Supporting Information

Rh(I)–Bisphosphine Catalyzed Asymmetric, Intermolecular Hydroheteroarylation of α-Substituted Acrylate Derivatives

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S1
S1 Materials and Methods

Unless noted, all reactions were performed in flame-dried glassware and carried out under an atmosphere of argon with magnetic stirring. Tetrahydrofuran (THF), diethylether (Et₂O), and dichloromethane (DCM) were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reagent. Anhydrous acetonitrile was purchased in the Sure Seal® from Aldrich Chemical Company. Column chromatography was performed on SiliCycle®SilicaFlash® P60, 40-63 µm 60 Å and in general were performed according to the guidelines reported by Still et al. Thin layer chromatography was performed on SiliCycle® 250 µm 60 Å plates. Preparative thin layer chromatography was performed on SiliCycle® 2000 µm 60 Å plates. Visualization was accomplished with UV light or KMnO₄ stain followed by heating.

¹H NMR spectra were recorded on Varian 300 or 400 MHz spectrometers at ambient temperature unless otherwise stated. Data is reported as follows: chemical shift in parts per million (ppm) from CDCl₃ (7.26 ppm), toluene-d₈ (7.09, 7.0, 6.98, 2.09 ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz). ¹³C NMR was recorded on Varian 300 or 400 MHz spectrometers (at 75 or 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from CDCl₃ (77.2 ppm) or toluene-d₈ (137.86 (1), 129.4 (3), 128.33 (3), 125.49 (3), 20.4 (5) ppm). High-resolution mass spectra (ESI) were obtained by Donald Dick of Colorado State University.

[Rh(cod)Cl]₂ was purchased from Pressure Chemical Company. L1–L11 were purchased from Strem Chemicals. CsOAc was purchased from commercial sources and dried at 60 °C over P₂O₅ under high vacuum overnight. Tert-butyl acrylate, 1a, 1b, 3a–3e and 3i were purchased from commercial sources, distilled off of stabilizers and stored over 3 Å molecular sieves. 3b-d₈ was purchased from Aldrich Chemical Company, distilled off of stabilizers and stored over 3 Å molecular sieves. 5-chlorobenzoxazole (1e) was purchased from AK Scientific. CD₃CN was purchased from Cambridge Isotope Laboratories and stored over 3 Å molecular sieves. 2-amino phenol starting materials for the synthesis of benzoxazoles 1e–1d, 1f and 1h were purchased from AK Scientific. 2-amino-5-methoxyphenol hydrochloride (for the synthesis of 1g) was purchased from Accela Chembio Inc. via Fisher Scientific. Teflon-lined screw caps were purchased from Fisher Scientific (03-340-14F).

[1] Still, W. C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923–2925.
**S2 Synthesis of [Rh(cod)OAc]₂**

[Rh(cod)OAc]₂ was synthesized according to a procedure adapted from Chatt and Venanzi. A flame-dried 100 mL round-bottom flask was charged with [Rh(cod)Cl]₂ (1.04 g, 2.11 mmol, 1 equiv) and KOAc (1.04 g, 10.6 mmol, 5.03 equiv), evaporated and backfilled with argon. Acetone (65 mL, freshly distilled over CaSO₄) was added and the reaction was heated at reflux for 6 h, at which point near complete conversion was observed by TLC (1:1 Hex:EtOAc, Rf [Rh(cod)Cl]₂ = 0.60; Rf [Rh(cod)OAc]₂ = 0.05, spots observed by UV and KMnO₄). An additional 1.03 g (4.98 equiv) KOAc was added, and the reaction was allowed to reflux overnight. At this point, the reaction was filtered through celite and rinsed with HPLC grade dichloromethane until all traces of orange had been washed from the celite. After concentration by rotary evaporation, the orange residue was recrystallized from HPLC grade EtOAc (~15 mL) to give [Rh(cod)OAc]₂ as red orange plates (750 mg, 66% yield). The melting point was collected under air, and product decomposition was observed beginning at 182 °C (reported MP = 197–198 °C). The mother liquor was concentrated to a brown residue which was further recrystallized from HPLC grade EtOAc (~15 mL) to give [Rh(cod)OAc]₂ as red orange plates (750 mg, 66% yield). The melting point was collected under air, and product decomposition was observed beginning at 182 °C (reported MP = 197–198 °C). The mother liquor was concentrated to a brown residue which was further recrystallized from HPLC grade EtOAc to give a second crop of [Rh(cod)OAc]₂ (269 mg, 24%). Rf = 0.05 (1:1 Hex:EtOAc); IR (Thin Film/NaCl) 2998, 2984, 2945, 2867, 2838, 1573 (s), 1412 (s).

**S3 Hydroheteroarylation (HH) of tert-butyl acrylate with azoles using [Rh(cod)OAc]₂ (full text, Chart 1, blue conditions)**

In a glove box, a 1-dram vial was equipped with a magnetic stirring bar and charged with [Rh(cod)OAc]₂ (2.7 mg, 0.005 mmol, 2.0 mol %) and dppe (4.0 mg, 0.010 mmol, 4.0 mol %). To this was added a solution of heterocycle 1 (0.25 mmol, 1.0 equiv), tert-butyl acrylate (0.50 mmol, 2.0 equiv) and 1,3,5-trimethoxybenzene (4.2 mmol, 0.025 mmol, 0.10 equiv) in PhMe (Aldrich 244511, 500 µL). The vial containing the resultant yellow suspension was then sealed with a Teflon-lined screw cap, removed from the glove box and heated to 120 °C in an aluminum heating block. After several minutes at 120 °C, reactions turned a homogeneous orange or dark red (with 1b). After 24 hours, the reactions were cooled to room temperature, concentrated, dissolved in CDCl₃ and analyzed by ¹H NMR spectroscopy (see section S5).

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[2] Chatt, J.; Venanzi, L. M. *J. Chem. Soc.* 1957, 4735–4741.
S4 Hydroheteroarylation (HH) of tert-butyl acrylate with azoles using [Rh(cod)Cl]₂ and CsOAc (full text, Chart 1, red conditions)³

In a glove box, a 1-dram vial was equipped with a magnetic stirring bar and charged with [Rh(cod)Cl]₂ (2.5 mg, 0.005 mmol, 2 mol %), dppe (4 mg, 0.010 mmol, 4 mol %) and CsOAc (12 mg, 0.06 mmol, 25 mol %). To this, was added a solution of heterocycle 1 (0.25 mmol, 1.0 equiv), tert-butyl acrylate (0.50 mmol, 2.0 equiv) and 1,3,5-trimethoxybenzene (4.20 mg, 0.025 mmol, 0.10 equiv) in PhMe (Aldrich 244511, 500 µL). The vial containing the resultant yellow suspension was then sealed with a teflon-lined screw cap, removed from the glove box and heated to 120 °C in an aluminum heating block. After several minutes at 120 °C, the reactions turned a heterogeneous orange or dark red (with 1b). After 24 hours, the reactions were cooled to room temperature, concentrated, dissolved in CDCl₃ and analyzed by ¹H NMR spectroscopy (see section S5). Particularly heterogeneous reactions were filtered through celite into the NMR tube prior to analysis.

S5 Hydroheteroarylation yield determination by ¹H NMR spectroscopy (full text, Chart 1)

For accurate integration, 4 scans were collected, and d₁ was set to 45 seconds to ensure complete relaxation of aryl resonances. All yields were determined relative to the H₃CO-resonance of 1,3,5-trimethoxybenzene at 3.77 ppm.

S6 Characterization data for products 2a–2d (full text, Chart 1)

2a. For characterization, two representative reactions were combined and purified by preparative thin layer chromatography (3:1 Hex:Acetone) to give 2a as a colorless oil. R₉ = 0.50 (3:1 Hex:Acetone); ¹H NMR (300 MHz, CDCl₃) δ 7.62-7.68 (m, 1H), 7.43-7.50 (m, 1H), 7.26-7.31 (m, 2H), 3.20 (t, 2H, J = 7.5 Hz), 2.84 (t, 2H, J = 7.5 Hz), 1.42 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 171.1, 165.9, 150.9, 141.3, 124.7, 124.2, 119.7, 110.4, 81.1, 32.1, 28.1, 24.2; IR (Thin Film/NaCl) 2979, 2933, 1731, 1616, 1574 cm⁻¹; LRMS (EI) m/z [C₁₄H₁₇NO₃] [(M⁺)⁺] calcd 247, found 247.

2b. Characterization data for 2b match that reported in the literature.³

2c. Flash column chromatography on silica gel (10:1 Hex:EtOAc) gave 2c as a colorless oil (87%). R₉ = 0.26 (10:1 Hex:EtOAc); ¹H NMR (400 MHz, CDCl₃) δ

[3] Ryu, J.; Cho, S. H.; Chang, S. Angew. Chem. Int. Ed. 2012, 51, 3677–3681.
7.29 (d, 1H, J = 8.0 Hz), 7.17 (t, 1H, J = 8.0 Hz), 7.09 (d, 1H, J = 7.2 Hz), 3.21 (t, 2H, J = 7.4 Hz), 2.83 (t, 2H, J = 7.4 Hz), 2.58 (s, 3H), 1.45 (s, 9H); 13C NMR (100 MHz, CDCl₃) δ 171.2, 165.0, 150.7, 140.6, 130.1, 124.8, 124.3, 107.7, 81.1, 32.4, 28.2, 24.4, 16.6; IR (Thin Film/NaCl) 2978, 1731, 1150 cm⁻¹; LRMS (EI) m/z [C₁₃H₁₉NO₃]⁺ ([M⁺]) calcd 261, found 261.

2d. For characterization, two representative reactions were combined and purified by preparative thin layer chromatography (2% EtOAc in DCM) to give 3d as a colorless oil. This was found to be the best purification method on small scale as the product is difficult to separate from residual starting material. Rₜ = 0.35 (98:2 DCM:EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, 1H, J = 7.6 Hz), 7.18 (t, 1H, J = 7.6 Hz), 7.08 (d, 1H, J = 7.6 Hz), 3.21 (t, 2H, J = 7.6 Hz), 2.85 (t, 2H, J = 7.6 Hz), 2.50 (s, 3H), 1.44 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 171.2, 165.6, 150.2, 141.0, 125.7, 124.2, 121.0, 117.0, 81.1, 32.2, 28.2, 24.3, 15.3; IR (ATR) 2978, 2929, 1729, 1612, 1574, 1141 cm⁻¹; LRMS (ESI+APCI) m/z [C₁₅H₂₀NO₃]⁺ ([M+H⁺]) calcd 262.0, found 262.1.

S7 Synthesis of 1b-D (full text, eq. 10 and Figure 3)

1b-D. To a solution of benzothiazole (1b) (250 mg, 1.85 mmol, 1.0 equiv) in THF (15 mL) at -78 °C was added tert-butyllithium (2.0 mL, 1.4 M in pentane, 2.8 mmol, 1.5 equiv) via syringe pump over 1 hour. An instantaneous color change from clear to yellow was observed. The reaction mixture was stirred for an additional 30 minutes at -78 °C, and then MeOH-d₄ (1.5 mL) was added dropwise at -78 °C. The reaction mixture was adsorbed onto silica gel and purified by flash column chromatography (7:1 Hex:EtOAc) to give 42 mg (0.31 mmol, 16%) 1b-D as a light yellow oil: Rₜ = 0.22 (5:1 Hex:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 8.13-8.16 (m, 1H), 7.95-7.98 (m, 1H), 7.42-7.55 (m, 2H) (Less than 1% ¹H observed at δ 9.00) (Figure S1); ²H NMR (300 MHz, PhMe-d₈) δ 8.23 (s) (see full text, Figure 3). Note: the azole C–H resonance appears at δ = 9.00 ppm in CDCl₃ and at δ = 8.23 ppm in PhMe-d₈.

