 5.0 mL of anhydrous Et_2O at room temperature and transferred into the flame-dried flask, and the solution was stirred for 5 min under inert atmosphere until ethyl iodoacetate (59.1 μL, 0.50 mmol) was added. After 5 min, $B(OMe)_3$ (27.9 μL, 0.25 mmol) was added. Then, the reaction was opened to the atmosphere by removing the stopper from the $CaCl_2$ drying tube. After another 5 min, 1.2 M Me_2Zn in toluene (0.85 mL, 1.0 mmol) was added at once followed immediately by dropwise addition of the substrate (0.25 mmol) in 1.0 mL of anhydrous Et_2O using a syringe pump (10 μL drops over 10 min). After 4 min, within the automated addition, another portion of 1.2 M Me_2Zn in toluene (0.85 mL, 1.0 mmol) was added to the reaction flask. The reaction was allowed to proceed for 1 h and was quenched with 10 mL of 1 M HCl. The mixture was extracted with three portions of Et_2O and dried over $MgSO_4$, and solvents were removed in vacuo. The product was purified by flash chromatography on silica gel as described below.

Ethyl 3-(4-Bromophenyl)-3-hydroxypropanoate, 3.[5a] Following the general procedure described above, **3** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 300:100:4) as a colorless oil (90% yield, 76% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.26 (t, J = 7.2 Hz, 3H), 2.65−2.74 (m, 2H), 3.46 (bs, 1H), 4.17 (q, J = 7.2 Hz, 2H), 5.08 (m, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 13.1, 42.1, 60.0, 68.6, 120.6, 126.4, 130.6, 140.5, 171.2. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (98:2) as mobile phase; retention times: t_1 (minor) = 11.3 min, t_2 (major) = 13.4 min.

Ethyl 3-Hydroxy-3-phenylpropanoate, 5.[5a] Following the general procedure described above, **5** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 300:100:4) as a colorless oil (79% yield, 77% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.25 (t, J = 7.1 Hz, 3H), 2.67−2.79 (m, 2H), 3.31 (d, J = 3.5 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 5.12 (m, 1H), 7.25−7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 43.3, 60.8, 70.2, 125.6, 127.7, 128.5, 142.5, 172.4. Ee determination by chiral HPLC analysis on Chiralcel OD using hexanes:*i*-PrOH (90:10) as mobile phase; retention times: t_1 (major) = 13.8 min, t_2 (minor) = 15.6 min.

Ethyl 3-(4-Fluorophenyl)-3-hydroxypropanoate, 6.[13] Following the general procedure described above, **6** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 300:100:4) as a colorless oil (70% yield, 76% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.26 (t, J = 7.2 Hz, 3H), 2.64−2.76 (m, 2H), 3.39 (bs,

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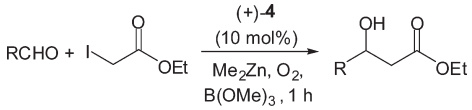
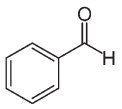
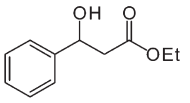
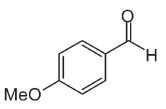
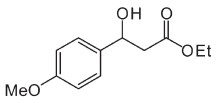
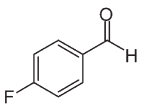
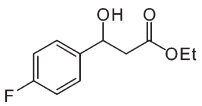
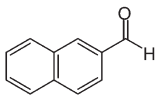
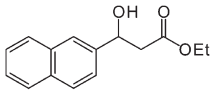
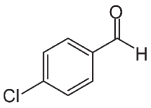
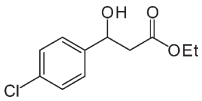
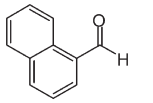
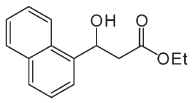
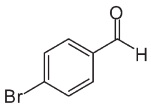
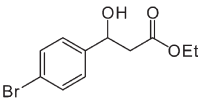
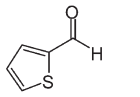
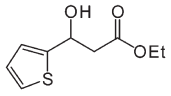
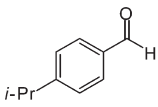
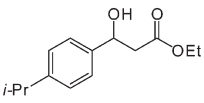
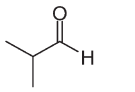
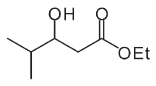
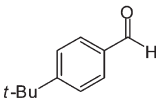
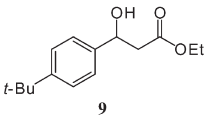
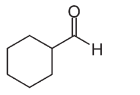
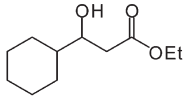
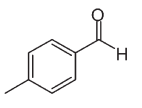
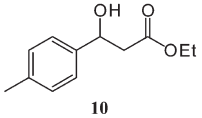
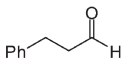
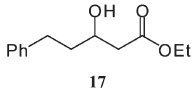
Table 1. Bisoxazolidine-Catalyzed Enantioselective Reformatsky Reaction[a]