Figure S1 ¹H NMR of 1b-D (top) and 1b (bottom) in CDCl₃

S5
S8 C–H reversibility experiment between 1c and 1b-D (full text, eq. 10 and Figure 3)

**S8.1 Reaction set-up**

[Rh(cod)OAc]₂ (3.2 mg, 0.006 mmol, 4.0 mol %) and dppe (4.8 mg, 0.012 mmol, 8.0 mol %) were weighed into a J. Young tube in the glove box. To this was added a solution of 1c (20 mg, 0.15 mmol, 1.0 equiv) and tert-butyl acrylate (88 µL, 0.60 mmol, 4.0 equiv) in 480 µL PhMe and 120 µL of a solution of 1b-D (42 mg, 0.31 mmol) and 1,3,5-trimethoxybenzene (8.2 mg, 0.05 mmol) in 200 µL PhMe. The J. Young tube was sealed and removed from the box. ¹H NMR analysis (300 MHz) of the reaction mixture prior to heating showed no ¹H resonance at δ = 8.36 ppm, and ²H NMR showed a corresponding single ²H resonance at δ = 8.23 ppm. The NMR tube was suspended in a 120 °C oil bath, and the reaction was removed periodically for ¹H and ²H NMR analysis (300 MHz). Crossover peaks for 1b-H and 1c-D began to populate the ¹H and ²H spectra over time (see full text, Figure 3).

**S8.2 Determination of percent conversion of 1b-D**

Percent conversion of 1b-D was approximated by comparing the integration values in the ¹H NMR for the aromatic resonance of starting material 1b-D at δ = 8.00 (J = 8.1 Hz) with the corresponding aromatic resonance of product 2b at δ = 7.87 (J = 8.7 Hz) (Figure S2).

![Figure S2](image)

**Figure S2** ¹H NMR of eq. 10 (full text) after 130 h at 120 °C. Percent conversion of 1b-D was determined by comparison of integration values for starting material 1b-D at δ = 8.00 (J = 8.1 Hz) with the corresponding aromatic resonance of product 2b at δ = 7.87 (J = 8.7 Hz)

**S8.3 Determination of percent ²H incorporation in products 2b and 2c**

The crude reaction mixture from the reversibility experiment was concentrated, dissolved in dichloromethane and pipetted onto a preparative TLC. Preparative TLC (2 x 13:1 Hex:Acetone) allowed fairly clean separation of 2b (contaminated with 1b) and 2c (contaminated with some 2b). ²H incorporation was determined by ¹H NMR analysis of fairly pure 2b and 2c (Figure S3 and S4).
**S9 General procedure for the synthesis of benzoxazoles 1c–1d and 1f–1h**

Benzoxazoles 1c–1d and 1f–1h were prepared from the corresponding 2-amino phenols according to a modified known procedure.\(^4\) To a flame-dried, round-bottom flask equipped with reflux condenser was charged the appropriate 2-amino phenol derivative (1.0 equiv) and trimethyl orthoformate (Aldrich 108456, 12 equiv). The dark red reaction mixture was heated to 110 °C overnight. After cooling to room temperature, trimethylorthoformate was removed by rotary evaporation, and the crude residue was purified by column chromatography, distillation or a combination of both.

\(^4\) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 9127–9130.
S10 Characterization data for benzoxazoles 1c–1d and 1f–1h

1c.\(^{[4–5]}\) Flash column chromatography on silica gel (2 x 7:1 Hex:EtOAc) followed by repeated (2x) kugelrohr distillation under reduced pressure yielded a colorless liquid (55%). \(R_f = 0.24\) (10:1 Hex:EtOAc); IR (thin film/NaCl) 3062, 3105, 3063, 3032, 2924, 1623, 1519, 1242, 1071 cm\(^{-1}\); LRMS (EI) \(m/z [C_8H_7NO]^+\) ([M]+) calcd 133, found 133. \(^1\)H and \(^{13}\)C NMR spectra match those reported in the literature.\(^{[4–5]}\) Full characterization data available in Ref. 5a.

1d. Kugelrohr distillation followed by flash column chromatography on silica gel (8:1 Hex:EtOAc) provided 1d as a white solid (61%). \(R_f = 0.22\) (10:1 hexanes:EtOAc); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 8.08\) (s, 1H), 7.61 (d, 1H, \(J = 8.0\) Hz), 7.27 (t, 1H, \(J = 7.6\) Hz), 7.18 (d, 1H, \(J = 7.2\) Hz), 2.55 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 152.4, 149.4, 139.7, 126.6, 124.6, 121.7, 118.0, 15.3\); IR (ATR) 3065, 2922, 1511, 1489 cm\(^{-1}\); LRMS (ESI+APCI) \(m/z [C_8H_8NO]^+\) ([M+H]+) calcd 134.1, found 134.0.

1f.\(^{[5a]}\) Flash column chromatography on silica gel (4:1 \(\rightarrow\) 3:1 Hex:EtOAc) followed by kugelrohr distillation yielded a white solid (17%) Note: this compound is quite volatile, and a good portion was lost while drying under high vacuum after the chromatography step. \(R_f = 0.31\) (3:1 Hex:EtOAc); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta -114.7\) (m). All other characterization data (\(^1\)H NMR, \(^{13}\)C NMR, IR and MS) match those reported in the literature.\(^{[5a]}\)

1g.\(^{[5a,5c]}\) Prepared with 2-amino-5-methoxyphenol hydrochloride according to the general procedure but with additional 1.1 equiv NEt\(_3\) to liberate the HCl salt. Flash column chromatography on silica gel (2:1 \(\rightarrow\) 1:1 Hex:EtOAc) yielded a white solid (90%). Full characterization data available in Ref. 5a.

1h.\(^{[5]}\) Flash column chromatography on silica gel (3:1 Hex:EtOAc) followed by kugelrohr distillation under reduced pressure yielded a white solid (35%). \(R_f = 0.25\) (3:1 Hex:EtOAc); IR (ATR) 3123, 3013, 2977, 2944, 2888, 2835, 1612, 1515 cm\(^{-1}\); LRMS (ESI + APCI) \(m/z [C_8H_8NO_2]^+\) ([M+H]+) calcd 150.1, found 150.1; \(^1\)H NMR and \(^{13}\)C NMR spectra match those reported in the literature.\(^{[5]}\) Full characterization data available in Ref. 5a.

\(^{[5]}\) (a) Lee, J. J.; Kim, J.; Jun, Y. M.; Lee, B. M.; Kim, B. H. *Tetrahedron* 2009, 65, 8821–8831.
(b) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* 2011, 13, 522–525.
(c) Wertz, S.; Kodama, S.; Studer, A. *Angew. Chem. Int. Ed.* 2011, 50, 11511–11515.
S11 Preparation of α-substituted acrylates 3g, 3h and 3j

3a-e and 3i were purchased from commercial sources, and 3f was prepared according to a known procedure.\(^6\) Full characterization data for 3f is found in Ref. 6b.

3g was prepared according to the two-step sequence below:

\[ \text{S1} \xrightarrow{1) \text{NaOEt, EtOH, 23 °C}} \text{S3} \xrightarrow{2) \text{Me}_2\text{Br, 23 °C → reflux ref. 7}} \text{3g} \]

S3 was prepared according to a procedure described by Gani et al.\(^7\) To a solution of NaOEt (126.5 mmol, 1.1 equiv, prepared by addition of Na(0) to EtOH) in EtOH (45 mL) was added ethyl acetoacetate (S1) (15.0 g, 115 mmol, 1.0 equiv) over about 1 minute. To the resultant yellow solution was then slowly added butyl bromide (S2) (16.0 mL, 149.5 mmol, 1.3 equiv, washed with NaHCO\textsubscript{3} and distilled before use). The reaction was heated to reflux for 24h at which point it was cooled and partitioned between Et\textsubscript{2}O and water in a separatory funnel. The aqueous layer was extracted with Et\textsubscript{2}O two times more, and the combined organic extracts were washed with brine and dried (MgSO\textsubscript{4}). Distillation under reduced pressure yielded 9.19g (43%) of crude product (contaminated with about 10% dialkylated product), which was taken to the next step without further purification.

3g was prepared from S3 according to a procedure modified from one described by Gellman et al:\(^6a\) To a solution of LiHMDS (7.43 g, 44.4 mmol, 1.1 equiv) in THF (250 mL) at -78 °C was added a solution of S3 (7.53 g, 40.4 mmol, 1.0 equiv) in THF (45 mL) via addition funnel. The reaction was stirred for an additional 75 minutes at -78 °C, and then paraformaldehyde (5.70 g, excess) was added in one portion. The ice bath was removed, and the reaction was allowed to stir at room temperature for an additional 4 h. At this point, the reaction was filtered through celite to remove excess paraformaldehyde and concentrated by rotary evaporation. The crude reaction mixture was purified by flash column chromatography on silica gel (30:1 → 10:1 Hex:EtOAc), and the purest fractions were combined to give 3g as a clear liquid (2.41 g, 15.4 mmol, 12% over 2 steps): \( R_f = 0.20 \) (40:1 Hex:EtOAc); \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 6.11 (m, 1H), 5.49 (m, 1H), 4.19 (q, 2H, \( J = \)

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\[ \text{ref. 6} \]

\[ \text{ref. 6a} \]

\[ \text{ref. 7} \]

\[ \text{Lee, H.; Park, J.; Kim, B. M.; Gellman, S. H. J. Org. Chem. 2003, 68, 1575–1578.} \]

\[ \text{Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. Angew. Chem. Int. Ed. 2011, 50, 8412–8415.} \]

\[ \text{Akhtar, M.; Botting, N. P.; Cohen, M. A.; Gani, D. Tetrahedron 1987, 43, 5899–5908.} \]
7.2 Hz), 2.29 (m, 2H), 1.40–1.48 (m, 2H), 1.29–1.37 (m, 2H), 1.29 (t, 3H, J = 7.2 Hz), 0.90 (t, 3H, J = 7.2 Hz); 13C NMR (100 MHz, CDCl3) δ 167.5, 141.2, 124.2, 60.6, 31.7, 30.7, 22.4, 14.3, 14.0; IR (ATR) 2958, 2931, 2873, 1716, 1631, 1153 cm⁻¹; LRMS (EI) m/z [C₉H₁₆O₂]⁺ ([M]+) calcd 156, found 156.

3h was prepared according to the two-step procedure of Gellman et al.:[6a]

![Diagram of the two-step procedure](image)

**S5.** To a solution of KOrBu (3.53 g, 31.4 mmol, 1.05 equiv) in THF (80 mL) at 0 °C was added ethyl acetoacetate (S1) (3.93 g, 30.2 mmol, 1.01 equiv) slowly. HOtBu (287 µL, 3.0 mmol, 0.10 equiv) was then added, and the reaction mixture was allowed to stir 30 minutes at 0 °C. Iodide S4 (5.52 g, 30.0 mmol, 1.0 equiv, distilled before use) was added in one portion, and the ice bath was removed. The reaction was heated to reflux for 24 h and then cooled to room temperature. After removal of THF by rotary evaporator, the reaction mixture was partitioned between Et₂O and saturated NaHCO₃. The aqueous layer was extracted with Et₂O two times more, and the combined organic layers were washed with brine and dried (MgSO₄). Flash column chromatography on silica gel (8% EtOAc in Hex) yielded 3.18 g of crude product, which was taken to the next step without further purification.

**3h.** To a solution of S5 (3.18 g, 17.1 mmol, 1.0 equiv) in THF (110 mL) at -78 °C was added a solution of LiHMDS (3.15 g, 18.7 mmol, 1.1 equiv) in THF (20 mL). The reaction mixture was allowed to stir for 30 minutes at -78 °C, and then paraformaldehyde (2.40 g, excess) was added as a solid in one portion. The ice bath was removed, and the reaction was allowed to stir at room temperature overnight. At this point, the reaction was filtered through celite to remove excess paraformaldehyde and concentrated by rotary evaporation. The crude reaction mixture was purified by flash column chromatography on silica gel (Hex → 2% → 4% → 8% → 15% EtOAc in Hex) to give 3h as a clear liquid (1.76 g, 11.3 mmol, 37% over two steps): Rf = 0.32 (4% EtOAc in Hex); ¹H NMR (400 MHz, CDCl₃) δ 6.15 (d, 1H, J = 1.6 Hz), 5.47 (m, 1H), 4.19 (q, 2H, J = 7.2 Hz), 2.18 (dd, 1H, J = 7.2, 1.2 Hz), 1.79 (m, 1H), 1.30 (t, 3H, J = 7.2 Hz), 0.89 (d, 6H, J = 6.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 167.7, 140.1, 125.6, 60.7, 41.5, 27.4, 22.4, 14.4; IR (ATR) 2957, 2934, 2870, 1715, 1630 cm⁻¹; LRMS (EI) m/z [C₉H₁₆O₂]⁺ ([M]+) calcd 156, found 156.
**3j** was prepared according to the two-step procedure of Gellman et al.:\(^6a\)

[Schematics and chemical structures][1]

To a solution of KO\(_2\)tBu (3.70 g, 33.0 mmol, 1.10 equiv) in THF (80 mL) at 0 °C was added ethyl acetoacetate (S1) (3.88 g, 29.8 mmol, 1.01 equiv) slowly. HO\(_2\)tBu (287 µL, 3.0 mmol, 0.10 equiv) was then added, and the reaction mixture was allowed to stir 30 minutes at 0 °C. Bromide S6 (7.50 g, 29.6 mmol, 1.0 equiv, prepared from 3-bromo-1-propanol according to a known procedure)\(^8\) was added in one portion, and the ice bath was removed. The reaction was heated to reflux for 36 h and then cooled to room temperature. After removal of THF by rotary evaporator, the reaction mixture was partitioned between Et\(_2\)O and H\(_2\)O. The aqueous layer was extracted with Et\(_2\)O two times more, and the combined organic layers were washed with brine and dried (MgSO\(_4\)). Flash column chromatography on silica gel (Hex \(\rightarrow\) 5% \(\rightarrow\) 8% \(\rightarrow\) 10% \(\rightarrow\) 15% EtOAc in Hex) yielded 4.89 g of crude product, which was taken to the next step without further purification.

**3j**. To a solution of S7 (4.89 g, 16.2 mmol, 1.0 equiv) in THF (110 mL) at -78 °C was added a solution of LiHMDS (2.97 g, 17.8 mmol, 1.1 equiv) in THF (20 mL). The reaction mixture was allowed to stir for 30 minutes at -78 °C, and then paraformaldehyde (2.30 g, excess) was added as a solid in one portion. The ice bath was removed, and the reaction was allowed to stir at room temperature overnight. At this point, the reaction was filtered through celite to remove excess paraformaldehyde and concentrated by rotary evaporation. The crude reaction mixture was purified by flash column chromatography on silica gel (Hex \(\rightarrow\) 2% \(\rightarrow\) 4% \(\rightarrow\) 6% \(\rightarrow\) 10% EtOAc in Hex) to yield **3j** as a clear liquid (3.59 g, 44% over two steps). Characterization data for **3j** match that reported in the literature.\(^9\)

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\(^{[8]}\) Trapella, C.; Fischetti, C.; Pela, M.; Lazzari, I.; Guerrini, R.; Calo, G.; Rizzi, A.; Camarda, V.; Lambert, D. G.; McDonald, J.; Regoli, D.; Salvadori, S. Bioorg. Med. Chem. 2009, 17, 5080–5095.

\(^{[9]}\) Wang, X.; Buchwald, S. L. J. Am. Chem. Soc. 2011, 133, 19080–19083.
**S12 Initial optimization of the asymmetric HH reaction of 4-methyl benzoxazole (1c) and ethyl methacrylate (3a) (full text, Table 1)**

**S12.1 Reaction set-up**

In a glove box, a 1 dram vial equipped with magnetic stirring bar was charged [Rh(cod)OAc]₂ (1.4 mg, 2.6 µmol, 2 mol %) and ligand (5.2 µmol, 4 mol %). To this was added a solution of 4-methylbenzoxazole (1c) (16.6 mg, 14.7 µL, 0.125 mmol, 1 equiv) and 4,4'-di-tert-butylbiphenyl (3.3 mg, 12.5 µmol, 0.10 equiv) in 250 µL of the appropriate solvent. Ethyl methacrylate (3a) (62 µL, 4 equiv up to 124 µL, 8.0 equiv) was then added, and the vial was sealed with a Teflon-lined screw cap. At this point, the vial was removed from the glove box and placed in an aluminum block set to the indicated temperature. After the reaction was heated for the indicated amount of time, it was cooled to room temperature. A 15 µL aliquot of the crude reaction mixture was removed and diluted with 500 µL 1:1 Hex:iPrOH. Note: in the case that solid precipitated at this point—acylate polymerized under some conditions listed in Table 1—the sample was filtered prior to analysis. Percent yield and percent ee of 4ca was determined with respect to 4,4'-di-tert-butylbiphenyl by LC analysis on a chiral stationary phase as described below.

**S12.2 Analysis of the HH reaction of 4-methylbenzoxazole (1c) and ethyl methacrylate (3a) by chiral HPLC**

**HPLC Method:** 4,4'-di-tert-butylibiphenyl (DTBB), ethyl methacrylate (3a), 4-methylbenzoxazole (1c) and both enantiomers of product 4ca are separated by the following method: Chiracel IB column, 94:6 Hex:10% iPrOH in Hex, 1 mL/min. Note: See section S19 (page S51) for HPLC traces of racemic and enantioenriched 4ca.

DTBB: 3.5 min

Ethyl methacrylate (3a): 3.9 min (3a has a very low absorbance)

4-methylbenzoxazole (1c): 6.0 min

First enantiomer 4ca: 7.3 min

Second enantiomer 4ca: 8.1 min

**Response factor calculation for 4ca:** Using stock solutions of appropriate concentrations of 4,4'-di-tert-butylibiphenyl (DTBB) and racemic 4ca, each of five HPLC vials was charged with DTBB (2.0 mg, 7.5 µmol), increasing amounts of racemic 4ca (to mimic 5, 10, 20, 40 and 80 percent yield 4ca assuming 20 percent loading of DTBB) and enough 1:1 Hex:iPrOH to make a total volume of 1000 µL:

**Vial 1:** 0.46 mg, 1.87 µmol 4ca

**Vial 2:** 0.93 mg, 3.75 µmol 4ca

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Vial 3: 1.86 mg, 7.51 µmol 4ca
Vial 4: 3.71 mg, 15.0 µmol 4ca
Vial 5: 7.43 mg, 30.0 µmol 4ca

Each of these five samples was analyzed by chiral HPLC according to the method above. The areas of both enantiomers of 4ca were summed together to give the total area of product 4ca. The ratio (Area 4ca:Area DTBB) (Y-axis) was plotted against the ratio [4ca]:[DTBB] (X-axis) for various wavelengths (DAD A–D) to give a response factor curve (Figure S5). The response factor curve was found to be highly linear for all wavelengths in the region analyzed, and the slope of each line gave the response factor, $R_f$ 4ca for a given wavelength (Figure S5):

- $R_f$ 4ca DAD A (254 nm): 0.17
- $R_f$ 4ca DAD B (254 nm): 0.20
- $R_f$ 4ca DAD C (210 nm): 0.69
- $R_f$ 4ca DAD D (230 nm): 1.18

**Percent yield 4ca:** Yields of 4ca were either reported as averages from those determined at each of these four wavelengths or from the wavelength that provided the cleanest spectrum.

**Percent ee 4ca:** Percent ee of 4ca was determined simply by subtraction of the areas of 4ca enantiomers.

![Response Factor Calculation for 4ca](image)

**Figure S5** Response factor curves for 4ca at various wavelengths
S13 General procedure for second generation optimization of the asymmetric HH reaction of 4-methyl benzoxazole (1c) and ethyl methacrylate (3a) (full text, Table 2)

In a glove box, a 1.5 dram vial equipped with magnetic stirring bar was charged [Rh(cod)OAc]₂ (6.8 mg, 12.6 µmol, 5 mol %) and ligand (25.2 µmol, 10 mol %). To this was added a solution of 4-methylbenzoxazole (1c) (33.3 mg, 29.5 µL, 0.25 mmol, 1.0 equiv), 4,4'-di-tert-butylbiphenyl (6.6 mg, 25.0 µmol, 0.10 equiv) and ethyl methacrylate (3a) (228 mg, 250 µL, 2.0 mmol, 8.0 equiv) in CH₃CN (500 µL). The vial was sealed with a Teflon-lined screw cap and removed from the glove box. The reaction was heated at 100 °C in an aluminum block for 24 h. After cooling to room temperature, a 15 µL aliquot of the crude reaction mixture was removed and diluted with 500 µL 1:1 Hex:iPrOH. Percent yield and percent ee were determined as described above for the initial reaction optimization (section S12.2).

Note: It was found that small changes in [Rh(cod)OAc]₂ to ligand ratio can influence the rate of formation of 4ca rather dramatically. For acceptable reproducibility, it was necessary to double the scale from 0.125 mmol 1c (initial reaction optimization, section S12.1) to 0.25 mmol 1c.

S14 General procedure for the asymmetric HH of methacrylate derivatives 3 with benzoxazoles 1 (full text, Chart 2)

In a glove box, a 1.5 dram vial equipped with magnetic stirring bar was charged [Rh(cod)OAc]₂ (6.8 mg, 12.6 µmol, 0.05 equiv), CTH-(R)-xylyl-P-Phos (18.9 mg, 25.2 µmol, 0.10 equiv) and CsOAc (12.0 mg, 62.5 µmol, 0.025 equiv) where applicable. To this was added a solution of benzoxazole 1 (0.25 mmol, 1.0 equiv), 4,4'-di-tert-butylbiphenyl (6.6 mg, 25.0 µmol, 0.10 equiv) and acrylate derivative (3a) (2.0 mmol, 8.0 equiv) in CH₃CN (500 µL). The vial was sealed with a Teflon-lined screw cap and removed from the glove box. The reaction was heated at 100 °C in an aluminum block for 48 h unless otherwise indicated. After cooling to room temperature, the reaction mixture was either concentrated directly (without CsOAc) or filtered through celite prior to concentration (with CsOAc). Crude reaction mixtures were analyzed by ¹H NMR spectroscopy if desired. Crude reaction mixtures were then adsorbed onto silica and purified by flash column chromatography on silica gel to give the corresponding products 4.