Entry	Substrate	Product	Yield[b]	ee[c]	Entry	Substrate	Product	Yield[b]	ee[c]
1		 **5**	79	77 (*S*)	8		 **11**	77	77 (*S*)
2		 **6**	70	76	9		 **12**	89	79
3		 **7**	86	78 (*S*)	10		 **13**	94	80
4		 **3**	90	76 (*S*)	11		 **14**	77	75
5		 **8**	82	79	12		 **15**	89	51
6		 **9**	79	79	13		 **16**	86	36
7		 **10**	83	78	14		 **17**	75	26

[a] General reaction conditions: Ethyl iodoacetate (59.1 μL, 0.50 mmol) was added to a solution of bisoxazolidine **4** (9.6 mg, 0.024 mmol) in 5.0 mL of anhydrous Et_2O. After 5 min, $B(OMe)_3$ (27.9 μL, 0.25 mmol) and 1.2 M Me_2Zn in toluene (0.85 mL, 1.0 mmol) were added at once, followed by dropwise addition of the aldehyde (0.25 mmol) in 1.0 mL of anhydrous Et_2O over 10 min. Within 4 min of the substrate addition, another portion of 1.2 M Me_2Zn in toluene (0.85 mL, 1.0 mmol) was added, and the reaction was stirred for 1 h. [b] Isolated yields. [c] Determined by chiral HPLC on Chiralcel OD and Chiralpak AS or by GC on 6-O-TBDMS-2,3-di-*O*-methyl-β-cyclodextrin and Lipodex E. Absolute configurations were determined as described in the literature.[5a]

1H), 4.18 (q, J = 7.1 Hz, 2H), 5.09 (m, 1H), 7.03 (dd, J = 8.6 Hz, 8.6 Hz, 2H), 7.34 (dd, J = 5.6 Hz, 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 43.3, 60.9, 69.6, 115.3 (d, J_{C-F} = 21.4 Hz), 127.3 (d, J_{C-F} = 8.1 Hz), 138.3 (d, J_{C-F} = 3.1 Hz), 162.2 (d, J_{C-F} = 245.7 Hz), 172.2. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (98:2) as mobile phase; retention times: t_1 (minor) = 10.5 min, t_2 (major) = 12.1 min.

Ethyl 3-(4-Chlorophenyl)-3-hydroxypropanoate, 7.[5a] Following the general procedure described above, **7** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 300:100:4) as a colorless oil (86% yield, 78% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.25 (t, J = 7.1 Hz, 3H), 2.65−2.74 (m, 2H), 3.44 (bs, 1H), 4.18 (q, J = 7.1 Hz, 2H), 5.10 (m, 1H), 7.21 - 7.41 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 43.2, 61.0, 69.6, 127.0, 128.6, 133.4, 141.0, 172.2. Ee determination by chiral HPLC analysis on Chiralpak AS using heptanes:*i*-PrOH (95:5) as mobile phase; retention times: t_1 (minor) = 21.1 min, t_2 (major) = 26.4 min.