Note 1: Racemic products were prepared in the same fashion but with 9.8 mg (12.6 µmol, 0.05 equiv) CTH-(R)-xylyl-P-Phos and 9.8 mg (12.6 µmol, 0.05 equiv) CTH-(S)-xylyl-P-Phos.
Note 2: Whereas most reactions were performed by placing the 1.5 dram vial in the bottom of the aluminum block, it was found that slight improvements in ee for epimerizable or lower ee products (4cc–4cd, 4aa and 4ea–4ha) could be achieved by filling the aluminum well with sand to such a level that the reaction solvent reached the top of the aluminum well.

S15 Comparison of reaction efficiency in presence or absence of CsOAc (full text, Chart 2, 4cf and 4aa)

Because subtle changes in rhodium to ligand ratio is known to influence reaction efficiency (vide supra), comparison of reactions with and without CsOAc were performed with the same stock solution of [Rh(cod)OAc]₂, CTH-(R)-xylyl-P-Phos, DTBB, benzoxazole 1 and acrylate 3. For instance, for the comparison of the reaction of benzoxazole (1a) and (3a), the following procedure was used:

15.5 mg (0.05 equiv) [Rh(cod)OAc]₂, 43.5 mg (0.10 equiv) CTH-(R)-xylyl-P-Phos, 68 mg (58 µL, 1.0 equiv) 1a, 15.4 mg (0.10 equiv) DTBB, 526 mg (574 µL, 8.0 equiv) 3a were dissolved in 1150 µL CH₃CN. 807 µL of the resultant solution was added to either an empty 1.5 dram vial or a 1.5 dram vial containing 12.0 mg (62.5 µmol, 0.25 equiv) CsOAc. Both vials were sealed with a Teflon-lined screw cap, removed from the box and heated to 100 °C in an aluminum block for 48 h. A 15 µL aliquot was removed from each reaction and subjected to chiral HPLC analysis (Chiracel IC column, 80:20 Hex:iPrOH, 1.0 mL/min, see characterization data for 4aa in section S16 and HPLC data for 4aa in section S19) to determine percent ee of 4aa. The reaction without CsOAc was then concentrated directly, whereas the reaction with CsOAc was filtered through celite prior to concentration. Percent yield of 4aa was determined with respect to DTBB by ¹H NMR analysis of the crude reaction mixture.

S16 Characterization data for products 4

4ca. Flash column chromatography on silica gel (7:1 Hex:EtOAc) yielded a colorless oil (88%). Rₚ = 0.20 (7:1 Hex:EtOAc); HPLC analysis – Chiracel IB column, 94:6 Hex:10% iPrOH in Hex, 1.0 mL/min, major enantiomer: 8.1 min, minor enantiomer: 7.3 min, 94% ee; [α]D₂⁵ = +13.7° (c = 0.995 g/100 mL, EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, 1H, J = 8.0 Hz), 7.15 (m, 1H), 7.07 (d, 1H, J = 7.6 Hz), 4.08-4.20 (m, 2H), 3.32 (dd, 1H, J = 15.2, 6.8 Hz), 3.12 (m, 1H), 3.01 (dd, 1H, J = 15.2, 7.2 Hz), 2.56 (s, 3H), 1.28 (d, 3H, J = 7.2 Hz), 1.20 (t, 3H, J = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 175.0, 164.2, 150.7, 140.6, 130.2, 124.8, 124.4, 107.8, 60.9, 37.9, 32.4, 17.2, 16.6, 14.2; IR (ATR) 2979, 2937, 1732, 1610 cm⁻¹; LRMS (ESI + APCI) m/z [C₁₄H₁₈NO₃]⁺ ([M+H]⁺) calcd 248.1, found 248.1.
**4cb.** Flash column chromatography on silica gel (7:1 → 5:1 Hex:EtOAc) yielded a colorless oil (68%). $R_f = 0.17$ (7:2 Hex$_2$O); HPLC analysis – Chiracel IB column, 94:6 Hex:10% iPrOH in Hex, 1.0 mL/min, major enantiomer: 9.5 min, minor enantiomer: 8.6 min, 94% ee; [α]$_D^{25}$ = +12.4° (c = 1.835 g/100 mL, CDCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29 (d, 1H, $J = 8.0$ Hz), 7.18 (m, 1H), 7.09 (d, 1H, $J = 7.6$ Hz), 3.71 (s, 3H), 3.35 (dd, 1H, $J = 15.2$, 6.8 Hz), 3.17 (m, 1H), 3.04 (dd, 1H, $J = 15.2$, 7.6 Hz), 2.59 (s, 3H), 1.31 (d, 3H, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 175.5, 164.1, 150.7, 140.6, 130.2, 124.9, 124.4, 107.8, 52.2, 37.8, 32.4, 17.2, 16.6; IR (ATR) 2976, 2952, 2923, 1736, 1625 cm$^{-1}$; LRMS (ESI + APCI) m/z [C$_{13}$H$_{16}$NO$_3$]$^+$ ([M+H]$^+$) calecd 234.1, found 234.1.

**4cc.** Flash column chromatography on silica gel (4:1 → 3:1 Hex:Et$_2$O) yielded a colorless oil (98%). $R_f = 0.22$ (4:1 Hex$_2$O); HPLC analysis – Chiracel IB column, 90:10 Hex:iPrOH, 1.0 mL/min, major enantiomer: 5.3 min, minor enantiomer: 4.9 min, 92% ee; [α]$_D^{25}$ = +6.2° (c = 3.560 g/100 mL, CDCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.26–7.30 (m, 6H), 7.18 (t, 1H, $J = 7.6$ Hz), 7.09 (d, 1H, $J = 7.6$ Hz), 5.15 (s, 2H), 3.37 (dd, 1H, $J = 15.6$, 7.2 Hz), 3.23 (m, 1H), 3.06 (dd, 1H, $J = 15.6$, 7.2 Hz), 2.58 (s, 3H), 1.34 (d, 3H, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.8, 164.0, 150.7, 140.6, 135.9, 130.2, 128.6, 128.3, 128.2, 124.9, 124.4, 107.8, 66.7, 37.9, 32.4, 17.2, 16.6; IR (ATR) 3063, 3033, 2975, 2938, 1734 cm$^{-1}$; LRMS (ESI + APCI) m/z [C$_{19}$H$_{20}$NO$_3$]$^+$ ([M+H]$^+$) calecd 310.1, found 310.2.

**4cd.** Flash column chromatography on silica gel (1:1 Hex:Et$_2$O) yielded a colorless oil (54%). $R_f = 0.20$ (3:1 Hex:EtOAc); HPLC analysis – Chiracel IB column, 98:2 Hex:iPrOH, 1.0 mL/min, major enantiomer: 13.4 min, minor enantiomer: 12.3 min, 84% ee; [α]$_D^{25}$ = +29.7° (c = 1.105 g/100 mL, CDCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.33 (d, 1H, $J = 8.0$ Hz), 7.23 (m, 1H), 7.13 (d, 1H, $J = 7.2$ Hz), 3.32–3.40 (m, 2H), 3.13–3.20 (m, 1H), 2.60 (s, 3H), 1.48 (d, 3H, $J = 6.8$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 161.4, 150.8, 140.4, 130.7, 125.2, 125.0, 121.6, 108.0, 33.2, 23.9, 18.0, 16.6; IR (ATR) 3062, 3033, 2984, 2942, 2244, 1610 cm$^{-1}$; LRMS (ESI + APCI) m/z [C$_{12}$H$_{13}$N$_2$O]$^+$ ([M+H]$^+$) calecd 201.1, found 201.1.

**4ce.** Flash column chromatography on silica gel (2 x 5:1 pentane:Et$_2$O) yielded a light yellow oil (15%). *Note: $^1$H NMR with respect to DTBB shows that 4ce is formed in 41% yield, but it is difficult to separate from starting material 1c*. $R_f = 0.17$ (5:1 pentane:Et$_2$O); HPLC analysis – Chiracel IC column, 90:10 Hex:iPrOH, 0.7 mL/min, 1$^{st}$ enantiomer: 7.8 min, 2$^{nd}$...
enantiomer: 8.3 min, < 5 % ee; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.29 (d, 1H, \(J = 8.1\) Hz), 7.17 (m, 1H), 7.08 (d, 1H, \(J = 7.5\) Hz), 4.14 (q, 2H, \(J = 7.2\) Hz), 3.65 (m, 1H), 3.03 (dd, 1H, \(J = 16.2, 6.9\) Hz), 2.68 (dd, 1H, \(J = 16.2, 7.5\) Hz), 2.59 (s, 3H), 1.48 (d, 3H, \(J = 6.9\) Hz), 1.22 (t, 3H, \(J = 7.2\) Hz), \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.6, 168.2, 150.6, 140.6, 130.3, 124.8, 124.3, 107.8, 60.8, 39.2, 31.0, 18.6, 16.6, 14.3; IR (ATR) 2979, 2935, 1734, 1625, 1608 cm\(^{-1}\); LRMS (ESI + APCI) \(m/z\) [C\(_{14}\)H\(_{18}\)NO\(_3\)]\(^+\) ([M+H]\(^+\)] calcld 248.1, found 248.1.

\[4\text{cf.}\] Flash column chromatography on silica gel (16:3 \(\rightarrow\) 4:1 \(\rightarrow\) 2:1 Hex:Et\(_2\)O) yielded a light golden oil (65%). \(R_f = 0.18\) (16:3 Hex:Et\(_2\)O); HPLC analysis – Chiracel IB column, 94:6 Hex:iPrOH in Hex, 1.0 mL/min, major enantiomer: 13.8 min, minor enantiomer: 17.1 min, 93% ee; \([\alpha]_D^{25} = -2.89^\circ\) (c = 2.395 g/100 mL, CDCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.26-7.30 (m, 3H), 7.15-7.22 (m, 4H), 7.08 (d, 1H, \(J = 7.2\) Hz), 3.64 (s, 3H), 3.36-3.45 (m, 1H), 3.24-3.31 (m, 1H), 3.06-3.15 (m, 2H), 2.93 (dd, 1H, \(J = 13.6, 7.2\) Hz), 2.56 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 174.4, 163.9, 150.7, 140.6, 138.2, 130.3, 129.2, 128.7, 126.8, 124.9, 124.4, 107.8, 52.1, 45.1, 38.1, 30.3, 16.6; IR (ATR) 3062, 3028, 2950, 2923, 2856, 1736, 1624 cm\(^{-1}\); LRMS (ESI + APCI) \(m/z\) [C\(_{19}\)H\(_{20}\)NO\(_3\)]\(^+\) ([M+H]\(^+\)] calcld 310.1, found 310.1.

\[4\text{cg.}\] Flash column chromatography on silica gel (10:1 Hex:EtOAc) yielded a colorless oil (93%). \(R_f = 0.22\) (DCM); HPLC analysis – Chiracel IC column, 98:2 Hex:iPrOH, 1.0 mL/min, major enantiomer: 9.9 min, minor enantiomer: 8.9 min, 95% ee; \([\alpha]_D^{25} = +4.4^\circ\) (c = 2.595 g/100 mL, CDCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.28 (d, 1H, \(J = 8.0\) Hz), 7.17 (m, 1H), 7.08 (d, 1H, \(J = 7.6\) Hz), 4.09-4.21 (m, 2H), 3.24-3.31 (m, 1H), 3.00-3.10 (m, 2H), 2.58 (s, 3H), 1.71-1.77 (m, 1H), 1.59-1.64 (m, 1H), 1.28-1.35 (m, 4H), 1.20 (t, 3H, \(J = 7.2\) Hz), 0.86-0.90 (m, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 174.5, 164.1, 150.5, 140.4, 130.0, 124.7, 124.2, 107.6, 60.6, 43.3, 31.8, 30.9, 29.0, 22.4, 16.4, 14.1, 13.8; IR (ATR) 2957, 2931, 2861, 1732 cm\(^{-1}\); LRMS (ESI + APCI) \(m/z\) [C\(_{17}\)H\(_{24}\)NO\(_3\)]\(^+\) ([M+H]\(^+\)] calcld 290.2, found 290.1.

\[10\] Compounds 4\text{cf} and 4\text{cj} have low negative specific rotations, whereas all other products 4 (made with same antipode of chiral ligand) have low to moderate positive specific rotations. It is not clear whether the observed negative specific rotations of 4\text{cf} and 4\text{cj} reflect a true, negative specific rotation or whether the observed negative specific rotation arises simply because the magnitude of specific rotation for these products is small relative to experimental error. In terms of HPLC data, 4\text{cj} is consistent with that of other compounds: the major enantiomer elutes second. 4\text{cf} is different than other compounds: the major enantiomer elutes first.
The crude reaction mixture was dried under high vacuum overnight to remove residual benzoxazole 1c, since it coelutes with 4ch. Flash column chromatography on silica gel (7:1 → 6:1 Hex:Et₂O) yielded a clear oil (85%). Rᵣ = 0.32 (5:1 Hex:Et₂O); HPLC analysis – Chiracel IC column, 98:2 Hex:iPrOH, 1.0 mL/min, major enantiomer: 10.2 min, minor enantiomer: 9.4 min, 94% ee; [α]D²⁵ = +5.6° (c = 3.070 g/100 mL, CDCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, 1H, J = 8.0 Hz), 7.17 (m, 1H), 7.08 (d, 1H, J = 7.6 Hz), 4.09-4.21 (m, 2H), 3.19-3.30 (m, 1H), 3.03-3.14 (m, 2H), 2.58 (s, 3H), 1.59-1.77 (m, 2H), 1.34-1.41 (m, 1H), 1.20 (t, 3H, J = 7.2 Hz), 0.90-0.94 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 175.0, 164.1, 150.7, 140.5, 130.2, 124.8, 124.4, 107.8, 60.7, 41.8, 41.6, 31.7, 26.1, 23.0, 22.1, 16.6, 14.3; IR (ATR) 3061, 2957, 2930, 2871, 1732, 1624 cm⁻¹; LRMS (ESI + APCI) m/z [C₁₇H₂₄NO₃]⁺ ([M+H]⁺) calecd 290.2, found 290.2.

Flash column chromatography on silica gel (DCM → 6% → 12% EtOAc in DCM) yielded a colorless oil (60%). Rᵣ = 0.23 (6% EtOAc in DCM); HPLC analysis – Chiracel IC column, 80:20 Hex:iPrOH, 1.0 mL/min, major enantiomer: 11.6 min, minor enantiomer: 10.8 min, 69% ee; [α]D²⁵ = +7.2° (c = 2.030 g/100 mL, CDCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, 1H, J = 7.6 Hz), 7.19 (t, 1H, J = 7.6 Hz), 7.10 (d, 1H, J = 7.6 Hz), 3.73 (s, 3H), 3.66 (s, 3H), 3.48-3.54 (m, 1H), 3.40 (dd, 1H, J = 15.6, 6.0 Hz), 3.21 (dd, 1H, 15.6, 8.0 Hz), 2.87 (dd, 1H, J = 16.8, 8.0 Hz), 2.71 (dd, 1H, J = 16.8, 5.6 Hz), 2.58 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.5 171.9, 163.1, 150.7, 140.5, 130.4, 125.0, 124.6, 107.8, 52.5, 52.0, 39.2, 35.0, 30.3, 16.6; IR (ATR) 3027, 2998, 2953, 2850, 1735 cm⁻¹; LRMS (ESI + APCI) m/z [C₁₅H₁₈NO₅]⁺ ([M+H]⁺) calecd 292.1, found 292.1.

Flash column chromatography on silica gel (2 x 5% → 10% EtOAc in Hex) yielded a very light brown oil (76%). Rᵣ = 0.26 (10% EtOAc in Hex); HPLC analysis – Chiracel IC column, 98:2 Hex:iPrOH, 1.0 mL/min, major enantiomer: 8.3 min, minor enantiomer: 7.5 min, 96% ee; [α]D²⁵ = -2.1° (c = 3.590 g/100 mL, CDCl₃),¹⁰⁰ ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, 1H, J = 8.0 Hz), 7.17 (m, 1H), 7.08 (d, 1H, J = 7.6 Hz), 4.10-4.21 (m, 2H), 3.56-3.65 (m, 2H), 3.26-3.33 (m, 1H), 3.04-3.11 (m, 2H), 2.57 (s, 3H), 1.49-1.84 (m, 4H), 1.21 (t, 3H, J = 7.2 Hz), 0.85 (s, 9H), 0.02 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 174.5, 164.2, 150.7, 140.6, 130.2, 124.8, 124.4, 107.8, 62.7, 60.8, 43.2, 31.1, 30.2, 28.6, 26.0, 18.4, 16.6, 14.3, -5.2; IR (ATR) 2953, 2928, 2856, 1733, 1610 cm⁻¹; LRMS (ESI + APCI) m/z [C₂₂H₃₆NO₄Si]⁺ ([M+H]⁺) calecd 406.2, found 406.3.
4aa. Flash column chromatography on silica gel (50:44:6 Hex:DCM:Et₂O) yielded a colorless oil (45%). R₉ = 0.13 (50:44:6 Hex:DCM:Et₂O); HPLC analysis – Chiracel IC column, 80:20 Hex:iPrOH, 1.0 mL/min, major enantiomer: 6.8 min, minor enantiomer: 6.4 min, 87% ee; [α]D²⁵ = +3.09° (c = 1.080 g/100 mL, CDCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.65-7.69 (m, 1H), 7.45-7.50 (m, 1H), 7.28-7.32 (m, 2H), 4.16 (q, 2H, J = 7.2 Hz), 3.35 (dd, 1H, J = 15.6, 7.2 Hz), 3.16 (m, 1H), 3.03 (dd, 1H, J = 15.6, 7.2 Hz), 1.32 (d, 3H, J = 7.2 Hz), 1.22 (t, 3H, J = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 175.0, 165.1, 150.9, 141.4, 124.8, 124.3, 119.8, 119.5, 61.0, 37.7, 32.3, 17.3, 14.3; IR (ATR) 2979, 2928, 1731, 1615, 1572 cm⁻¹; LRMS (ESI + APCI) m/z [C₁₃H₁₆NO₃]⁺ ([M+H]⁺) calcd 234.1, found 234.1.

4ea. Flash column chromatography on silica gel (DCM → 2% → 5% → 10% Et₂O in DCM) yielded a colorless oil (35%). Rᵣ = 0.30 (8:1 Hex:Acetone); HPLC analysis – Chiracel IB column, 94:6 Hex:10% iPrOH in Hex, 1.0 mL/min, major enantiomer: 9.1 min, minor enantiomer: 8.4 min, 90% ee; [α]D²⁵ = +8.9° (c = 1.155 g/100 mL, CDCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, 1H, J = 2.0 Hz), 7.39 (d, 1H, J = 8.8 Hz), 7.27 (dd, 1H, J = 8.8, 2.0 Hz), 4.16 (q, 2H, J = 7.2 Hz), 3.34 (dd, 1H, J = 15.6, 7.2 Hz), 3.10-3.10 (m, 1H), 3.03 (dd, 1H, J = 15.6, 7.2 Hz), 1.32 (d, 3H, J = 7.2 Hz), 1.22 (t, 3H, J = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 174.6, 166.4, 149.3, 142.4, 129.7, 124.9, 119.7, 111.0, 60.8, 37.4, 32.1, 17.1, 14.1; IR (ATR) 3096, 2980, 2938, 1732, 1568, 1451 cm⁻¹; LRMS (ESI + APCI) m/z [C₁₃H₁₅ClNO₃]⁺ ([M+H]⁺) calcd 268.1, found 268.0.

4fa. The crude reaction mixture was dried under high vacuum overnight to remove residual benzoxazole 1f, since it coelutes with 4fa. Flash column chromatography on silica gel (5:2 Hex:Et₂O) yielded a light yellow oil (31%). Rᵣ = 0.26 (5:2 Hex:Et₂O); HPLC analysis – Chiracel IC column, 94:6 Hex:10% iPrOH in Hex, 1.0 mL/min, major enantiomer: 9.1 min, minor enantiomer: 8.4 min, 90% ee; [α]D²⁵ = +3.0° (c = 0.970 g/100 mL, CDCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, 1H, J = 2.0 Hz), 7.39 (d, 1H, J = 8.8 Hz), 7.27 (dd, 1H, J = 8.8, 2.0 Hz), 4.15 (q, 2H, J = 7.2 Hz), 3.34 (dd, 1H, J = 15.6, 7.2 Hz), 3.10-3.10 (m, 1H), 3.03 (dd, 1H, J = 15.6, 7.2 Hz), 1.32 (d, 3H, J = 7.2 Hz), 1.22 (t, 3H, J = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 174.8, 165.6 (d, J = 3.1 Hz), 160.5 (d, J = 242 Hz), 150.8 (d, J = 14.6 Hz), 137.7, 120.0 (d, J = 9.9 Hz), 112.2 (d, J = 24.4), 98.6 (d, J = 28.1 Hz), 61.0, 37.6, 32.3, 17.3, 14.3; ¹⁹F NMR (376 MHz, CDCl₃) δ -116.1 (ddd, J = 9.2, 8.8, 4.8 Hz); IR (ATR) 3081, 2980, 2939, 2909, 1730, 1623 cm⁻¹; LRMS (ESI + APCI) m/z [C₁₃H₁₅FNO₃]⁺ ([M+H]⁺) calcd 252.1, found 252.1.
**4ga.** Flash column chromatography on silica gel (DCM → 1% → 2% → 4% → 10% → 30% EtOAc in DCM) yielded a light golden oil (48%). $R_f = 0.24$ (4% EtOAc in DCM); HPLC analysis – Chiracel IC column, 90:10 Hex:iPrOH, 1.0 mL/min, major enantiomer: 14.7 min, minor enantiomer: 13.5 min, 88% ee; $[\alpha]_D^{25} = +3.1^\circ$ (c = 1.580 g/100 mL, CDCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.52 (d, 1H, $J = 8.8$ Hz), 7.00 (d, 1H, $J = 2.4$ Hz), 6.89 (dd, 1H, $J = 15.2$, 6.8 Hz), 3.12 (m, 1H), 2.98 (dd, 1H, $J = 15.2$, 7.2 Hz), 1.30 (d, 3H, $J = 7.2$ Hz), 1.22 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 175.0, 164.0, 158.0, 151.7, 135.1, 119.7, 112.3, 95.5, 60.9, 56.1, 37.7, 32.3, 17.2, 14.3; IR (ATR) 2978, 2939, 2907, 2836, 1729, 1615 cm$^{-1}$; LRMS (ESI + APCI) m/z [C$_{14}$H$_{18}$NO$_4$]$^+$ ([M+H]$^+$) calcd 264.1, found 264.1.