Ethyl 3-Hydroxy-3-(4-isopropylphenyl)propanoate, 8.[5a] Following the general procedure described above, **8** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 300:100:4) as a colorless oil (82% yield, 79% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.24 (d, J = 6.9 Hz, 6H), 1.26 (t, J = 7.1 Hz, 3H), 2.66−2.80 (m, 2H), 2.90 (sept, J = 6.9 Hz,1H), 3.18 (d, J = 3.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 5.11 (m, 1H), 7.21 (d, J = 8.0 Hz, 2H) 7.30 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 23.9, 33.8, 43.3, 60.8, 70.2, 125.7, 126.6, 139.9, 148.5, 172.4. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (96:4) as mobile phase; retention times: t_1 (minor) = 20.1 min, t_2 (major) = 22.7 min.

Ethyl 3-(4-*tert*-Butylphenyl)-3-hydroxypropanoate, 9.[5a] Following the general procedure described above, **9** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 300:100:4) as a colorless oil (79% yield, 79% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.26 (t, J = 7.2 Hz, 3H), 1.31 (s, 9H), 2.67−2.80 (m, 2H), 3.17 (d, J = 3.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 5.11 (m, 1H), 7.31

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(d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 31.3, 34.5, 43.2, 60.8, 70.1, 125.4, 139.5, 150.7, 172.4. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (96:4) as mobile phase; retention times: t_1 (minor) = 18.3 min, t_2 (major) = 20.8 min.

Ethyl 3-Hydroxy-3-(4-tolyl)propanoate, 10.[13] Following the general procedure described above, **10** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 300:100:4) as a colorless oil (83% yield, 78% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.26 (t, J = 7.1 Hz, 3H), 2.34 (s, 3H), 2.66−2.74 (m, 2H), 3.22 (bs, 1H), 4.17 (q, J = 7.1 Hz, 2H), 5.08 (m, 1H), 7.15 (d, J = 7.8 Hz, 2H), 7.26 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 21.1, 43.3, 60.8, 70.2, 125.6, 129.2, 137.4, 139.6, 172.4. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (95:5); retention times: t_1 (minor) = 18.4 min, t_2 (major) = 21.1 min.

Ethyl 3-Hydroxy-3-(4-methoxyphenyl)propanoate, 11.[5a] Following the general procedure described above, **11** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 300:100:4) as a colorless oil (77% yield, 77% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.26 (t, J = 7.2 Hz, 3H), 2.64−2.79 (m, 2H), 3.19 (d, J = 3.1 Hz, 1H), 3.81 (s, 3H), 4.18 (q, J = 7.2 Hz, 2H), 5.08 (m, 1H), 6.88 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 43.3, 55.2, 60.8, 69.9, 113.9, 126.9, 134.7, 159.2, 172.4. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (95:5); retention times: t_1 (minor) = 10.4 min, t_2 (major) = 14.6 min.

Ethyl 3-Hydroxy-3-(2-naphthyl)propanoate, 12.[5a] Following the general procedure described above, **12** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 300:100:4) as a colorless oil (89% yield, 79% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.25 (t, J = 7.1 Hz, 3H), 2.76−2.86 (m, 2H), 3.44 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 5.29 (m, 1H), 7.46−7.48 (m, 3H), 7.81−7.83 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 43.3, 60.9, 70.4, 123.7, 124.4, 125.9, 126.2, 127.6, 128.0, 128.3, 133.0, 133.2, 139.9, 172.4. Ee determination by chiral HPLC analysis on Chiralpak AS using hexanes:*i*-PrOH (95:5); retention times: t_1 (minor) = 29.8 min, t_2 (major) = 34.6 min.

Ethyl 3-Hydroxy-3-(1-naphthyl)propanoate, 13.[14] Following the general procedure described above, **13** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 300:100:4) as a colorless oil (94% yield, 80% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.27 (t, J = 7.1 Hz, 3H), 2.79−2.92 (m, 2H), 3.44 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 5.91 (m, 1H), 7.45−7.53 (m, 3H), 7.69 (d, J = 7.1 Hz, 1H) 7.78 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 8.05 (d, J = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.2, 42.7, 61.0, 67.3, 122.8, 122.9, 125.5, 125.6, 126.2, 128.2, 129.0, 130.0, 133.7, 138.0, 172.7. Ee determination by chiral HPLC analysis on Chiralcel OD using heptanes:*i*-PrOH (90:10); retention times: t_1 (major) = 16.2 min, t_2 (minor) = 21.3 min.