**4ha.** Flash column chromatography on silica gel (1% → 2% → 4% → 10% → 30% EtOAc in DCM) yielded a colorless oil (56%). $R_f = 0.15$ (2% EtOAc in DCM); HPLC analysis – Chiracel IB column, 93:7 Hex:iPrOH in Hex, 1.0 mL/min, major enantiomer: 17.1 min, minor enantiomer: 15.8 min, 77% ee; $[\alpha]_D^{25} = +7.4^\circ$ (c = 1.830 g/100 mL, CDCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.34 (d, 1H, $J = 9.2$ Hz), 7.16 (d, 1H, $J = 2.4$ Hz), 6.89 (dd, 1H, $J = 15.2$, 7.2 Hz), 3.13 (m, 1H), 2.99 (dd, $J = 15.6$, 7.6 Hz), 1.31 (d, 3H, $J = 6.8$ Hz), 1.22 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.9, 165.9, 157.2, 145.5, 142.2, 113.2, 110.6, 103.0, 60.9, 56.1, 37.7, 32.4, 17.2, 14.3; IR (ATR) 2979, 2938, 2907, 2835, 1730, 1571 cm$^{-1}$; LRMS (ESI + APCI) m/z [C$_{14}$H$_{18}$NO$_4$]$^+$ ([M+H]$^+$) calcd 264.1, found 264.1.

**S17 Mechanistic experiments**

**S17.1 Synthesis of 1c-D**

1c-D. In the glove box, a 1.5 dram vial was charged with [Rh(cod)OAc)$_2$ (27.5 mg, 0.05 mmol, 2 mol %) and dppe (40.5 mg, 0.10 mmol, 4 mol %). To this was added a solution of 1c (339 mg, 300 µL, 2.55 mmol, 1.0 equiv) in PhMe (2000 µL). MeOH-d$_4$ (910 µL) was added, and the vial was sealed with a Teflon-lined stir cap. The reaction was removed from the glove box and heated to 120 °C in an aluminum heating block for 24 h. At this point, the crude reaction mixture was adsorbed onto silica gel and purified by flash column chromatography (7:1 Hex:EtOAc). The obtained product 1c-H/D was subjected to the same reaction, purification sequence 3 times more until < 95% azole $^1$H was observed by $^1$H NMR spectroscopy (Figure S6).

S20
S17.2 Reaction of 1c-D and 3a in CH₃CN (full text, Figure 6, eq. 12)

**Reaction set-up:** In the glove box, a 1.5 dram vial containing [Rh(cod)OAc]₂ (6.8 mg, 12.6 µmol, 5 mol %) and CTH-(R)-xylyl-P-Phos (18.9 mg, 25.2 µmol, 10 mol %) was charged with a solution of 1c-D (32.6 mg, 0.25 mmol, 1.0 equiv) and DTBB (6.6 mg, 25.0 µmol, 0.10 equiv) in 500 µL CH₃CN. Ethyl methacrylate (3a) (228 mg, 250 µL, 2.0 mmol, 8.0 equiv) was added, and the vial was sealed with a Teflon-lined stir cap. The reaction was removed from the glove box and heated to 100 °C in an aluminum block for 12 h.

**Percent yield and percent ee determination:** Percent yield and percent ee of 4ca was determined by LC analysis of the crude reaction mixture on a chiral stationary phase as described above for initial reaction optimization (S12.2). 4ca: 42%, 96% ee

**Determination of percent ¹H incorporation in 1c:** Percent ¹H incorporation in 1c was determined by ¹H NMR analysis of the crude reaction mixture (Figure S7).
**Determination of percent deuterium incorporation in 4ca:** Percent $^2$H incorporation in product 4ca was determined by $^1$H NMR analysis of pure 4ca obtained by flash column chromatography on silica gel (2 x 7:1 Hex:EtOAc) (Figure S8).

[Chemical structure image]

Figure S8 Percent $^2$H incorporation in 4ca determined by $^1$H NMR analysis of pure 4ca (full text, Figure 6, eq. 12)

**S17.3 Reaction of 1c-D and 3a in CD$_3$CN (full text, Figure 6, eq. 13)**

**Reaction set-up:** In the glove box, a 1.5 dram vial containing [Rh(cod)OAc]$_2$ (6.8 mg, 12.6 µmol, 5 mol %) and CTH-(R)-xylyl-P-Phos (18.9 mg, 25.2 µmol, 10 mol %) was charged with a solution of 1c-D (32.6 mg, 0.25 mmol, 1.0 equiv) and DTBB (6.6 mg, 25.0 µmol, 0.10 equiv) in 500 µL CD$_3$CN. Ethyl methacrylate (3a) (228 mg, 250 µL, 2.0 mmol, 8.0 equiv) was added, and the vial was sealed with a Teflon-lined stir cap. The reaction was removed from the glove box and heated to 100 °C in an aluminum block for 12 h.

**Percent yield and percent ee determination:** Percent yield and percent ee of 4ca was determined by LC analysis of the crude reaction mixture on a chiral stationary phase as described above for initial reaction optimization (S12.2). 4ca: 47%, 96% ee

**Determination of percent $^1$H incorporation in 1c:** Percent $^1$H incorporation in 1c was determined by $^1$H NMR analysis of the crude reaction mixture (Figure S9).
Figure S9 Percent $^1$H incorporation in 1c determined by $^1$H NMR analysis of crude reaction mixture (full text, Figure 6, eq. 13)

Determination of percent deuterium incorporation in 4ca: Percent $^2$H incorporation in product 4ca was determined by $^1$H NMR analysis of pure 4ca obtained by flash column chromatography on silica gel (2 x 7:1 Hex:EtOAc) (Figure S10).

Figure S10 Percent $^2$H incorporation in 4ca determined by $^1$H NMR analysis of pure 4ca (full text, Figure 6, eq. 13)

S17.4 Reaction of 1c and 3b-d₈ in CH₃CN (full text, Figure 6, eq. 14)

Reaction set-up: In the glove box, a 1.5 dram vial containing [Rh(cod)OAc]₂ (6.8 mg, 12.6 µmol, 5 mol %) and CTH-(R)-xylyl-P-Phos (18.9 mg, 25.2 µmol, 10 mol %) was charged with a solution of 1c (32.0 mg, 0.25 mmol, 1.0 equiv) and DTBB (6.6 mg, 25.0 µmol, 0.10 equiv) in 500 µL CH₃CN. Ethyl methacrylate (3b-d₈) (216 mg, 214 µL, 2.0 mmol, 8.0 equiv) was added, and the vial was sealed with a Teflon-lined stir cap. The reaction was removed from the glove box and heated to 100 °C in an aluminum block for 26 h.
Percent yield and percent ee determination: Percent ee of 4cb was determined by LC analysis on a chiral stationary phase as described above for initial reaction optimization (S12.2). Percent yield of 4cb was determined with respect to DTBB by $^1$H NMR analysis of the crude reaction mixture.

Determination of percent $^1$H incorporation in 4ca: Percent $^1$H incorporation in product 4cb was determined by $^1$H NMR analysis of pure 4cb obtained by flash column chromatography on silica gel (7:1 Hex:EtOAc) (Figure S11).

Note: The total percent $^1$H incorporation in 4cb exceeds the one hundred percent that would be expected were 1c the only $^1$H source. We account for greater than one hundred percent $^1$H incorporation by invoking reversible C–H activation at the β-position of product 4cb and protonation with CH$_3$CN (vide infra, section S17.6).

Figure S11 Percent $^1$H incorporation in 4cb determined by $^1$H NMR analysis of pure 4cb (full text, Figure 6, eq. 14)

S17.5 Epimerization experiments (full text, Figure 8, eq. 15–17)

S17.5.1 General procedure

In the glove box, a 1.5 dram vial containing [Rh(cod)OAc]$_2$ (3.4 mg, 6.3 µmol, 5 mol %), CTH-(R)-xylyl-P-Phos (9.5 mg, 12.6 µmol, 10 mol %) was charged with a solution of 1c (16.6 mg, 15.0 µL, 0.125 mmol, 1.0 equiv), DTBB (3.3 mg, 12.5 µmol, 0.10 equiv) and 4 (0.063 mmol, 0.5 equiv) in 250 µL CH$_3$CN. The appropriate acrylate 3 (1.0 mmol, 8.0 equiv) was added, and the vial was sealed with a Teflon-lined stir cap. The reaction was removed from the glove box and heated to 100 °C in an aluminum block for 48 h. Percent yield and percent ee of products 4 were determined from the crude reaction mixture as described below.
S17.5.2 A note on HPLC retention times

Slight variation in retention time across products 4 is sometimes observed. We attribute this at least in part to the very low polarity of typical column conditions. We use a premade solution of 10 % iPrOH in Hex as the polar component. The concentration of this mixture can vary from batch to batch. Moreover, polar solvents such as CD$_3$CN or CDCl$_3$ introduced from the crude reaction or from NMR samples can discernably modify retention times.

S17.5.3 A note on HPLC analysis of racemic mixtures (see also section S19)

We make racemic CTH-xylyl-Phos (rac-L11) in situ by mixing small (< 10 mg) quantities of (R)- and (S)-L11. Racemic samples prepared in this way can have ee's up to three percent. In general, the major enantiomer prepared from in situ rac-L11 is the same as that when (R) catalyst is used. This pattern may simply be random, or it could arise from differences in purity or physical properties between catalysts (while the R-catalyst is a fine, free-flowing white powder that is easily weighed, the S catalyst is a clumpy yellow solid that is difficult to weigh).

S17.5.4 Reaction of 1c, 3a and 4ha (77% ee) (full text, Figure 8, eq. 15)

DTBB, 1c, 3a, both enantiomers of 4ha and both enantiomers of 4ca are all separable on Chiracel IB column, 94:6 Hex:10% iPrOH in Hex, 1 mL/min:

- DTBB: 3.4 min
- Ethyl methacrylate (3a): 3.9 min (3a has a very low absorbance)
- 4-methylbenzoxazole (1c): 6.2 min
- First enantiomer 4ca: 7.6 min (minor)
- Second enantiomer 4ca: 8.5 min (major)
- First enantiomer 4ha: 17.5 min (minor)
- Second enantiomer 4ha: 19.0 min (major)

Percent ee of 4ca and 4ha were determined by HPLC analysis (see HPLC data on next page, Figure S12).

Percent yield 4ca was determined by HPLC analysis with respect to DTBB as described in initial reaction optimization (S12.2).

Percent yield 4ha was determined with respect to DTBB by $^1$H NMR.

Results:

- w/o CsOAc—4ca: 70%, 95% ee; 4ha: > 95%, 50% ee
- w/ 25 mol % CsOAc—4ca: 81%, 95% ee; 4ha: > 95%, 50% ee
**Figure S12** HPLC data from epimerization study of 4ha in presence of 1c and 3a (Full text, Figure 8, eq. 15). Top: pure 4ha (77% ee); Middle: reaction mixture w/o CsOAc; Bottom: reaction mixture w/ CsOAc
**S17.5.5 Reaction of 1c, 3a and 4ga (88% ee) (full text, Figure 8, eq. 16)**

Percent yield and percent ee 4ca were determined as for the reaction of 1c, 3a and 4ha above (S17.5.4 and S12.2). Note: Both enantiomers of 4ga elute after 20 min using Chiracel IB column, 94:6 Hex:10% iPrOH in Hex, 1 mL/min.

For ee analysis of 4ca, see Figure S13 below.

Percent ee 4ga was determined by HPLC analysis: Chiracel IC column, 90:10 Hex:iPrOH, 1 mL/min:

First enantiomer 4ga: 13.8 min (minor)

Second enantiomer 4ga: 14.8 min (major)

DTBB, 1c, 3a and 4ca elute before 7.5 min.

For ee analysis of 4ga, see Figure S14 on next page.

Percent yield 4ga was determined with respect to DTBB by $^1$H NMR.

**Results:** 4ca: > 95%, 95% ee; 4ga: > 95%, 74% ee

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**Figure S13** HPLC data from epimerization study of 4ga in the presence of 1c and 3a (Full text, Figure 8, eq. 16). Crude reaction mixture under conditions that separate enantiomers of 4ca. Note: Both enantiomers of 4ga elute after 20 min under these column conditions
Figure S14 HPLC data from epimerization study of 4ga in the presence of 1c and 3a (Full text, Figure 8, eq. 16).
Top: pure 4ga (88% ee); Middle: racemic 4ca; Bottom: crude reaction mixture. Note: ee data for 4ca was obtained under conditions that give better separation for 4ca (see Figure S13 above)
S17.5.6 Reaction of 1c, 3c and 4ca (95% ee) (full text, Figure 8, eq. 17)

Relevant species are all separable under column conditions used for initial reaction optimization (S12.2):

DTBB: 3.4 min
3c: 4.8 min
4-methylbenzoxazole (1c): 6.2 min
First enantiomer 4ca: 7.6 min (minor)
Second enantiomer 4ca: 8.5 min (major)
First enantiomer 4cc: 13.6 min (minor)
Second enantiomer 4cc: 19.1 min (major)

Percent yield and percent ee 4ca were determined as for the reaction of 1c, 3a and 4ha above (S17.5.4 and S12.2) (see Figure S15 on next page).

Percent ee 4cc was determined by HPLC analysis (see Figure S15 on next page), and percent yield 4cc was determined with respect to DTBB by 1H NMR.

Results: 4cc: > 95%, 90% ee; 4ca: > 95%, 93% ee
Figure S15 HPLC data from epimerization study of 4ca in the presence of 1c and 3c (Full text, Figure 8, eq. 17). Top: pure 4ca (95% ee); Middle: racemic 4cc; Bottom: crude reaction mixture
**S17.6 Epimerization–labeling experiments of 4ha and 4ca in CD$_3$CN (full text, Figure 10, eq. 18–19)**

In the glove box, a 1.5 dram vial containing [Rh(cod)OAc]$_2$ (3.4 mg, 6.3 µmol, 13 mol %), CTH-(R)-xylyl-P-Phos (9.5 mg, 12.6 µmol, 26 mol %) was charged with a solution of 4ha (75% ee) or 4ca (95% ee) (0.05 mmol, 1.0 equiv) in 105 µL CD$_3$CN. The vial was sealed with a Teflon-lined screw cap, removed from the glove box and heated to 100 °C in an aluminum block for 48 h. The crude reaction mixture was adsorbed onto silica gel and purified by flash column chromatography—4ha: 3:1 Hex:EtOAc and 4ca: 7:1 Hex:EtOAc. Percent $^2$H incorporation was determined by $^1$H NMR analysis of the pure products (Figure S16–S17). Percent ee 4ha and 4ca determined by LC analysis of crude or purified reaction (Figure S18–S19, next page).

**Figure S16** $^1$H NMR spectrum of pure 4ha in CDCl$_3$ (full text, Figure 10, eq. 18)

**Figure S17** $^1$H spectrum of pure 4ca in CDCl$_3$ (full text, Figure 10, eq. 19)
Figure S18 HPLC data from epimerization reaction of 4ha in CD$_3$CN (full text, Figure 10, eq. 18). Top: 4ha (spiked with DTBB) 75% ee; Bottom: purified 4ha (20% ee) after reaction (full text, Figure 10, eq. 18)
Figure S19 HPLC data from epimerization reaction of 4ca in CD$_3$CN (full text, Figure 10, eq. 19). Top: 4ca (95% ee); Bottom: crude 4ca (91% ee) after reaction (full text, Figure 10, eq. 19)
Data File C:\CHEM32\DATA\3-507-CF_PURE_94-6_2.D
Sample Name: 3-507-CF Pure

Injection Date : 4/25/2014 6:53:22 PM  Seq. Line : 6
Sample Name : 3-507-CF Pure  Location : Vial 1
Acq. Operator : TAD  Inj. : 1
Acq. Instrument : Instrument 1  Actual Inj Volume : 10 µl
Different Inj Volume from Sequence ! Inj Volume : 2 µl
Acq. Method : C:\CHEM32\METHODS\ODH 94-6 HEX-10-1-HEX-IPA 15 MIN.M
Last changed : 1/10/2014 8:22:21 PM by tad
Analysis Method : C:\CHEM32\METHODS\IC 80-20 1ML-1UL 4MIN.M
Last changed : 12/1/2014 5:17:49 PM
(modified after loading)

DADTA, Sig=254.4 Ref=360,100 (3-507-CF_PURE_94-6_2.D)

| Peak RetTime | Width | Area   | Height | Area % |
|--------------|-------|--------|--------|--------|
| 1 7.297 MIN | 0.2463| 3098.53076 | 209.67038 | 49.3438 |
| 2 8.028 MIN | 0.2321| 3180.93677 | 228.38246 | 50.6562 |

Data File C:\CHEM32\DATA\4-127-CF_PURE.D
Sample Name: 4-127-CF Pure

Injection Date : 7/18/2014 2:48:41 PM  Seq. Line : 1
Sample Name : 4-127-CF Pure  Location : Vial 1
Acq. Operator : TAD  Inj. : 1
Acq. Instrument : Instrument 1  Actual Inj Volume : 10 µl
Different Inj Volume from Sequence ! Inj Volume : 2 µl
Acq. Method : C:\CHEM32\METHODS\ODH 94-6 HEX-10-1-HEX-IPA 12 MIN.M
Last changed : 5/27/2014 11:31:49 AM by TAD
Analysis Method : C:\CHEM32\METHODS\IC 80-20 1ML-1UL 4MIN.M
Last changed : 12/1/2014 5:18:01 PM
(modified after loading)

DADTA, Sig=254.4 Ref=360,100 (4-127-CF_PURE.D)

| Peak RetTime | Width | Area   | Height | Area % |
|--------------|-------|--------|--------|--------|
| 1 7.331 MIN | 0.3365| 320.97537 | 15.89954 | 2.9698 |
| 2 8.111 MIN | 0.3063| 1.04871e4 | 570.63306 | 97.0302 |
Data File C:\CHEM32\DATA\4-157-CF PURE IC_80-20.D
Sample Name: 4-157-CF PURE

Injection Date : 9/10/2014 9:34:48 PM  Seq. Line : 10
Sample Name : 4-157-CF PURE  Location : Vial 15
Acq. Operator :  Inj : 1
Acq. Instrument : Instrument 1  Inj Volume : 1 μL
Different Inj Volume from Sequence !  Actual Inj Volume : 2 μL
Acq. Method : C:\CHEM32\METHODS\IC 80-20 1ML-1UL 20MIN.M
Last changed : 8/4/2012 4:38:14 PM
Analysis Method : C:\CHEM32\METHODS\IC 80-20 1ML-1UL 40MIN.M
Last changed : 12/2/2014 6:31:02 AM
(modified after loading)

DAD1, Sign=254.4 Ref=360,100 (4-157-CF PURE IC_80-20.D)

| Peak Ret Time Type | Width [min] | Area [mAU*] | Height [mAU] | Area % |
|--------------------|-------------|-------------|-------------|-------|
| #                  |             |             |             |       |
| 1                  | 11.459      | 0.2479      | 4122.81689  | 277.29398 52.3727 |

Data File C:\CHEM32\DATA\4-160-CF PURE_2.D
Sample Name: 4-160-CF PURE_2

Injection Date : 9/15/2014 11:11:46 AM  Seq. Line : 2
Sample Name : 4-160-CF PURE_2  Location : Vial 1
Acq. Operator :  Inj : 1
Acq. Instrument : Instrument 1  Inj Volume : 1 μL
Different Inj Volume from Sequence !  Actual Inj Volume : 2 μL
Acq. Method : C:\CHEM32\METHODS\IC 80-20 1ML-1UL 15MIN.M
Last changed : 5/21/2013 8:22:23 PM
Analysis Method : C:\CHEM32\METHODS\IC 80-20 1ML-1UL 40MIN.M
Last changed : 12/2/2014 6:31:02 AM
(modified after loading)

DAD1, Sign=254.4 Ref=360,100 (4-160-CF PURE_2.D)

| Peak Ret Time Type | Width [min] | Area [mAU*] | Height [mAU] | Area % |
|--------------------|-------------|-------------|-------------|-------|
| #                  |             |             |             |       |
| 1                  | 10.774      | 0.2286      | 1013.88898  | 73.93015 15.5383 |
| 2                  | 11.620      | 0.2513      | 5511.22119  | 365.47467 84.4617 |

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Table 1. Crystal data and structure refinement for $[\text{Rh(cod)OAc}]_2$

| Characteristic                        | Value                  |
|---------------------------------------|------------------------|
| Identification code                   | rovis139_0m            |
| Empirical formula                     | C$_{20}$H$_{30}$O$_4$Rh$_2$ |
| Formula weight                        | 540.26                 |
| Temperature                           | 120(2) K               |
| Wavelength                            | 0.71073 Å              |
| Crystal system                        | Triclinic              |
| Space group                           | $P-1$                  |
| Unit cell dimensions                  | $a = 8.9223(8)$ Å, $b = 9.9063(8)$ Å, $c = 12.6748(11)$ Å |
|                                       | $\alpha = 103.826(4)^\circ$, $\beta = 90.574(5)^\circ$, $\gamma = 112.147(4)^\circ$ |
| Volume                                | 1001.31(15) Å$^3$      |
| Z                                      | 2                      |
| Density (calculated)                  | 1.792 Mg/m$^3$         |
| Absorption coefficient                | 1.670 mm$^{-1}$        |
| F(000)                                | 544                    |
| Crystal size                          | 0.21 x 0.14 x 0.10 mm$^3$ |
| Theta range for data collection       | 1.66 to 33.41°         |
| Index ranges                          | -13<=h<=13, -15<=k<=15, -19<=l<=19 |
| Reflections collected                 | 27291                  |
| Independent reflections               | 7666 [R(int) = 0.0256]  |
| Completeness to theta = 33.41°        | 98.3 %                 |
| Absorption correction                 | Semi-empirical from equivalents |
| Max. and min. transmission            | 0.8495 and 0.7248      |
| Refinement method                     | Full-matrix least-squares on F$^2$ |
| Data / restraints / parameters        | 7666 / 0 / 237         |
| Goodness-of-fit on F$^2$               | 1.088                  |
| Final R indices [I>2sigma(I)]         | R1 = 0.0324, wR2 = 0.0722 |
| R indices (all data)                  | R1 = 0.0604, wR2 = 0.0909 |
| Largest diff. peak and hole           | 0.831 and -0.492 e.Å$^{-3}$ |
Table 2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for Rovis139_0m. U(eq) is defined as one third of the trace of the orthogonalized $U^0$ tensor.