Ethyl 3-Hydroxy-3-(thiophen-2-yl)propanoate, 14.[5a] Following the general procedure described above, **14** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 300:100:4) as a colorless oil (77% yield, 75% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.27 (t, J = 7.2 Hz, 3H), 2.82−2.91 (m, 2H), 3.47 (d, J = 4.2 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 5.37 (m, 1H), 6.95−6.98 (m, 2H), 7.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 43.1, 66.5, 69.1, 123.6, 124.8, 126.7, 146.2, 171.9. Ee determination by chiral HPLC analysis on Chiralcel OD using heptanes:*i*-PrOH (90:10); retention times: t_1 (major) = 11.7 min, t_2 (minor) = 30.3 min.

Ethyl 3-Hydroxy-4-methylpentanoate, 15.[15] Following the general procedure described above, **15** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 500:100:6) as a colorless oil (89% yield, 51% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.92 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.71 (m, 1H), 2.40 (dd, J = 9.5 Hz, 16.3 Hz, 1H), 2.50 (dd, J = 2.8 Hz, 16.3 Hz, 1H), 2.89 (d, J = 3.2 Hz, 1H), 3.78 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 17.7, 18.3, 33.1, 38.4, 60.6, 72.6, 173.4. Ee determination by chiral GC analysis on Lipodex E (25 m × 0.25 mm). Initial temperature 50 °C for 60 min, then 10 °C/min until 70 °C, then 70 °C for 20 min; retention times: t_1 (major) = 69.3 min, t_2 (minor) = 69.9 min.

Ethyl 3-Cyclohexyl-3-hydroxypropanoate, 16.[5c] Following the general procedure described above, **16** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 500:100:6) as a colorless oil (86% yield, 36% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.96−1.31 (m, 5H), 1.27 (t, J = 7.2 Hz, 3H), 1.38 (m, 1H), 1.62−1.71 (m, 2H), 1.71−1.81 (m, 2H), 1.86 (m, 1H), 2.41 (dd, J = 9.5 Hz, 16.3 Hz, 1H), 2.51 (dd, J = 2.9 Hz, 16.3 Hz, 1H), 2.87 (d, J = 3.8 Hz, 1H), 3.78 (m, 1H), 4.17 (q, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 26.0, 26.1, 26.4, 28.2, 28.8, 38.6, 43.0, 60.6, 72.1, 173.5. Ee determination by chiral GC analysis on 6-*O*-TBDMS-2,3-di-*O*-methyl-β-cyclodextrin (5 m × 0.25 mm). Temperature at 60 °C; retention times: t_1 (major) = 150 min, t_2 (minor) = 175 min.

Ethyl 3-Hydroxy-5-phenylpentanoate, 17.[16] Following the general procedure described above, **17** was obtained after purification by flash chromatography (pentane:Et_2O:EtOH = 500:100:6) as a colorless oil (75% yield, 26% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.26 (t, J = 7.2 Hz, 3H), 1.74 (m, 1H), 1.85 (m, 1H), 2.44 (dd, J = 8.6 Hz, 16.6 Hz, 1H), 2.50 (dd, J = 3.5 Hz, 16.5 Hz, 1H), 2.70 (m, 1H), 2.83 (m, 1H), 3.09 (bs, 1H), 4.02 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 7.16−7.20 (m, 3H), 7.25−7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.1, 31.7, 38.1, 41.3, 60.7, 67.1, 125.9, 128.3, 128.4, 141.7, 173.0. Ee determination by chiral HPLC analysis on Chiralcel OD using heptanes:*i*-PrOH (90:10); retention times: t_1 (major) = 12.1 min, t_2 (minor) = 14.2 min.

■ ASSOCIATED CONTENT

Supporting Information. General procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: cw27@georgetown.edu.

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