|       | x       | y       | z       | U(eq)  |
|-------|---------|---------|---------|--------|
| C(1)  | 11185(3)| 3719(3)| 996(2)  | 43(1)  |
| C(2)  | 11027(4)| 2227(3)| 620(2)  | 44(1)  |
| C(3)  | 12303(4)| 1664(3)| 901(3)  | 56(1)  |
| C(4)  | 11961(4)| 1056(4)| 1908(3)| 55(1)  |
| C(5)  | 11088(3)| 1809(3)| 2684(2)| 43(1)  |
| C(6)  | 11523(3)| 3366(3)| 3063(2)| 40(1)  |
| C(7)  | 13027(4)| 4514(3)| 2762(3)| 52(1)  |
| C(8)  | 12633(4)| 4949(3)| 1736(3)| 52(1)  |
| C(9)  | 6809(3) | 2434(3)| 326(2) | 33(1)  |
| C(10) | 5711(3) | 1618(3)| -737(2)| 43(1)  |
| C(11) | 6606(3) | 1843(3)| 3161(2)| 32(1)  |
| C(12) | 5456(3) | 824(3) | 3773(2)| 48(1)  |
| C(13) | 9422(4) | 6740(3)| 2170(2)| 41(1)  |
| C(14) | 10686(4)| 7718(3)| 3145(2)| 48(1)  |
| C(15) | 10581(4)| 6895(3)| 4048(2)| 47(1)  |
| C(16) | 8887(4) | 5745(3)| 4038(2)| 41(1)  |
| C(17) | 7478(4) | 6039(3)| 4031(2)| 44(1)  |
| C(18) | 7485(4) | 7585(4)| 4051(3)| 58(1)  |
| C(19) | 7226(4) | 7723(3)| 2891(3)| 52(1)  |
| C(20) | 7881(4) | 6784(3)| 2061(2)| 43(1)  |
| O(1)  | 7876(2) | 1635(2)| 2960(2)| 45(1)  |
| O(2)  | 6221(2) | 2832(2)| 2924(2)| 44(1)  |
| O(3)  | 7602(2) | 1773(2)| 635(2) | 46(1)  |
| O(4)  | 6848(3) | 3703(2)| 817(2) | 46(1)  |
| Rh(1) | 7636(1) | 4800(1)| 2475(1)| 31(1)  |
| Rh(2) | 9513(1) | 2405(1)| 1854(1)| 30(1)  |
Table 3. Bond lengths [Å] and angles [°] for Rovis139_0m.

| Bond | Length [Å] |
|------|------------|
| C(1)-C(2) | 1.392(4) |
| C(1)-C(8) | 1.509(4) |
| C(1)-Rh(2) | 2.085(2) |
| C(2)-C(3) | 1.517(4) |
| C(2)-Rh(2) | 2.096(3) |
| C(3)-C(4) | 1.524(4) |
| C(4)-C(5) | 1.494(4) |
| C(5)-C(6) | 1.398(4) |
| C(5)-Rh(2) | 2.080(3) |
| C(6)-C(7) | 1.518(4) |
| C(6)-Rh(2) | 2.106(3) |
| C(7)-C(8) | 1.540(4) |
| C(9)-O(3) | 1.244(3) |
| C(9)-O(4) | 1.249(3) |
| C(9)-C(10) | 1.511(3) |
| C(11)-O(1) | 1.245(3) |
| C(11)-O(2) | 1.249(3) |
| C(11)-C(12) | 1.511(3) |
| C(13)-C(20) | 1.398(4) |
| C(13)-C(14) | 1.521(4) |
| C(13)-Rh(1) | 2.107(3) |
| C(14)-C(15) | 1.540(4) |
| C(15)-C(16) | 1.510(4) |
| C(16)-C(17) | 1.393(4) |
| C(16)-Rh(1) | 2.081(3) |
| C(17)-C(18) | 1.524(4) |
| C(17)-Rh(1) | 2.097(3) |
| C(18)-C(19) | 1.532(4) |
| C(19)-C(20) | 1.506(4) |
| C(20)-Rh(1) | 2.087(2) |
| O(1)-Rh(2) | 2.0954(17) |
| O(2)-Rh(1) | 2.0999(17) |
| O(3)-Rh(2) | 2.0894(18) |
| O(4)-Rh(1) | 2.0958(18) |
| Bond                  | Angle (°)  |
|----------------------|------------|
| C(2)-C(1)-C(8)       | 123.8(3)   |
| C(2)-C(1)-Rh(2)      | 70.98(15)  |
| C(8)-C(1)-Rh(2)      | 112.41(18) |
| C(1)-C(2)-C(3)       | 123.6(3)   |
| C(1)-C(2)-Rh(2)      | 70.14(15)  |
| C(3)-C(2)-Rh(2)      | 113.35(19) |
| C(2)-C(3)-C(4)       | 111.5(2)   |
| C(5)-C(4)-C(3)       | 112.7(2)   |
| C(6)-C(5)-C(4)       | 125.6(3)   |
| C(6)-C(5)-Rh(2)      | 71.48(15)  |
| C(4)-C(5)-Rh(2)      | 111.17(19) |
| C(5)-C(6)-C(7)       | 122.8(3)   |
| C(5)-C(6)-Rh(2)      | 69.51(15)  |
| C(7)-C(6)-Rh(2)      | 114.17(18) |
| C(6)-C(7)-C(8)       | 111.5(2)   |
| C(1)-C(8)-C(7)       | 112.7(2)   |
| O(3)-C(9)-O(4)       | 125.6(2)   |
| O(3)-C(9)-C(10)      | 116.5(2)   |
| O(4)-C(9)-C(10)      | 117.9(2)   |
| O(1)-C(11)-O(2)      | 126.0(2)   |
| O(1)-C(11)-C(12)     | 116.4(2)   |
| O(2)-C(11)-C(12)     | 117.7(2)   |
| C(20)-C(13)-C(14)    | 123.0(3)   |
| C(20)-C(13)-Rh(1)    | 69.76(15)  |
| C(14)-C(13)-Rh(1)    | 113.72(17) |
| C(13)-C(14)-C(15)    | 111.6(2)   |
| C(16)-C(15)-C(14)    | 112.2(2)   |
| C(17)-C(16)-C(15)    | 124.5(3)   |
| C(17)-C(16)-Rh(1)    | 71.13(15)  |
| C(15)-C(16)-Rh(1)    | 112.29(18) |
| C(16)-C(17)-C(18)    | 123.3(3)   |
| C(16)-C(17)-Rh(1)    | 69.90(15)  |
| C(18)-C(17)-Rh(1)    | 113.54(19) |
| C(17)-C(18)-C(19)    | 111.1(2)   |
| C(20)-C(19)-C(18)    | 112.6(2)   |
C(2)-Rh(2)-C(6)  91.03(11)

Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å² x 10³) for Rovis139_0m. The anisotropic displacement factor exponent takes the form: -2π² [h² a² U₁₁ + ... + 2hk a* b* U₁₂]

|     | U₁₁    | U₂₂    | U₃₃    | U₁₂    | U₁₃    | U₁₂ |
|-----|--------|--------|--------|--------|--------|------|
| C(1)| 43(2)  | 48(2)  | 38(2)  | 18(1)  | 14(1)  | 14(1)|
| C(2)| 42(2)  | 49(2)  | 32(1)  | 8(1)   | 12(1)  | 11(1)|
| C(3)| 40(2)  | 48(2)  | 70(2)  | -4(2)  | 19(2)  | 17(1)|
| C(4)| 43(2)  | 51(2)  | 73(2)  | 11(2)  | -5(2)  | 25(2)|
| C(5)| 39(2)  | 50(2)  | 46(2)  | 20(1)  | 0(1)   | 21(1)|
| C(6)| 36(2)  | 52(2)  | 32(1)  | 7(1)   | -1(1)  | 21(1)|
| C(7)| 34(2)  | 46(2)  | 62(2)  | -5(2)  | -3(1)  | 11(1)|
| C(8)| 43(2)  | 41(2)  | 65(2)  | 12(2)  | 20(2)  | 8(1)|
| C(9)| 29(1)  | 35(1)  | 31(1)  | 11(1)  | 5(1)   | 9(1)|
| C(10)| 44(2) | 47(2)  | 32(1)  | 5(1)   | -4(1)  | 15(1)|
| C(11)| 27(1) | 32(1)  | 35(1)  | 9(1)   | 5(1)   | 9(1)|
| C(12)| 41(2) | 54(2)  | 54(2)  | 29(2)  | 18(1)  | 15(1)|
| C(13)| 51(2) | 35(1)  | 40(2)  | 16(1)  | 9(1)   | 16(1)|
| C(14)| 43(2) | 38(1)  | 53(2)  | 6(1)   | 0(1)   | 9(1)|
| C(15)| 45(2) | 47(2)  | 42(2)  | 5(1)   | -7(1)  | 15(1)|
| C(16)| 50(2) | 46(2)  | 27(1)  | 9(1)   | 0(1)   | 19(1)|
| C(17)| 51(2) | 53(2)  | 31(1)  | 7(1)   | 9(1)   | 26(1)|
| C(18)| 62(2) | 54(2)  | 57(2)  | -3(2)  | 9(2)   | 33(2)|
| C(19)| 54(2) | 36(1)  | 70(2)  | 9(1)   | -3(2)  | 23(1)|
| C(20)| 54(2) | 34(1)  | 42(2)  | 15(1)  | -5(1)  | 15(1)|
| O(1)| 37(1)  | 54(1)  | 59(1)  | 32(1)  | 21(1)  | 22(1)|
| O(2)| 35(1)  | 42(1)  | 62(1)  | 24(1)  | 10(1)  | 16(1)|
| O(3)| 43(1)  | 43(1)  | 48(1)  | -1(1)  | -12(1) | 20(1)|
| O(4)| 64(1)  | 38(1)  | 35(1)  | 3(1)   | -11(1) | 21(1)|
| Rh(1)| 36(1) | 28(1)  | 29(1)  | 7(1)   | 0(1)   | 13(1)|
| Rh(2)| 24(1) | 35(1)  | 31(1)  | 10(1)  | 4(1)   | 11(1)|
| H(1)   | x     | y     | z     | U(eq) |
|--------|-------|-------|-------|-------|
| 10685  | 4075  | 466   | 51    |
| H(2)   | 10429 | 1707  | -129  | 53    |
| H(3A)  | 13390 | 2502  | 1037  | 67    |
| H(3B)  | 12318 | 855   | 272   | 67    |
| H(4A)  | 11296 | -43   | 1673  | 66    |
| H(4B)  | 13005 | 1204  | 2292  | 66    |
| H(5)   | 10568 | 1237  | 3225  | 51    |
| H(6)   | 11254 | 3699  | 3820  | 48    |
| H(7A)  | 13868 | 4087  | 2626  | 63    |
| H(7B)  | 13473 | 5431  | 3381  | 63    |
| H(8A)  | 12413 | 5878  | 1964  | 62    |
| H(8B)  | 13595 | 5174  | 1323  | 62    |
| H(10A) | 6363  | 1419  | -1326 | 64    |
| H(10B) | 5165  | 2247  | -905  | 64    |
| H(10C) | 4893  | 660   | -668  | 64    |
| H(12A) | 5226  | -233  | 3399  | 72    |
| H(12B) | 4437  | 985   | 3796  | 72    |
| H(12C) | 5958  | 1057  | 4520  | 72    |
| H(13)  | 9889  | 6546  | 1463  | 49    |
| H(14A) | 10518 | 8662  | 3446  | 57    |
| H(14B) | 11788 | 7993  | 2900  | 57    |
| H(15A) | 11351 | 6382  | 3945  | 56    |
| H(15B) | 10913 | 7647  | 4769  | 56    |
| H(16)  | 8846  | 4983  | 4444  | 49    |
| H(17)  | 6616  | 5448  | 4431  | 53    |
| H(18A) | 8538  | 8380  | 4421  | 69    |
| H(18B) | 6610  | 7743  | 4473  | 69    |
| H(19A) | 6046  | 7400  | 2682  | 63    |
| H(19B) | 7770  | 8795  | 2883  | 63    |
| H(20)  | 7454  | 6617  | 1288  | 52    |
